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DOCTORAL THESIS

**Effectiveness of two treatment components
for fibromyalgia: cognitive restructuring and mindfulness
combination, and pain neuroscience education**

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THESIS PRESENTED BY COMPENDIUM OF PUBLICATIONS

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*A Angélica, una mujer del sur de Chile
que me descubrió el sufrimiento del dolor crónico.
A tothom que pateix, encara, la falta de respostes
i viu en la desesperació del dolor crònic.*

Agraïments

Jenny: no puc imaginar una tutora i directora de tesi millor que tu. Tot aquest camí ha estat el millor aprenentatge tant professional com personal. Tens l'habilitat de convertir un doctorat en una aventura d'inspiració i motivació continua.

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La meva família: que m'heu recolzat de forma incondicional en tot moment.

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ABBREVIATIONS

AAQ-II: Acceptance and Action Questionnaire
ACR: American College of Rheumatology
ACT: Acceptance and Commitment Therapy
BBAT: Body Basic Awareness Therapy
BDI: Beck Depression Inventory
BFI: Brief Fatigue Inventory
BPI: Brief Pain Inventory
CBT: Cognitive Behavioural Therapy
CNS: Central Nervous System
CPCI: Chronic Pain Coping Inventory
CPSI: Chronic Pain Sleep Inventory
CPSS: Chronic Pain Self-efficacy Scale
CRPS: Complex Regional Pain Syndrome
CSQ: Coping Strategies Questionnaire
CSSSU: Central Sensitivity Syndromes Specialised Unit
DRG: Dorsal Root Ganglion
EAET: Emotional Awareness and Expression Therapy
ESS: Epworth Sleepiness Scale
EULAR: European League Against Rheumatism
FIQ: Fibromyalgia Impact Questionnaire
FM: Fibromyalgia
FSS: Fatigue Severity Scale
HADS: Hospital Anxiety and Depression Scale
KNAP: Knowledge and Attitudes of Pain Questionnaire
MAF: Multidimensional Assessment of Fatigue
MBSR: Mindfulness-Based Stress Reduction
MFI: Multidimensional Fatigue Inventory
MOS: Medical Outcomes Study
MPI: Multidimensional Pain Inventory
MPP: Multicomponent Physiotherapy Program
MPQ: McGill Pain Questionnaire
NRS: Numeric Rating Scale
PCS: Pain Catastrophising Scale
PGIC: Patient Global Impression of Change
PIPS: Psychological Inflexibility in Pain Scale
PNE: Pain Neuroscience Education
PSI: Prefrontal Symptoms Inventory
PSQI: Pittsburgh Sleep Quality Index
PSS: Perceived Stress Scale
RCT: Randomised Control Trial
SF-12: 12-Item Short Form Health Survey
SF-36: 36-Item Short Form Health Survey
SSQ: Stanford Sleep Questionnaire
STAI: State-Trait Anxiety Inventory
TAU: Treatment-as-usual
TE: Therapeutic Exercise
VAS: Visual Analogue Scale
WPI: Widespread Pain Index

ABSTRACT

INTRODUCTION

THESIS APPROACH AND OBJECTIVES

**PHASE I: SYSTEMATIC REVIEW OF PSYCHOLOGICAL
INTERVENTIONS IN FIBROMYALGIA**

**PHASE II: COGNITIVE RESTRUCTURING AND MINDFULNESS
TRAINING COMBINATION EFFECTIVENESS**

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GENERAL DISCUSSION

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Abstract

ABSTRACT

Background/Objectives. Fibromyalgia is a highly prevalent disease (affecting 2-4% of general population). Psychological therapies for fibromyalgia have gradually evolved and continues to do so, but there is incongruous evidence in relation to effectiveness. This thesis aims in a first phase at reviewing psychological treatment effectiveness. Based on the review's findings, a second phase presents a study aimed at evaluating the effectiveness of cognitive restructuring and mindfulness combination, and a third phase presents a study on evaluating the effectiveness of a new pain neuroscience education tool.

Methods. In the first phase, a review of 72 selected articles about psychological treatments for fibromyalgia was conducted. In the second phase, 330 subjects were recruited and randomly allocated to (1:1:1) treatment-as-usual, to a complete multicomponent treatment including cognitive restructuring and mindfulness training or to a multicomponent treatment without cognitive restructuring and mindfulness training. Differences were then analysed. The third phase consisted of three parts: 1) a qualitative analysis of a study of effectiveness of a new pain neuroscience education tool; 2) a study of effectiveness of the tool (written and video-based); 3) a correlation analysis between patients' pain neuroscience knowledge and health status.

Results. In the first phase, all the studied psychological interventions show improvements in at least one variable. CBT and mindfulness training remain the most studied interventions and multicomponent treatments continue to be the trend approach. Education, present in several studies, might act as a mediator variable. In the second phase, cognitive restructuring and mindfulness training included in a multi-component treatment are proven to be significantly effective when compared to a multi-component treatment without these two components. In the third phase, general positive feedback of the new pain neuroscience education tool is presented and shows to be significantly effective in both written and video-based formats. Moreover, a significant correlation between patients' pain neuroscience knowledge and health status is demonstrated.

Conclusions. Cognitive restructuring, mindfulness training, and pain neuroscience education, all included in a multicomponent treatment, seem to be effective for the treatment of fibromyalgia.

Key Words. Fibromyalgia, Psychological Interventions, Multicomponent treatment, Cognitive Restructuring, Mindfulness, Pain Neuroscience Education

ABSTRACT

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THESIS APPROACH AND OBJECTIVES

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GENERAL DISCUSSION

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Introduction

1. INTRODUCTION

1.1 Fibromyalgia

Fibromyalgia (FM) is a chronic and complex disease characterised mainly by musculoskeletal pain, fatigue and sleep disorders, and often accompanied by associated manifestations such as cognitive problems, psychological distress, stiffness, skin tenderness, irritable bowel syndrome, headaches, dizziness, fluid retention, and restless legs (Lee et al., 2017). It is a highly prevalent disease (2-4% of general population) and is mostly diagnosed in women between the ages of 20 and 50 (Häuser et al., 2015).

Fibromyalgia has been associated with a significant socioeconomic burden (Lacasse et al., 2016). Several health economic studies found that direct costs for both patients and healthcare funders, such as medical services, and losses in time and productivity from paid and unpaid work due to the sickness (Berger et al., 2010; Lacasse et al., 2016; Tarricone, 2006) could be three times higher than the costs for patients with other conditions but similar sociodemographic characteristics (Berger et al., 2017).

Functional and detrimental psychosocial consequences of overall chronic pain conditions have been well reported with effects on the experience of pain, disability and health-related quality of life (Turk et al., 2016). Health-related quality of life is increasingly evaluated in patients with fibromyalgia, as they present a poorer health status than patients with other many chronic diseases such as diabetes, hypertension, congestive heart failure, rheumatoid arthritis and osteoarthritis, among others (Lee et al., 2017).

1.2 Psychosocial factors in pain

To understand the mechanisms that contribute to the development and maintenance of pain, comprehending the influence of psychological factors is essential. Without recognising these basic components in the definition, important nuances are lost, at a corresponding cost to the comprehension and clinical management of pain (Craig & MacKenzie, 2021). Since pain is an unpleasant experience or perception, behaviours, cognitions, emotions, and social factors are involved in a complex and multidirectional relationship. Thanks to scientific advances, it is now possible to understand that psychosocial factors are not only a consequence of chronic pain conditions but also play a crucial role in the influence, development, maintenance,

and in treatment outcomes (Edwards et al., 2016). In other words, its implication is not only consequential but also causal.

Behaviour might be the more visible element. As early as 1984 Fordyce stressed the importance of highlighting that pain problems are expressed by the patient's behaviour. Only if the person manifests changes in behaviour can we conclude that the person is in pain; without visible or audibly significant changes in behaviour we can scarcely conclude the person is in pain, although there might be sensation of pain or nociception (Fordyce, 1984). In addition to being a clinical indicator of pain, pain behaviours were also found to be an influential and causal factor: these behaviours in turn may act to promote the acquisition, generalisation or extinction of chronic pain. The fear-avoidance model of chronic pain outlines a vicious circle of chronic disability and suffering in which individuals experiencing pain may become trapped (Vlaeyen et al., 2016).

It is worth noting that cognitive strategies are not entirely separable from behavioural approaches since behaviour is influenced by cognitive processes and vice-versa. Thus, cognitive strategies in pain management are based on the acknowledgement that behaviour is influenced by cognitive processes and environmentally deep-rooted contingencies (Fordyce, 1984). Cognition is a fundamental element involved in the subjective perception of pain that requires learning, cognitive-evaluation, recall of past events and active decision making (Hansen and Streltzer, 2005; Moriarty et al., 2011). In this regards, neural systems of cognition and pain have increasingly shown a bi-directional modulatory role where cognitive changes are affected by pain and vice versa (Khera & Rangasamy, 2021).

There is extensive literature that provides support for the idea that pain uses cognitive resources, alters neural plasticity and modifies activity and expression in different chemical and cellular neuromediators (Moriarty et al., 2011). Besides Fibromyalgia, chronic back pain, migraines, diabetic neuropathy, Complex Regional Pain Syndrome (CRPS), peripheral neuropathic pain syndromes, rheumatoid arthritis and multiple sclerosis have been used to investigate the disruption of cognitive processing (Alemanno et al., 2019; Calandre et al., 2002; Cousins et al., 2015; Curatolo et al., 2017; Dick and Rashid, 2007; Gil-Gouveia et al., 2015; Huang et al., 2017; Jensen et al., 2018; Martinsen et al., 2018; Oláh et al., 2020; Said et al., 2019). The main cognitive parameters investigated include: attention, memory, learning, psychomotor ability, processing speed, and executive function (Khera & Rangasamy, 2021).

Attention might be the most studied cognitive factor that modifies pain experience. Already in the 80s and 90s several studies found that

pain is perceived as less intense when subjects are distracted (Bushnell et al., 1999; Levine et al., 1982; Miron et al., 1989; Rode et al., 2001). However, other studies suggested that in some cases, focusing on pain might have a paradoxical effect on decreasing its intensity (Keogh et al., 2000). On the inverse relationship of influence between pain and attention, clinical studies over the past decade have investigated the effect of chronic pain on attention. Recent studies found reduced accuracy on attentional switching and divided attention tasks in subjects with fibromyalgia (Moore et al., 2019).

Emotional processes in chronic pain are increasingly acknowledged (Lumley et al., 2011) and gaining interest since negative emotions and stress have been associated to greater pain and disability (Caes et al., 2017; Edwards et al., 2016; Vachon-Préseau et al., 2016). Clinical studies indicate that mood, attitudes and emotional states influence pain associated with chronic conditions (Villemure and Bushnell, 2002). Different theories of emotions suggest that neural systems could also underlie the emotional modulation of pain. Ploghaus et al. (1992) found an implication of anxiety-related pain modulation which they related to connections between the entorhinal cortex and amygdala (Pitkanen et al., 2000). Several other studies focused on neural circuitry associated to influences of the positive affect on pain processing (Ashby et al., 1999) and to the evaluation of aversive and rewarding stimuli (Becerra et al., 2001). This supports the idea that pleasantly charged stimuli (either positive or negative) can quickly modulate pain perception (Villemure & Bushnell, 2002).

Although traditional models described pain based on the consequences in terms of behaviours, cognition and emotions, recent evidence highlights the importance of analysing pain from a broader social environment. Neuroscience research indicates a significant overlap between the experience of pain and social pain (Sturgeon & Zautra, 2016). The environment around the person plays an important role as pain behaviours can be directly or indirectly and positively or negatively reinforced (Fordyce et al., 1982). Prior experiences related to some sort of reinforcement and other events outside the patient can contribute to an influence on the course and persistence of the pain condition (Fordyce, 1984). The recent social communication model of pain integrates an insight of social determinants of pain with biological and psychological systems (Craig, 2018). The model incorporates innovative features such as the importance of the status prior to the painful event, the personal disposition that leads each individual to react in a certain way, the impact of the immediate physical and social environment, and the

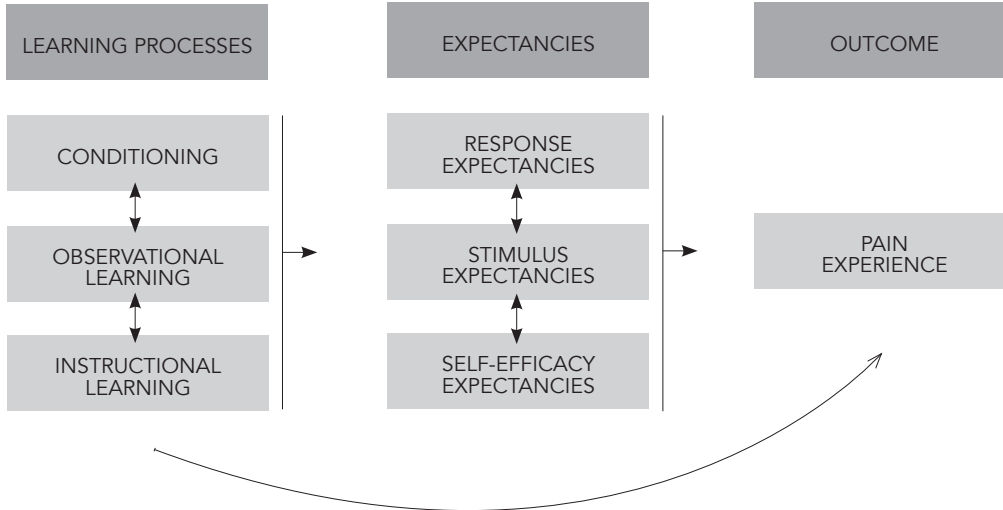
acknowledged explicitness in humans but also nonhuman animals (Craig, 2015).

1.3 Pain processing: Learning mechanisms and expectancies

Behavioural, cognitive, emotional and social factors not only play a role in the development and maintenance of pain but can also act as mediators and/or moderators of pain mechanisms in which learning and expectancies seem to be the main protagonists (Figure 1).

Figure 1: Schematic depiction of the influence of expectancies on pain, including the learning processes that influence these expectancies. Probable mediators and/or moderators are behaviour, emotions, and cognitions. All elements in the model may also feed back to preceding elements.

Source: Peerdeman et al., 2016



The reason why pain experience can increase or decrease can be explained by learning mechanisms. Flor and Herman (2012) classified learning processes into implicit and explicit, which are related to conscious and unconscious processes, respectively. Implicit learning refers to unconscious changes in behaviour because of experience, and explicit learning refers to semantic and episodic memory processes that are based on the conscious reproduction of a coded memory stimuli. Several studies have shown that conditioning and pain modulation habitually involve both conscious awareness

and unconscious systems (Amanzio & Benedetti, 1999; Benedetti et al., 2003; Lovibond & Shanks, 2002). While it seems that indeed both conscious and unconscious processes are involved, certain specific mechanisms might be related to one or other system. For instance, the generalisation of pain (transfer of previously learned information to novel stimuli and situations) seems to be an active cognitive process that occurs only after explicit learning (Dunsmoor & Murphy, 2015; Guttman & Kalish, 1956; Pearce, 1987). Explicit learning and expectations might be essential for generalisation of learned pain modulation (Kragel et al., 2018; Kroban et al., 2018).

Research on placebo effects underscores the importance of expectations in the development and maintenance of pain (Peerdeman et al., 2016). Higher expectations about recovery have been associated with perceived changes to pain cognitions and self-management through education and with lower pain intensity compared to subjects that did not perceive any changes to pain cognition and self-management. These findings emphasise the significance of effective pain education centred on the reconceptualisation of pain and its management (Mittinty et al., 2018).

1.4 Neurobiology of pain

From an anatomical and physiological perspective, pain occurs in four basic pathways: transduction, transmission, modulation and perception (Osterweis et al., 1987; Yam et al., 2018). Initially, noxious stimuli are first transduced to signals through A delta and C fibres and the signals are projected to the Dorsal Root Ganglion (DRG). The sensory input is then transmitted to the Central Nervous System (CNS) (Bourne et al., 2014) through the spinothalamic tracts to the nucleus of the thalamus and subsequently to the brainstem reticular formation, hypothalamus and higher cortical centres, where pain perception takes place. Modulation of ascending pain occurs at the spinal cord level and descending pain modulatory pathways play a role inhibiting the communication between neurones of ascending pathways. Chronic pain conditions are associated to abnormal functioning of this neural system. As for instance, in the circumstances of persistent noxious stimulation, an upregulation of A delta and C fibres is observed, and this is responsible for central sensitization resulting in hyperalgesia (Bourne et al., 2014).

It is uncertain to what degree new pain-related learning can occur out of consciousness, but increasing evidence is aiming at disclosing this intricacy (Jensen et al., 2015). While conscious learning mechanisms have been generally researched by reinforcing

specific behaviours, in attempting to gain a deeper understanding of the transition from acute to chronic pain, unconscious learning mechanisms have been generally researched by employing physiological measures or techniques, such as neuroimaging methods. There is much neurobiological research that suggests brain changes play a role in persistent pain and represent biological mechanisms. This phenomenon can be considered a product of learning associated with neuroplastic change. For example, the amygdala (located in the limbic system) has been associated with the emotional-affective component of pain: its modulation and the cortico-limbic circuit is implicated in chronic pain syndromes such as CRPS and Chronic Pelvic Pain (Thompson and Neugebauer, 2017).

1.5 Current treatments for FM

Treatments for FM have evolved in line with advances in approaches to general chronic pain. Important events in the past century constituted a turning point and led to a paradigm shift from a medical to a biopsychosocial model of pain. For instance, Melzack and Wall (1965) offered a physiological explanation for the effects of psychology on pain perception, and Turk and Okifuji (1999) described individual and psychosocial differences among patients. From that point forward, a multifactorial and multidimensional frame in which physical and psychosocial elements interact in chronic pain has been progressively researched with more promising results (Moix, 2011; Van Houdenhove and Luyten, 2011).

1.5.1 Pharmacotherapeutic approaches

Pharmacotherapy for management in FM targets pain modulatory mechanisms. However, this remains a challenge for healthcare professionals. Although there is no approved specific-fibromyalgia pharmacological treatment, there are several medications that seem to show some efficacy. Overall, Serotonin-noradrenaline reuptake inhibitors, gabapentinoids, and tricyclic antidepressants have moderate efficacy in FM, and pure opioids have a minor role in FM pain management. New drugs targeting FM mechanisms are being sought (Northcott et al., 2017). However, it is generally agreed that the impact of these drugs on cognitive domains, although inconsistent, may lead to a reduction of attention, memory encoding and processing, psychomotor performance and reaction time (Cherrier et al., 2009; Hindmarch et al., 2005; Salinsky et al., 2010).

1.5.2 Non pharmacotherapeutic approaches

The key element of treatment for chronic pain conditions is non-pharmacological (education, therapeutic exercise and psychological interventions) (Northcott et al., 2017) and this is what is recommended for FM by the European League Against Rheumatism (EULAR) (McFarlanne et al., 2017).

1.5.2.1 Psychological interventions

Psychological therapies, albeit slowly, have continued to evolve in line with gradual advances in the specific mechanisms involved in pain. Although there is plenty of evidence in support of the involvement of psychological components in a holistic approach for pain disorders (Miró, 2010), there is incongruous evidence in relation to the effectiveness of psychological treatment. In agreement with evidence-based review regarding psychological interventions in chronic pain (APS, 2018), there is level II evidence for Cognitive Behavioural Therapy (CBT) (group-delivered), and for Acceptance and Commitment Therapy (ACT) (group-delivered and online delivery) for the treatment of pain conditions in adults. However, in this review (APS, 2018) there was scarce research and insufficient evidence to suggest the effectiveness of any other treatments.

CBT is the most common approach for FM (Heller et al., 2021) and for chronic pain in general (Pardos-Gaston et al., 2021). CBT for chronic pain is a psychotherapeutic approach aimed at diminishing pain perception. Generally, this includes both cognitive and behavioural techniques such as cognitive restructuring, behavioural activation, activity pacing, sleep hygiene and relaxation therapy. There is evidence for the efficacy of CBT in decreasing pain catastrophising in FM patients (Lazaridou et al., 2017). Prevention of the conversion from acute to chronic pain has also been associated with CBT (Khera & Rangasamy, 2021). A systematic review and meta-analysis regarding efficacy, acceptability and safety of cognitive behavioural therapies in FM (Bernardy et al., 2017) endorsed the tolerability and efficacy of these therapies in reducing symptoms and disability in FM when compared to waiting list, attention controls, treatment as usual, and active non-pharmacological therapies. This also concurs with other systematic reviews of CBTs in FM (Köllner et al., 2017). Other systematic reviews found that results of CBTs were equally effective in reducing pain and improving health-related quality of life compared to some antidepressants and convulsants (Nüesch et al., 2013).

ACT is based on the psychological flexibility model that is gradually growing in effectiveness for chronic pain (Yu & McCracken, 2016). Psychological flexibility refers to the subject's ability to be conscious and full contact with the present moment without the need to defend oneself and to remain or change one's behaviour in favour of one's goals (Yu & McCracken, 2016). This therapy integrates six core therapeutic processes: acceptance, cognitive defusion, self-as-context, committed action, values, and contact with the present moment (Feliu-Soler et al., 2018). The main objective of ACT in pain is to enable the subject with chronic pain to reestablish one's life based on established values despite the pain symptomatology. The therapy is oriented to better manage the subject's pain and, while it is not the main objective, the pain itself is reduced. Acceptance helps to embrace undesirable sensations (such as pain) to not fight against it, which leads to destructive experiential avoidance. Cognitive defusion contributes to difference between thoughts and experiences related to pain. Self-as-context relates to experiencing distinctively the observed pain-related feelings and thoughts, and the person who observes. Values, committed action, and present-focus provide a sense of goals in life and enable the subject to connect to herself/himself despite the presence of pain (Feliu-Soler et al., 2018).

Another approach that blends similar processes to ACT is mindfulness (McCracken and Vowles, 2014). A systematic review of mindfulness and acceptance-based interventions for FM patients found moderate effects of these interventions compared to control in depression, anxiety, mindfulness, sleep quality, health-related quality of life, and pain (Haugmark et al., 2019). Changes in impact of the disease in patients with FM mediated by psychological inflexibility and produced by Mindfulness-Based Stress Reduction (MBSR) were found when compared to an established multidisciplinary intervention for FM and to a control group (Pérez-Aranda et al., 2019b). Mechanisms of MBSR might be associated to reduced pain catastrophising, increased pain acceptance, self-efficacy and psychological flexibility (Pardos-Gascón et al., 2021; Pérez-Aranda et al., 2019b; Turner et al., 2016). Studies concerning neurobiological bases of cognitive variables have been useful in understanding its role in FM. The relationship between mindfulness and brain structures related to body awareness, perspective taking, emotion regulation, and attention management, has been recurrently studied (Feliu-Soler et al., 2020). Significant associations between bed nucleus of the stria terminalis clunes with depressive symptomatology, perceived stress, non-judging mindfulness facet and functional impairment have been observed (Feliu-Soler et al., 2020).

The psychodynamic approach for chronic pain assumes that pain experience is influenced by early events that configure one's sense of self and how we cope with stressors and threats such as chronic pain (Morgan, 2019). In this regard, from a psychodynamic perspective, the fact that subjects with negative interactions with significant others and poor social support tend to show unsatisfactory response to conventional treatments (Broderick et al., 2016; Turk et al., 1998) makes them unsuited to usual treatments (Turk, 2005). Thus, interventions that concretely aim at interpersonal issues might lead to improve pain outcomes (Morgan, 2019). Evidence-based results have shown the effectiveness of psychodynamic therapy in disabling pain syndromes such as irritable bowel syndrome (Hypanthis et al., 2009). Brief psychodynamic therapy also showed to be as equally effective as cognitive therapy in terms of distress, disease impact and health-related quality of life for FM patients (Romeo et al., 2019).

The fact that chronic pain patients seem to have high intrapersonal or emotional conflicts (Lumley & Schubiner, 2019) has led to the difficult challenge of addressing emotional factors to improve self-management of other variables. For example, opioid misuse has been associated with certain difficulties in emotional regulation (Lutz et al., 2018). There is a growing trend of therapies related to emotional management in chronic pain contexts. Emotional Awareness and Expression Therapy (EAET) which combines psycho-dynamic techniques, experiential techniques, prolonged exposure, written expression, and therapeutic rescripting, has shown significant improvements in pain-related symptomatology (Lumley et al., 2018). Likewise, Boersma et al. (2019) concluded that a hybrid emotion-focused treatment might be an acceptable and efficacious option for chronic pain individuals with comorbid emotional conflicts.

1.5.2.2 Pain Neuroscience Education

Along with with psychological interventions and therapeutic exercise, pain education is a key element of non-pharmacological treatment. Cognitive functions that enhance learning, determine an individual's efficiency to deal with different circumstances, such as pain conditions. Maladaptive beliefs regarding physical exercise are common among patients with chronic pain (Harding & Williams 1995) and these often lead to a sedentary lifestyle and detachment from physical therapy recommendations (Dysvik et al. 2004). Frequent barriers to physical therapy recommendations and recovery beyond maladaptive beliefs, are catastrophising, increased psychological inflexibility and consequently avoidance. This activates the vicious circle of fear-avoidance of physical activity and musculoskeletal pain

(Vlaeyen et al., 2016). In the same way that cognitive strategies and increasing psychological flexibility to promote positive behavioural changes (Curtin & Norris, 2017; McCracken & Keogh, 2009; Pérez-Aranda et al., 2019b) are key components in breaking this vicious circle by decreasing rumination, other approaches addressing cognitive and behavioural aspects can be reinforcing in breaking this vicious circle. As for instance, Pain Neuroscience Education (PNE) (Jay et al., 2018).

First pain biology explanations, as a therapeutic strategy, might seem to emerge after randomised controlled trials (RCTs) showed to be of clinical benefit approximately in the early 2000's (Moseley & Butler, 2017). However, over the decades there has been a transition from a classical biomedical education (i.e., aspects related to biomechanics and neurobiology) to PNE (i.e., aspects related to pain neurobiology and pain processing). PNE is focused on the reconceptualization of pain-related cognitive aspects (within a biopsychosocial model) that highlight the poor association of the patient's pain experience with any evidence of danger or safety (Moseley, 2015).

In terms of clinical outcomes, it seems that increased pain-related knowledge has been associated to increased self-management and positive health outcomes in FM patients (Camerini et al., 2013; Musekamp et al., 2019). In a recent systematic review and meta-analysis, it was found that adding PNE to a multimodal treatment including exercise might improve functional status, pain-related symptoms, depression and anxiety for FM patients (Saracoglu et al., 2022). Optimum duration and dosage of PNE sessions seem to be increasingly debated and researched. Higher dosages of PNE would appear to lead to greater improvements in pain severity (Amer-Cuenca et al., 2019).

Research indicates that manipulation of information and context regarding a stimulus could modulate pain (Robins et al., 2016). In other words, the effects of explaining pain mechanisms and therefore modifying patients' beliefs about the meaning of their noxious stimulus might have real effects on their pain experience (Moseley & Butler, 2015). The impact of age and cognitive capacity on PNE efficacy is still to be known but the importance of cognitive-developmental considerations when providing medical-related information in paediatric settings was acknowledged in a 2007 review (Robins et al., 2016).

PNE promotes cognitive and behavioural changes through learning updated information regarding the biology and mechanisms of pain which can lead to different ways of cognitive processing and

consequently to modify maladaptive and fearful responses to flexible and adaptive ones (Robins et al., 2016).

1.6 Effectiveness of non-pharmacological techniques

Understanding the effectiveness of different non-pharmacological strategies contributes to the understanding of the mechanisms that influence the development and maintenance of pain conditions. The gradual effectiveness and implementation of multidisciplinary treatments in both scientific and clinical settings is an important therapeutic advance. However, more studies regarding the effectiveness and contribution of each of the non-pharmacological approaches to concrete outcomes are needed. Likewise, more reviews that bring together all existing data to evaluate and compare their effects are essential.

Lami et al. (2013) conducted a review of psychological treatments that might lead to significant clinical benefits. The authors presented quantitative research of 58 scientific studies that provided psychological management of FM. The study's quality exploration of the 58 papers proved high score variability of internal and external validity among studies due to the inclusion of experimental, quasi-experimental and single-case design studies. In relation to the studied variables, it was identified that most studies focused on direct symptoms of the disease, such as fatigue and pain. Some studies also implemented interventions aimed at improving symptoms related to sleep disturbances and psychological variables, such as depression, anxiety, general psychopathology and impact of disease. In agreement with the authors, mediating variables were insufficiently evaluated in most studies, such as pain catastrophising, self-efficacy, pain anxiety and pain coping styles. Regarding types of intervention, CBT was pinpointed as the most implemented and studied treatment and was aimed at training individuals to manage pain.

This review is a major contribution to the knowledge of the current non-pharmacological therapies and variables evaluated for FM. However, the review did not present results on the effectiveness of treatments. Although the presentation of the current status of treatments is extremely important in the exercise of collecting information and diverse studies, results in terms of effectiveness are crucial. This work aims to update these data and furthermore to study the effectiveness of these therapies.

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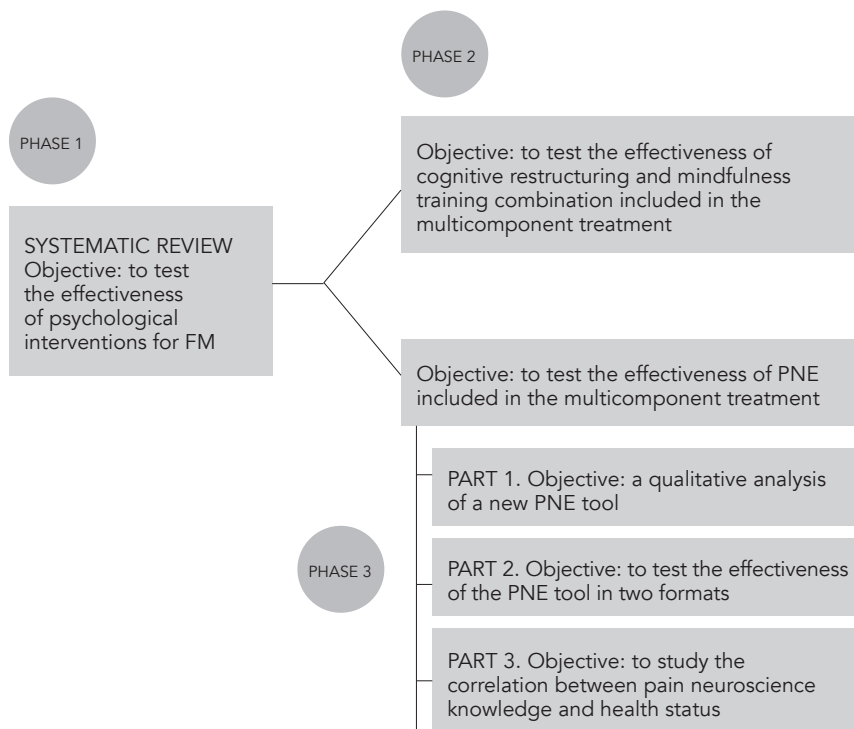
Thesis approach and objectives

2. THESIS APPROACH AND OBJECTIVES

2.1 Thesis approach

This thesis is divided into three phases that give rise to three studies.

Figure 1: The three phases of the thesis



The first phase is an updated systematic review of the previous review by Lami et al. (2013) that analyses the effectiveness of these interventions. This concludes that the study of multidisciplinary programs remains significant, that there is a continuing trend of CBT as a stand-alone treatment or as part of multidisciplinary programs, and reveals elements that could act as mediators, such as education.

The second phase is based on the findings presented in our review. CBT followed by mindfulness training seem to be the most common strategies included in multicomponent treatments for

FM, although their added value within these treatments has not been studied. Following this, the second phase presents a study aimed at evaluating the effectiveness of cognitive restructuring and mindfulness combination within a multidisciplinary programme.

The third phase is also based in the findings of our review. Education seems to be a transversal element across several treatments, although its effectiveness has not been studied in isolation. For this reason, this third phase is aimed at evaluating the effectiveness of PNE and its relationship to health status. For this purpose, this study has been divided into three parts: 1) a qualitative study of a new PNE tool, 2) a quantitative study to evaluate the effectiveness of the tool and 3) a correlation analysis between patients' pain neuroscience knowledge and their health status.

2.2 Objectives

2.2.1 Overall objectives

1. To study the effectiveness of current psychological interventions in FM **(Phase I)**
2. To study the effectiveness of cognitive restructuring and mindfulness training combination on FM patients' health status **(Phase II)**
3. To study the effectiveness of PNE on FM patients' health status **(Phase III)**

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**Phase I: Systematic
Review of Psychological
Interventions in
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3. PHASE I: SYSTEMATIC REVIEW OF PSYCHOLOGICAL INTERVENTIONS IN FIBROMYALGIA

3.1 Introduction

The present review attempts to carry out an update of psychological interventions in FM management, thereby making further progress in the comparison of treatment effectiveness. The last systematic review conducted by Lami et al. includes studies carried out until 2013, therefore, we aim to update this review. We intend to perform a systematic review from 2013 to 2019, trying to bring light to the following questions: 1) Which direction are psychological interventions taking in FM? and 2) What are the most effective interventions?

3.2 Method

The systematic review is an update of the previous review carried out by Lami et al. (2013) and was performed according to the PRISMA-statement (Preferred Reporting Items for Systematic reviews and Meta-Analyses) (Moher et al., 2009). Reproducing the review by Lami et al. (2013), the exhaustive bibliographic search through the Web of Science (complete database), was as follows: fibromyalgia (Title) AND intervention OR treatment OR therapy (Title). The search applied from January 2013 – the year after the review by Lami et al. (2013) - to December 2019.

The search identified 759 articles. After a complete review of all titles, 450 articles were excluded on presenting overall diagnoses including other syndromes or conditions besides FM. The 83 articles considered after this were fully analysed and some were excluded due to a lack of proper psychological intervention description. Consequently, 72 articles were finally included in the review.

3.3 Eligibility Criteria

The subsequent inclusion criteria were set to select the studies: (1) empirical articles (experimental, quasi-experimental, or single-case design studies) published in scientific journals; (2) written in English or Spanish; and (3) adult samples (18 years or over) with FM diagnosis according to the American College of Rheumatology (ACR) criteria (Wolfe et al., 2010).

3.4 Study Evaluation

Qualitative information was captured in a table to attain specific characteristics related to the treatment, to the studied outcomes and to methodology. Studies were examined and interpreted according to a quality evaluation tool developed by Berra and colleagues (2008) for critically appraising research articles or to evaluate evidence during the development of systematic reviews. This tool assesses by means of 27 items related to: study question or objective, participants, comparability between groups, definition and measure of main variables; analysis and confusion, results, conclusions, external validity and applicability, and conflict of interest.

3.5 Results

Overall, 98.6% of the studies showed effectiveness of the treatment studied in at least 1 dependent variable. CBT remains the most common treatment for fibromyalgia, both as a stand-alone treatment or included in a multicomponent program. Other interventions show promising results, such as ACT, mindfulness, relaxation and guided imagery approaches, and educational procedures.

Moreover, encouraging outcomes for specific variables have been found in new emerging approaches. For instance, EAET, Body Basic Awareness Therapy (BBAT), Group Music Imagery, Best Possible Self, Time In, Group Solving Therapy, Forgiveness Education and psychotherapy along with spiritual care. However, there is no evidence of superior techniques. All treatments seem to be beneficial when compared with control groups in at least one variable. Relaxation and education seem to be transversal elements across several treatments that might act as mediator variables.

Outcome measures among the studies are pain, pain-related variables, pain-related psychological variables, fatigue, quality of life, depression, anxiety, sleep variables, physiological variables and global score of some questionnaires. The questionnaires used to measure these outcomes are Visual Analogue Scale (VAS), Numeric Rating Scale (NRS), Brief Pain Inventory (BPI), Multidimensional Pain Inventory (MPI), McGill Pain Questionnaire (MPQ), Fibromyalgia Impact Questionnaire (FIQ), Widespread Pain Index (WPI), Multidimensional Fatigue Inventory (MFI), Brief Fatigue Inventory (BFI), Fatigue Severity Scale (FSS), Multidimensional Assessment of Fatigue (MAF), 36-Item Short Form Health Survey (SF-36), 12-Item Short Form Health Survey (SF-12), EuroQoL, COOP/WONCA Functional Assessment Charts, Hospital Anxiety and Depression Scale (HADS), State-Trait Anxiety Inventory

(STAI), Beck Depression Inventory (BDI), Psychological Inflexibility in Pain Scale (PIPS), Acceptance and Action Questionnaire (AAQ-II), Chronic Pain Coping Inventory (CPCI), Coping Strategies Questionnaire (CSQ), Pain Catastrophising Scale (PCS), Chronic Pain Self-efficacy Scale (CPSS), Pittsburgh Sleep Quality Index (PSQI), Medical Outcomes Study (MOS), Chronic Pain Sleep Inventory (CPSI), Stanford Sleep Questionnaire (SSQ), Epworth Sleepiness Scale (ESS), Prefrontal Symptoms Inventory (PSI), SCOPA, Patient Global Impression of Change (PGIC) and Perceived Stress Scale (PSS). The validation studies of all instruments are referenced in the papers included in the table.

Specific treatment modalities were analysed, such as smart-telephone intervention and internet-delivery. Telephone treatment was observed in 2.7% of the studies and 13.9% of interventions were performed and conducted online. The remaining studies (83.4%) carried out standard on-site treatments. Also, virtual reality was used as a treatment modality in 6 studies (8.3%), half of which were implemented using internet-delivery format and half via an on-site format. Finally, 6% of studies combined interventions using more than one format, such as group therapy and online techniques.

Treatment frequency varies among all selected studies, although most interventions implemented weekly sessions (52.2%). Mean treatment duration was 23 hours; however, these might be estimated data since some studies did not report this, and in another treatment time depended on the patients' availability. The number of sessions of most interventions varied between 9 and 20. Mean duration of each session was 1.8 hours, with sessions lasting from 1h to 3 hours.

Pain arises as the most evaluated outcome. Fatigue was a primary outcome in 14 studies (19.4%). Quality of life was often assessed as both primary and secondary outcome. Depression and anxiety are the two most evaluated psychological variables. Regarding pain-related psychological variables, catastrophising was assessed in 11 studies (15.27%), and coping skills and self-efficacy were assessed in 17 studies (23.6%). Sleep variables were particularly studied after specific cognitive-behavioural treatments aimed at treating pain-related insomnia in several studies. Some physiological variables included heart rate variability, pro-inflammatory cytokine levels and plasma SP level, each evaluated in one study. In addition to assessing specific variables, the global score of some questionnaires was used as primary outcome measurement. The most common tool is the FIQ, which evaluates the impact of the disease on several variables (physical capacity, work, fatigue and others) and was evaluated in 28 studies (38.8%). Furthermore, the PGIC and PSS were found in 4 studies (5.5%) each.

3.6 Discussion

This work allowed us to discover in detail the characteristics of the research aimed at verifying the effectiveness of different psychological techniques in patients with fibromyalgia carried out from 2013 to 2019 inclusive. These new data enable us to shed light on strengths and weaknesses regarding research methodology. This work also provides evidence in relation to applied techniques and how they are implemented. Finally, these results contribute to learning more about the effectiveness of the interventions. Likewise, when comparing our results with those of the last review, our results allow us to observe whether there has been any change in research topic trends.

In accordance with Merlo (2019), all this data represents a significant progress in the role of psychological approaches in the integration of clinical practice. However, it seems difficult to state that one intervention is more effective than others. In fact, among the studies included in this review, when comparing outcome differences between two different psychological interventions, most studies do not conclude the superiority of one over another (Chouchou et al., 2018; Kohl et al., 2014; Lumley et al., 2017; Miles, 2013; Moiola, 2017). It is also difficult to determine the effectiveness of each therapy due to the fact that the composition of each intervention presented in this systematic review does not seem to be totally independent from the others. For example, several times CBT studies included a variety of elements (mindfulness techniques, or life and values components, among others). Therefore, studying specific techniques rather than whole therapies could be more revealing.

When analysing the interventions from the present review, we found two transversal elements across several treatments: relaxation and education. This led us to think that, beyond the specific theoretical frame, there are two mediator variables: relaxation as a state, and patients' pain-related knowledge. In other words, relaxation and pain-related knowledge might induce cognitive and behavioural changes.

In terms of general patient education, 51.4% of the studies included some type of educational component. Some studies focused the research on specific educational barriers. These showed that cognitive aspects might lead to difficulties in understanding parts of the treatment and, consequently, might lead to impede improvements in health outcomes. For instance, Castel et al. (2013) implemented an adapted multidisciplinary programme for low educational levels and demonstrated a reduction in key FM symptoms. Pires et al. (2016) pointed out memory and concentration problems as possible

barriers for significant health changes in FM patients. In this last research, after implementing an adapted programme for patients with cognitive deficits, results proved the need for and success of an adjusted educational programme.

Other studies highlight the importance of pain-related educational aspects to achieve health improvements. These include not only educational components related to psychological processes (psychoeducation), but also education related to the syndrome's characteristics and physiology. Camerini et al. (2013) associated self-management and health outcomes with increased knowledge acquisition through a personalised, especially designed internet-based treatment. The authors found that increased knowledge about FM modified patients' amount of exercise; at the same time, it increased self-management and positively impacted patients' health status. Along the same lines, Butler & Moseley (2003) pointed out that learning about pain physiology reduces the threat value of pain, and consequently decreases the activation of protective systems thereby diminishing pain triggers. We believe that emphasising transversal factors might help us to unify different perspectives.

3.7 Conclusions

More studies regarding the effectiveness of psychological interventions are needed, both as stand-alone treatments and as part of multicomponent treatments. Further studies related to specific treatment techniques to evaluate specific variables are crucial. Finally, more studies in relation to transversal elements, such as education, are essential.

3.8 Scientific Production: Published Articles

3.8.1 Reference

Albajes, K., & Moix, J. (2021). Psychological interventions in fibromyalgia: an updated systematic review. *Mediterranean Journal of Clinical Psychology*, 9(1). <https://cab.unime.it/journals/index.php/MJCP/article/view/2759>

3.8.2 Data of the Journal

Mediterranean Journal of Clinical Psychology
Open Access Peer-Reviewed International Journal in Clinical Psychology
Impact factor: 0.393

3.8.3 Abstract

Background: There is a growing development of psychological approaches for fibromyalgia. The current scientific community advocates a biopsychosocial approach to pain management programme. Psychological interventions seem to contribute to an overall health improvement, although the reason for their success is still unclear. The aim of this review is to analyse which direction psychological interventions are taking in fibromyalgia and whether any intervention has proved to be more effective than others. **Method:** We conducted an updated search of a previous review, from 2013 to 2019 using web of science (all data base). Overall, according to the inclusion/exclusion criteria 72 original studies were identified. This review encompasses an exhaustive analysis of fundamental characteristics (participants' and interventions' characteristics, control group, target variables, quality of studies and outcome measures) and compares results with the intention of evaluating effectiveness of different interventions. **Results:** CBT remain as the most common treatment for fibromyalgia, both as a stand-alone treatment or as part of a multidisciplinary program. Other interventions show promising results, such as ACT, mindfulness, relaxation and guided imagery approaches, and educational procedures. In addition, encouraging outcomes for specific variables have been found in new emerging approaches. For instance, EEAE, Body Basic Awareness Therapy (BBAT), Group Music Imagery, Best Possible Self, Time In, Group Solving Therapy, Forgiveness Education and psychotherapy along with spiritual care. However, there is no evidence of superior techniques. All treatments seem to be beneficial when compared with control groups in at least one variable. Relaxation and education seem to be transversal elements across several treatments that might act as mediator variables. **Conclusions:** More studies regarding pain-related psychological variables and emphasising on transversal factors might contribute to unify different perspectives. **Key words:** Systematic Review; Psychological Intervention; Chronic pain; Literature Review; Clinical Psychology.

3.8.4 Access

The article can be accessed via the following link: <https://cab.unime.it/journals/index.php/MJCP/article/view/2759>

3.8.5 Article

A copy of the published article is attached as Appendix 1

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**Phase II: Cognitive
restructuring and
mindfulness training
combination effectiveness**

4. PHASE II: COGNITIVE RESTRUCTURING AND MINDFULNESS TRAINING COMBINATION EFFECTIVENESS

4.1 Introduction

FIBROWALK is an evidence-based multicomponent treatment that integrates Treatment-as-usual (TAU), Therapeutic Exercise (TE), self-management patient education, cognitive restructuring, mindfulness training and PNE. Even though there is plenty of evidence of the effectiveness of this program for FM, there is no evidence of the contribution of specific psychological components in FIBROWALK. Therefore, the aim of this study is to test the effectiveness of the sum of two of its components (cognitive restructuring and mindfulness training).

4.2 Methods

The primary aim of this Randomised Control Trial (RCT) was to evaluate the effectiveness of two video-based multidisciplinary treatment programs for FM (one with all components aforementioned [FIBROWALK], and another one with all components but cognitive restructuring and mindfulness [Multicomponent Physiotherapy Program: MPP]), and to compare them to TAU only. Treatment effectiveness of the two programs was determined by improvements in functional impairment (primary outcome), pain, anxious-depressive symptoms, kinesiophobia, and physical function.

A three-arm RCT was carried out, with assessments at pre- and post treatment. The required sample size was estimated to be n= 51 participants per study arm. A total of 337 patients with FM participated in the study from June 2020 to January 2021. All participants were consecutively recruited from the Vall d'Hebron University Hospital – Central Sensitivity Syndromes Specialised Unit (CSSSU) and were assessed by a rheumatologist and a physical therapist to ensure they met the selection criteria. The inclusion criteria were as follows: (a) fulfilment the FM classification criteria according to 2010/2011 American College of Rheumatology (ACR; Wolfe et al., 2010), (b) 18 years of age or older, and (c) written informed consent. Individuals suffering from terminal illnesses (e.g., advanced cancer) or those reporting programmed interventions

which could interrupt the participation in the study (e.g. major surgery) were excluded.

Participants who voluntarily agreed to participate in the study were assigned to TAU + video-based FIBROWALK, to TAU + video-based MPP or to only TAU. Both FIBROWALK and MPP were delivered as add-ons to TAU. The FIBROWALK program consisted of weekly 60-minute videos that were presented over the course of 12 weeks. Subjects participated in the virtual training from home. Each video was comprised of different components of the program. The FIBROWALK intervention included PNE, therapeutic physical exercise, Self-management Patient Education (SPE), cognitive restructuring, and mindfulness training. MPP included all components except cognitive restructuring and mindfulness training.

4.3 Outcome measures

The Fibromyalgia Impact Questionnaire Revised (FIQR; Bennett et al., 2009) was used to assess the functional impairment experienced by participants during the previous week. The Visual Analog Scale (VAS) for pain (i.e., intensity of perceived pain during last week, from 0 = “no pain”, to 10 = “unbearable pain”) from the FIQR was used to assess pain intensity (Bennett et al., 2009). The Tampa Scale for Kinesiophobia (TSK; Miller et al., 1991) was used to assess fear of movement. The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). The Physical Function subscale from the 36-Item Short Form Survey (SF-36; Ware & Sherbourne, 1992) assessed perceived level of physical functioning.

4.4 Results

4.4.1 Primary outcome

A total of 387 patients with FM were assessed for eligibility. Fifty-seven did not meet the eligibility criteria, and therefore, a total of 330 patients were finally included and randomised [TAU (n = 110), TAU+FIBROWALK (n = 110) and TAU+MPP (n = 110)]. The participants' mean age was approximately 53 years old (SD = 9.11; range: 20–77). There were no statistically significant differences between treatment arms in demographic or baseline clinical characteristics.

4.4.2 Secondary outcome

Patients allocated to FIBROWALK showed greater reductions in perceived pain intensity, kinesiophobia, anxiety and depressive symptoms and increased physical functioning compared to the TAU

only group (all $p < .001$), with medium-to-large effect sizes ($d = 0.51$ – 1.48). Similarly, significant treatment effects ($p < .05$) in favor of the MPP arm were found when compared to TAU in perceived pain intensity ($d = .39$), kinesiophobia ($d = 1.13$), and depressive symptoms ($d = 0.37$) (all $p < .05$). No differences between MPP and TAU were found in the other outcomes. When comparing FIBROWALK and MPP arms, statistically significant effects in favor of the former were found in pain intensity, depression, and physical functioning (all $p < .05$), with small-to-medium effect sizes ($d = 0.24$ – 0.49).

4.4.3 Baseline differences between “Responders” and “Non-Responders” to treatment and Number Needed to Treat (NNT)

In the FIBROWALK arm, individuals classified as responders indicated less anxiety ($p = .02$), depressive symptoms ($p = .02$) and better physical functioning ($p = .03$) prior to treatment compared to non-responders. MPP responders were older ($p = .05$), men (100% men vs. 94% of women; $p = .05$), reported less pain ($p < .001$), had less functional impairment ($p = .03$), and better physical functioning ($p = .01$) than “non-responders”. Forty-two subjects (42%) in the FIBROWALK arm and 33 subjects in the MPP arm (34%) showed a clinically significant improvement in their FIQR total score at post-treatment (i.e., $\geq 20\%$) so were considered responders, whereas only four subjects (4%) from the TAU only arm achieved the status of responder. The absolute risk reduction in the FIBROWALK arm in comparison with TAU only was 38% (95% CI = 27.59–48.41%), with an NNT = 3 (95% CI = 2.1 to 3.6). The absolute risk reduction obtained in the MPP versus TAU only was 29.67% (95% CI = 19.56–39.79%), with an NNT = 4. The absolute risk reduction obtained in the FIBROWALK versus the MPP arm was 8.33% (95% CI = - 5.13 to 21.78%) with an NNT = 13. As in this latter case, the 95%CI for the absolute risk reduction extended from a negative number (FIBROWALK may not benefit) to a positive number (FIBROWALK may benefit), the NNT result had no interpretable meaning.

4.5 Discussion

Both the video-based FIBROWALK and MPP multicomponent treatments, when compared to TAU only, were found to be efficacious with small-to-large clinical effects. The superiority of these two programs over TAU only was corroborated by the low Number Needed to Treat (NNT) values. Compared to TAU only,

individuals in the FIBROWALK arm showed larger improvements in all clinical outcomes; participants in the MPP program showed greater improvements in functional impairment, perceived pain and kinesiophobia compared to TAU only. Therefore, FIBROWALK intervention showed superior effects in improving pain, anxious-depressive symptoms and physical functioning compared to MPP. These findings suggest a broader and stronger therapeutic effect by combining psychological ingredients with physiotherapy interventions based on PNE and therapeutic exercise.

These findings provide also additional evidence of the effectiveness of video-based FIBROWALK, which was initially obtained in a pilot study during the first lockdown due to COVID-19 pandemic in Spain (Serrat et al., 2021b) and confirmed existing evidence of the efficacy of PNE combined with TE in people with FM (Barrenengoa-Cuadra et al., 2021; Ceballos-Laita et al., 2021; Louw et al., 2016b).

4.6 Conclusions

This RCT supports the short-term effectiveness of the video-based multicomponent programs FIBROWALK and MPP for FM and provides evidence that cognitive restructuring and mindfulness-based techniques can be key ingredients in the management of FM.

4.7 Scientific Production: Published Articles

4.7.1 Reference:

Serrat M, Albajes K, Navarrete J, Almirall M, Lluch Girbés E, Neblett R, Luciano JV, Moix J, Feliu-Soler A. Effectiveness of two video-based multicomponent treatments for fibromyalgia: The added value of cognitive restructuring and mindfulness in a three-arm randomised controlled trial. *Behav Res Ther.* 2022 Nov;158:104188. doi: 10.1016/j.brat.2022.104188. Epub 2022 Sep 8. PMID: 36116229. *Maybe Serrat and Klara Albajes contributed equally to this article and should be considered co-first authors.*
Albert Feliu and Jenny Moix share senior authorship

4.7.2 Data of the Journal

Behaviour Research and Therapy
Impact Factor 5.321

4.7.3 Abstract

Background/Objectives. The aim of this study was to examine the effectiveness of two video-based multidisciplinary programs

(FIBROWALK) and the multidisciplinary Physiotherapy Program (MPP) for patients with fibromyalgia (FM) compared to treatment-as-usual (TAU) only. We posit that FIBROWALK, due to inclusion of specific psychological ingredients (cognitive restructuring and mindfulness), can help patients with FM to experience more ubiquitous clinical improvement than TAU or MPP alone. **Methods.** A total of 330 patients with FM were recruited and randomly allocated (1:1:1) to TAU only, TAU+FIBROWALK, or TAU+MPP. FIBROWALK and MPP consisted of weekly videos on pain neuroscience education, therapeutic exercise and self-management patient education, but only the FIBROWALK intervention provided cognitive restructuring and mindfulness. Both programs were structurally equivalent. Between-group differences in functional impairment, pain, kinesiophobia, anxious-depressive symptoms and physical functioning were evaluated at post-treatment following Intention-To-Treat and complete-case approaches. **Results.** Compared to TAU only, individuals in the FIBROWALK arm showed greater improvements in all clinical outcomes; similarly, participants in the MPP program also showed greater improvements in functional impairment, perceived pain and kinesiophobia compared to TAU only. The FIBROWALK intervention showed superior effects in improving pain, anxious-depressive symptoms and physical functioning compared to MPP. **Conclusions.** This RCT supports the short-term effectiveness of the video-based multidisciplinary programs FIBROWALK and MPP for FM and provides evidence that cognitive-behavioural and mindfulness-based techniques can be key ingredients in multidisciplinary treatment programs. Trial registration number: NCT04571528 **Keywords:** Fibromyalgia; Virtual multidisciplinary treatment; Pain Neuroscience Education; Therapeutic Exercise; Cognitive Behaviour Therapy; Mindfulness.

4.7.4 Access

The article can be accessed via the following link:

<https://www.sciencedirect.com/science/article/pii/S0005796722001590>

4.7.5 Article

A copy of the published article is attached as Appendix 2

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Phase III: PNE Effectiveness

5. PHASE III: PNE EFFECTIVENESS

5.1 Introduction

Pain neuroscience knowledge refers to the understanding of the biological and processing mechanisms involved in the phenomenon of pain. Helping patients to comprehend what is happening in their own body provides a base for enhanced self-informed intervention choices, self-management and self-monitoring (Moseley & Butler, 2015). Pain Neuroscience Education (PNE) is an effective educational strategy as a complement of an all-inclusive multidisciplinary programme compatible with a biopsychosocial model (Louw et al. 2016a). This strategy incorporates the multidimensionality of pain experience and aids individuals reconceptualise pain by understanding the multiple neurophysiological, neurobiological, physical and sociological components that might underpin individual pain experience (Moseley 2007; Moseley & Butler 2015). The use of PNE has been associated to reductions in pain, improved function, decreased fear of movement, and less catastrophising (Meeus et al. 2010; Moseley 2002, 2003a; Téllez-García et al. 2014; Van Oosterwijck et al. 2013; Vibe Fersum et al. 2013). Pain education is currently an essential element in any treatment for fibromyalgia (Cunningham & Kashikar-Zuck, 2013). In the same way, developing and translating materials, and assessing their usefulness in specific conditions is essential before evaluating their effect on health status. For this reason, this study aims to evaluate the usefulness of 9 fact sheets on the neuroscience of pain translated to Spanish, and then to analyse its correlation with health status.

5.2 Methods

This phase is divided into three parts: 1) qualitative analysis of a new pain neuroscience tool (9 sheets); 2) quantitative study to evaluate the effectiveness of this tool in two formats, written and video-based; and 3) correlation analysis between patients' pain neuroscience knowledge and their health status.

5.2.1 Part I: Qualitative analysis of a new pain neuroscience tool

The aim of this part was to analyse the quality of a new pain neuroscience tool based on feedback regarding the structure and content of each fact sheet, and on assessing whether the subjects acquire pain neuroscience knowledge. **Design.** Ten participants were recruited for this qualitative analysis. The educational procedure comprised 11 individual and online live sessions. The first and last sessions were introductory and closure

sessions explaining and concluding the purpose of the research. The remaining 9 sessions were focused on each of the 9 fact sheets. The ten subjects responded to the semi-structured interview about the fact sheets and responded to the Spanish version of the Knowledge and Attitudes of Pain questionnaire (S-KNAP). **Results.** The qualitative analysis is divided into four categories to record participants' feedback: 1) format and presentation; 2) perception of personal contribution; 3) perception of learning; 4) content-related questions. According to this classification, the results follow in the same order: 1) all participants found the sheets configuration very useful and engaging; 2) a personal contribution of the content was perceived and they reported feeling related to all concepts; 3) a change of pain-related beliefs was observed in six participants from the beginning, while the remaining four participants denied having learned anything at the beginning but changed their position after the third session; 4) participants scored 23 out of 26 (4 participants), 20 out of 26 (3 participants), and 12 out of 26 (2 participants). When comparing perception of learning to actual learning, an equivalence between perceived change of beliefs and their scores in the S-KNAP was found. Participants that expressed having learned or changed specific contents scored higher in the S-KNAP at the final session. **Conclusions.** The present qualitative results suggest a progressive (perceptual and actual) meaningful learning, along with a change of beliefs in pain-related concepts.

5.2.2 Part 2: Quantitative study to evaluate the effectiveness of this tool in two formats written and video-based

The aim of this part was to evaluate the effectiveness of this PNE tool in two formats, written and video-based after. **Design.** A total of 337 participants were included. The study was conducted using a three-arm controlled design: one control group (who received no PNE tool) and two active groups that were provided with the fact sheets in two different formats (written and video-based). Both active groups were assessed on pain neuroscience knowledge after having had access to the fact sheets. A comparative study of the three groups was conducted using ANOVA. **Results.** Significant differences in pain neuroscience knowledge of both PNE groups were found compared to the control group. When comparing both PNE groups, no significant differences were found. **Conclusions.** The results of the study are significantly robust: the fact sheets have proven to be effective in providing adequate knowledge in both written and video-based formats.

5.2.3 Part 3: Correlation analysis between patients' pain neuroscience knowledge and their health status.

This work aims at analysing the correlation between participants' pain neuroscience knowledge and health status at the end of a multicomponent treatment. **Design.** The same 337 participants recruited in Part I were included in this Part. All participants completed at the end of the multicomponent treatment a battery of questionnaires aimed at measuring patients' pain neuroscience knowledge and patients' health status (functional impairment, physical functioning, anxiety, depression symptoms and kinesiophobia). The Pearson correlation coefficient was used to measure the linear correlation between patients' pain neuroscience knowledge and patients' health status. **Results.** There was a significant correlation between pain neuroscience knowledge and all health outcomes: functional impairment, physical functioning, anxiety, depression symptoms and kinesiophobia. **Conclusions.** The results of the study are significantly robust: there is a correlation between pain neuroscience knowledge and all the study outcomes at the end of the treatment.

5.3 Discussion

The three parts of this study contribute to evaluate the effectiveness of the PNE. First the effectiveness of a new PNE tool (the 9 fact sheets) is proved, and then the effectiveness of the PNE is demonstrated by its significant correlation to health status: participants who know more about pain are those with better health status. The proven effectiveness of this tool in two formats opens many options for implementing PNE in the clinical field. The written format can be a suitable tool for specific circumstances where the accessibility to information is difficult, such as in situations where access to technology or the Internet is not possible. The video-based format can be a helpful tool for virtual and/or face-to-face programs, or in general as a support tool for clinicians. The validation of the fact sheets in terms of usefulness also contributes to the scientific field. Having an effective pain neuroscience education tool opens the possibility for studies in relation to clinical knowledge and clinical improvement. Studying and analysing PNE tools using quantitative and qualitative research contribute to standardising high quality PNE tools, and this study provides the Spanish validation of a new PNE tool in two different formats for clinicians and researchers working with FM subjects.

5.4 Conclusions

This study validates a highly valuable tool of PNE and confirms the importance of pain neuroscience knowledge in the health status of fibromyalgia patients.

5.5 Scientific Production

The manuscript is under review

5.5.1 Abstract

Background/Objectives. Pain Neuroscience Education is an effective educational strategy that incorporates the multidimensionality of pain experience and aids individuals to reconceptualise pain by understanding the biological and processing mechanisms involved in the phenomenon of pain. The use of PNE has been associated to reductions in pain, improved function, decreased fear of movement, and less catastrophising, and is currently an essential element in any treatment for fibromyalgia. This study aims to evaluate the usefulness of 9 fact sheets on the neuroscience of pain translated to Spanish and to analyse the correlation of 337 subjects' pain-related knowledge and health status. **Methods.** This study encompasses both quantitative and qualitative research carried out in three parts. The first part aims at analysing the quality of the fact sheets based on collected qualitative feedback; the second part aims at evaluating the effectiveness of a new pain neuroscience tool in two formats, written and video-based; and the third part aims at analysing the correlation between participants' pain neuroscience knowledge and health status. **Results.** The qualitative results of the fact sheets suggest a progressive (perceptual and actual) meaningful learning, along with a change of beliefs in pain-related concepts. The fact sheets have also proven to be effective in providing adequate knowledge in both written and video-based formats. Finally, there is a correlation between pain neuroscience knowledge and all the study outcomes (functional impairment, physical functioning, anxiety, depression symptoms and kinesiophobia). **Conclusions.** This study validates a very valuable tool of PNE and confirms the importance of pain neuroscience knowledge in the health status of fibromyalgia patients. **Keywords.** Pain Neuroscience Education, PNE, Fibromyalgia, Qualitative Research.

5.5.2 Article

A copy of the manuscript is attached attached as Appendix 3.

ABSTRACT

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General Discussion

6. GENERAL DISCUSSION

This thesis aimed at studying effective interventions for FM. For this purpose, firstly, a review was carried out regarding all current studies related to psychological interventions conducted for FM. Once the systematic review was conducted, the aim was focused on the effectiveness demonstrated among two specific psychological techniques and the third technique of pain-related knowledge.

For this purpose, three different phases for the different objectives were developed. The first phase presented the systematic review and conclusive results were identified. All psychological interventions demonstrated effectiveness on at least one variable. Pain-related education or psychoeducation was part of several interventions. Finally, multidisciplinary treatments remain increasingly studied and recommended but the added value of their individual components within the treatment has not been studied.

The second phase sought to study the effectiveness of two psychological techniques combined included in FIBROWALK (a well-established multidisciplinary program for FM) (Serrat et al., 2020a; Serrat et al., 2020b; Serrat et al., 2021a; Serrat et al., 2021b). The study concluded with prominent results: superior health outcomes (functional impairment, pain, kinesiophobia, anxious depressive symptoms and physical functioning) were found in the multidisciplinary program with both cognitive restructuring and mindfulness training.

In the third phase, the effect of another element included in the multi-component treatment, PNE, was studied by assessing the effectiveness of a new tool in two formats (written and video-based), by gathering qualitative feedback on this tool and by analysing its correlation with health status (functional impairment, physical functioning, anxiety, depression symptoms and kinesiophobia). Both written and video-based formats were equally effective when compared to a control group. The feedback collected suggested effectiveness in terms of quality, understanding and both perceived and actual learning. Finally, a significant correlation was found between pain neuroscience knowledge and all health outcomes (functional impairment, physical functioning, anxiety, depression symptoms and kinesiophobia) at the end of a multicomponent treatment.

A major contribution of the two multidisciplinary components was demonstrated. These results have important implications as there are few studies that separately assess the contribution of multidisciplinary treatment components. In addition to

demonstrating the contribution of each of these elements, these results also show a stronger and broader therapeutic effect from the combination of psychological therapy, therapeutic exercise and PNE than from therapeutic exercise and PNE alone (Wilson & Cramp, 2018). This is consistent with the concept “synergistic effect” described by Heller et al., (2021) in which all components of a multidisciplinary treatment combined might have greater effect than the sum of each of them separately. A similar concept is that of Fordyce (1973) of symbiotic interaction from the contribution of several disciplines.

6.1 Cognitive restructuring and mindfulness training

The effectiveness shown in the results is compatible with previous results regarding CBT and mindfulness treatments alone (Haugmark et al., 2019) but also adds the additional value of these techniques in a multidisciplinary therapy. In addition, the superior results in physical function of the treatment with the psychological component, agree with previous research concluding that CBT, when used not only for mood disorders but also for chronic conditions, is related to improvements in overall physical function (Bennett & Nelson, 2006; Williams et al., 2002). When considering specific cognitive restructuring for pain, the demonstrated effectiveness is also consistent with other studies of cognitive restructuring for pain improvements (de la Vega, 2019, Jan et al., 2022). Studies related to mindfulness training techniques in pain also seem to be in line with these results (Lauche et al., 2013). Finally, all the above-mentioned results are in line with the importance attributed to psychological factors in the processing mechanisms of pain (Bennett & Nelson, 2006; Kundakci et al., 2021; Williams et al., 2002).

It is worth noting that cognitive behavioural therapy is the first-line therapy of choice and mindfulness training is gaining popularity in chronic pain; however there are many other therapies with increasing and promising results that similarly address cognitive aspects (Albajes & Moix, 2021).

6.2 Pain Neuroscience Education

In relation to pain neuroscience education, a correlation between pain knowledge and health status was found after completing the multidisciplinary program. One important cognitive area in pain is the meaning (what the person assumes pain means). This study demonstrated that participants’ meaning of pain is related to their

state of health. The fact that knowledge correlates with health status and clinical improvement, is very important as it highlights the importance of the educational component in FM treatments and highlights the implication it may have on cognitive and behavioural consequences, thus complementing both psychological therapy and therapeutic exercise. Therefore, it also indicates the importance of developing more educational tools and knowledge assessment tools in order to investigate this relationship and confirm adequate knowledge.

6.3 Cognitive changes as mediating variables

Following the systematic review, the thesis sought to study the effectiveness of two components of a multicomponent treatment: cognitive restructuring and mindfulness training combined, and PNE. Cognitive restructuring, one main element in CBT, involves recognition, defiance and reformulation of maladaptive cognitions to develop alternative, balanced and adaptive thoughts (Roditi & Robinson, 2011). Mindfulness training intends to nonjudgmentally accept thoughts as they are. PNE is a strategy that teaches patients to rethink the way they view pain. These three techniques are focused on cognitive factors that play a role in pain.

Cognition, defined as the brain's ability to obtain, process, save, and recover information (Khera & Rangasamy, 2021), is a core element in pain processing (Craig & MacKenzie, 2021). There is mounting evidence corroborating the prominence of cognitive mechanisms in controlling painful experiences. Differences in disability and emotional distress, qualitative variations in the origin of the experience, greater reliance on medication, and greater pain, have been observed when pain is perceived as remarkably threatening or beyond the person's capacity to cope (Craig & MacKenzie, 2021). Modulation of cognitive domains affecting pain perception occur after neuroplastic adaptations of the brain to chronic pain (Khera & Rangasamy, 2021).

Modalities of therapies that reinforce the role of cognition and cortical perception in the pathophysiology of pain have shown positive effects (Kikkert et al., 2019). For instance, focusing on cognitive processing, such as strategies that target catastrophising patterns, reduces pain (Darnall et al., 2020; Federeoff et al., 2014; Sullivan et al., 2012). The results of this study are in accordance with other studies related to cognitive strategies for health improvements (Cosio, 2020). For example, mindfulness training has been shown to improve cognitive performance (Sevinc et al., 2021) and the interest

in the effects on several cognitive function is growing (Whitfield et al., 2021). Finally, cognitive changes such as catastrophising and self-efficacy have also been associated with pain education (Burns et al., 2020).

6.4 Future implications

6.4.1 Research Implications of other mediator variables : Emotional and Social factors

Since there is a multidirectional relationship among behavioural, cognitive, emotional and social elements in pain, considering all elements in the management of pain is of paramount importance. Therapeutic exercise seems to successfully address behavioural elements (and consequently other factors) in chronic diseases in general (Geidl et al., 2014), and the present work describes the implication of cognitive factors based on psychological approaches and PNE within a multidisciplinary approach to pain management. However, several psychological factors are not yet sufficiently studied and have a significant implication in chronic pain, such as social factors and emotions.

Emotional factors such as pain-related fear, pain anxiety, high arousal of negative emotions, social rejection and attachment insecurity occur not only in response to pain but also trigger, maintain or exacerbate pain (Caes et al., 2017; Clauw & Chrousos, 1997; Edwards et al., 2016; Vachon-Pressseau et al., 2016). A vast amount of neuroscience research states a strong link between pain pathways in the CNS and emotions that are sensitised both by early traumatic experiences and pain (Goldenberg, 2010). Following this, according to psychological research, it seems that emotional awareness, expression and experiencing play a significant role in pain experience (Lumley et al., 2011). The presence of adverse, traumatic or emotionally conflicting psychosocial experiences is high among FM patients (Lumley et al., 2017). In past FIBROWALK programs (the program used for these two studies), a significant higher baseline score of the depression scale was found among participants that did not respond to the treatment (Serrat et al., 2021a). To address depression levels, therapy for this symptomatology could be done before starting treatment and it might enhance treatment outcomes. In addition, considering the co-morbid relationship between depression and pain, a more individualised and emotion-orientated treatment adjusted to the patient's circumstances could be a beneficial supplement. Integrating emotional components into cognitive-behavioural models of persistent pain has been increasingly suggested (Lumley et al., 2011). Social research shows the potential

significance of emotional communication, attachment, empathy, and rejection. A therapy addressed at gaining emotion awareness and expression developed for chronic pain conditions (Emotional Awareness and Expression Therapy), showed superior results to a basic educational intervention and some advantages over CBT on FM patients (Lumley et al., 2017). An additional Emotional Awareness and Expression Therapy for patients presenting high scores on emotional conflicts could help to enhance final outcomes of a multidisciplinary program (Ziadni et al., 2020).

When looking at social factors, these are not frequently considered even though the biopsychosocial model for chronic pain is increasingly highlighted. Social factors can elicit pain in the absence of nociceptive stimuli and therefore are sufficient to cause pain (Ashton-James, 2019). Therefore, the sociocultural environment does not merely influence or modulate pain but helps to construct and to constitute pain. Pain equals a combination of: 1) evaluation of sensations as unpleasant; 2) feelings of distress and 3) the construal of actual or potential of harm. In this regard, evaluation is shaped by context, feelings are shaped by the context, and the construal is fundamentally socially grounded. The context translates to our own context but also the situation we are in. It is something that we learn from experience, and it is also what we construct and interpret by looking at our social world (Ashton-James, 2019). Since pain-related beliefs and behaviours are significantly linked to the patient's social environment, further studies evaluating these variables would contribute to future therapeutic and preventive strategies to reduce chronic pain statistics.

6.4.2 Clinical Implications: The Psychologists in Multidisciplinary Departments

The high impact of healthcare professionals on patients' pain (Mistiaen et al., 2016) and the existing involvement of psychosocial factors in pain should lead to a debate on the role of psychologists in the field of pain. Multidisciplinary treatments are increasingly more common and non-pharmacological are progressively recommended. Several barriers have been identified that can interfere in multidisciplinary treatments, for instance, health professionals that are often reluctant to work as a team (Nicholas, 2004). A well-functioning interdisciplinary program involves a team of health professionals from different disciplines working within a biopsychosocial framework and therefore collaborating in assessment and treatment toward a set of shared goals (Association for the Study of Pain, 2022; Stanos & Houle, 2006). Psychologists are slowly being included in pain

departments or clinics. However, their role is often minor and their functions are sometimes replaced by other functions. The importance of the psychological factors that are being given to pain management should grow in parallel with the participation of psychologists in multidisciplinary treatments.

6.5 Future research

Future studies should focus on the aforementioned limitations. In addition, further studies should be carried out with the following characteristics in mind: 1) More studies on the effectiveness of the components of multidisciplinary programmes are needed to understand their contribution to building increasingly standardised programmes with greater effectiveness; 2) More studies in relation to techniques rather than therapies can help us to understand more precisely the therapeutic mechanisms, and to further delineate the causes of effective outcomes. In addition, not only the therapeutic techniques but also the desired outcomes need to be more precise. As indicated by Duruk et al. (2022), more studies of non-pharmacological treatments for fibromyalgia should be conducted on an individualised basis and according to the predominant symptom. Furthermore, in agreement with Kohl et al., (2013) it is important to assess the antecedent characteristics on which different techniques are most effective.

6.6 Research proposals

This thesis has been prepared in collaboration with two departments (Body in Mind, University of South Australia, and Department of Psychology, Wayne State University, USA) that have contributed greatly to the understanding of the complexity of pain management. From these two collaborations we understand the importance of continuing to add effort and knowledge to increase the effectiveness of treatments for fibromyalgia. Thus, we present below two proposals to continue the work initiated in this thesis.

In the first place we propose a study directed to the emotional and social factors in an individualised way in specific cases of high levels of depressive symptomatology or in which the presence of adverse, traumatic or emotionally conflicting experiences is detected and that can interfere in some way in the treatment. Thus, a study is proposed based on a first assessment related to this symptomatology, and a subsequent brief EAET intervention developed by Mark Lumley

and his team at Wayne State University. The aim of this study would be to increase the number of participants with effective results.

Secondly, we propose a study to validate the S-KNAP questionnaire to measure pain neuroscience knowledge. The questionnaire has been developed by Anneke Beetsma from Hanze University. The aim of this study would be to have a questionnaire available for further studies in relation to knowledge in pain neuroscience.

6.7 Limitations

The limitations of this thesis are mostly those presented in each of the studies. First, many of the studies presented in the review do not adequately describe the therapy, making it difficult to make a complete analysis. In these terms, for example, it was difficult to consider elements such as pain education, as it is an element that has sometimes been either overlooked or included without having been mentioned. Secondly, the studies were conducted in daily clinical practice in a specialised tertiary care hospital so strict eligibility criteria could not be applied. In addition, long-term studies could not be carried out either. Thirdly, an assessment of participants' knowledge of pain neuroscience prior to the program was not carried out, so that the increase in knowledge could not be correlated with clinical improvement, and consequently only knowledge and health status at a specific point in time were assessed.

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7. GENERAL CONCLUSIONS

Several conclusions can be drawn from this thesis:

1

There are numerous psychological interventions that show effective results for FM in at least one variable.

2

Multicomponent treatments have a strong presence and are increasingly recommended.

3

Cognitive restructuring and mindfulness combination are effective in improving the impact of the disease, anxiety, depression, physical functioning and kinesiophobia compared to a control group.

4

Patients' feedback of the fact sheets is overall positive and these are effective in two formats (written and video-based).

5

A significant correlation between patients' pain neuroscience knowledge and health outcomes has been demonstrated, therefore those patients who demonstrate to have more pain neuroscience knowledge correlate with those who have better health outcomes.

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ABSTRACT

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APPENDIX 1:
Systematic Review of psychological Interventions
in Fibromyalgia

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Clinical Psychology

Psychological Interventions in Fibromyalgia: An Updated Systematic Review

Klara Albajes¹, Jenny Moix¹*

Abstract

Background: There is a growing development of psychological approaches for fibromyalgia. Current scientific community advocates a biopsychosocial approach to pain management programme. Psychological interventions seem to contribute to an overall health improvement; however, the reason of their success is still unclear. The aim of this review is to analyze which direction psychological interventions are taking in fibromyalgia and whether there is any intervention proved to be more effective than others.

Method: We conducted an updated search of a previous review, from 2013 to 2019 using web of science (all data base). Overall, according to the inclusion/exclusion criteria 72 original studies were identified. This review encompasses an exhaustive analysis of fundamental characteristics (participants' and interventions' characteristics, control group, target variables, quality of studies and outcome measures) and compares results with the intention of evaluating effectiveness of different interventions.

Results: CBT remain as the most common treatment for fibromyalgia, both as a stand-alone treatment or included in a multicomponent program. Other interventions show promising results, such as ACT, mindfulness, relaxation and guided imagery approaches, and educational procedures. Also, encouraging outcomes for specific variables have been found in new emerging approaches. For instance, Emotional Expression Acknowledgment and Exposure (EEAE), Body Basic Awareness Therapy (BBAT), Group Music Imagery, Best Possible Self, Time In, Group Solving Therapy, Forgiveness Education and psychotherapy along with spiritual care. However, there is no evidence of superior techniques. All treatments seem to be beneficial when compared with control groups in at least one variable. Relaxation and education seem to be transversal elements across several treatments that might act as mediator variables.

Conclusions: More studies regarding pain-related psychological variables and emphasising on transversal factors might contribute to unify different perspectives.

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1. Introduction

Fibromyalgia (FM) is a chronic and complex nondegenerative syndrome associated with three main characteristics: pain, fatigue and sleep disorders (Bellato et al., 2012). Patients affected by FM can present a wide range of other symptoms, such as psychological distress. Comorbidity in fibromyalgia is high; that is, patients affected by fibromyalgia have more probability of suffering from other conditions than healthy subjects (Walitt et al., 2015). Furthermore, fibromyalgia affects emotions, family and society. It even affects economic systems due to medical cost and work disability.

It is difficult to describe fibromyalgia in specific terms due its symptom complexity and comorbidity. For this reason, diagnosis can be difficult (Walitt et al., 2015). In the same way, aetiology and treatment can be equally complicated. The medical approach does not establish the aetiology of FM and, therefore, specific medical treatments do not show effectiveness (Belenguer et al., 2009).

The understanding of pain and particularly fibromyalgia needs to be approached from wider models such as the gate control theory (Dickenson, 2002). This model entirely changed the approach to and the complexity of pain management. Not only did it give rise to a more advanced understanding of physiological patterns, but also it incorporated the crucial meaning of subjective components in pain (Miró, 2003).

Currently, the scientific community advocates a biopsychosocial approach for pain management, considering pharmacological and nonpharmacological treatments in a multidisciplinary programme. Indeed, the 2016 revised EULAR1 (European League of Association for Rheumatology) recommendations suggest that management should involve graduated and sequentially added therapies, emphasising education and nonpharmacological techniques (Macfarlane et al., 2017; Okifuji & Hare, 2010).

An increasing interest for a biopsychosocial approach and for the integration of clinical psychology, not only in chronic pain but also in overall chronic conditions (Conversano et al., 2021; Merlo, 2019), is reflected on recent scientific research. For instance, clinical psychological factors have been studied among patients with several medical conditions: type 2 diabetes mellitus (Martino et al., 2020a); inflammatory bowel disease (Martino et al., 2020b); cancer progression and survival probability (Di Giuseppe et al., 2020) and hyperthyroidism (Vita et al., 2020).

Similarly, the evidence of the influence of psychosocial aspects on chronic pain (Wilson et al., 2020) and concretely in FM has been demonstrated: psychological interdependence between FM and Menopause (Conversano et al., 2019); overlap of FM and somatic symptom disorder

and bodily distress syndrome (Häuser et al., 2020) and FM impact on depressive symptoms (Hirsch et al., 2019).

Although there is plenty of evidence supporting the involvement of psychological elements in a holistic approach for pain disorders (Miró, 2003), there is inconsistent evidence regarding psychological treatment effectiveness. According to an evidence-based review regarding psychological interventions in chronic pain (APS, 2018), there is level II evidence for CBT (group-delivered), and for ACT (group-delivered and online delivery) for the treatment of pain disorder in adults. However, in this review (APS, 2018) there was insufficient evidence to indicate the effectiveness of any other intervention.

According to the review by Glombiewski et al. (2010), psychological interventions for fibromyalgia are effective in reducing sleep problems, depression, functional status, and catastrophising. The authors conclude that cognitive-behavioural treatment is significantly better. However, these results do not concur with other research that controverted the effectiveness of CBT in comparison with other treatments (Bennet & Nelson, 2006; Van Koulil et al., 2007). Gómez-de-Regil and Estrella-Castillo (2020) carried out a systematic review of studies analyzing the effect of psychotherapy on physical pain in patients with FM and found that even though all studies showed a reduction in pain, only in half of them the differences were significant.

Lami et al. (2013) carried out the last systematic review of psychological interventions that might be of greater clinical benefit. The authors presented a quantitative description of 58 studies that contributed to psychological management of FM. The study's quality analysis of the 58 papers showed high score variability of internal and external validity among studies, due to the inclusion of experimental, quasi-experimental and single-case design studies. Regarding the variables studied, it was detected that most studies focused on direct symptoms of the disease, such as pain and fatigue. Some studies also implemented interventions aimed at enhancing symptoms related to sleep disturbances and psychological variables, such as depression, anxiety, general psychopathology and impact of disease. According to the authors, mediating variables were poorly evaluated in most studies, such as pain catastrophising, self-efficacy, pain anxiety and pain coping styles. Regarding types of intervention, CBT was indicated as the most implemented and studied treatment and was aimed at training patients to manage pain. However, as previously mentioned, this review is completely descriptive; therefore, the authors did not compare treatment effectiveness.

Thus, the present review attempts to carry out an update of psychological interventions in FM management, making further progress to compare treatment effectiveness. The research

conducted by Lami et al. includes studies carried out until 2013; therefore, we aim to update this review. We intend to perform a systematic review from 2013 to 2019, trying to bring light to the following questions: 1) Which direction are psychological interventions taking in FM? and 2) What are the most effective interventions?

2. Method

2.1 Search Strategy

The systematic review is an update of the previous review carried out by Lami et al. (2013) and was performed according to the PRISMA-statement (Preferred Reporting Items for Systematic reviews and Meta-Analyses) (Moher et al., 2009). Reproducing the review by Lami et al. (2013), the exhaustive bibliographic search through the Web of Science (complete database), was as follows: fibromyalgia (Title) AND intervention OR treatment OR therapy (Title). The search applied from January 2013 – the year after the review by Lami et al. (2013) - to December 2019.

The search identified 1033 articles; however, a vast amount of articles, due to the keyword combination, was perceived. Several scientific articles regarding psychological technique titles did not respond to the keywords (e.g., *Mindfulness Meditation Alleviates Fibromyalgia Symptoms in Women: Results of a Randomized Clinical Trial* (Cash et al., 2015)). A second search was therefore executed, broadening the spectrum. It enlarged the quest from *Title* to *Topic* in the Web of Science and was described as follows: fibromyalgia (Topic) AND intervention OR treatment OR therapy (Topic). This second search identified 4,274 articles. As a result of the unmanageable number of articles, the research was restrained to psychological-related interventions. Therefore, the search was as follows: fibromyalgia (Topic) AND psychological intervention OR psychological treatment OR psychological therapy OR psychotherapy (Topic). This last search identified 759 articles. After a complete review of all titles, 450 articles were excluded on presenting overall diagnoses including other syndromes or conditions besides FM. The 83 articles considered after this were fully analysed and some were excluded due to a lack of proper psychological intervention description. Therefore, 72 articles were included in the present review (Fig. 1).

2.2 Eligibility Criteria

The subsequent inclusion criteria were set to select the studies: (1) empirical articles (experimental, quasi-experimental, or single-case design studies) published in scientific journals; (2) written in English or Spanish; and (3) adult samples (18 years or over) with FM diagnosis according to the American College of Rheumatology (ACR) criteria (Wolfe et al., 2010).

2.3 Study Evaluation

Qualitative information was captured in a table to attain specific characteristics related to the treatment, to the studied outcomes and to methodology. Studies were examined and interpreted according to a quality evaluation tool developed by Berra and colleagues (2008) for critically appraising research articles or to evaluate evidence during the development of systematic reviews. This tool assesses by means of 27 items related to: study question or objective, participants, comparability between groups, definition and measure of main variables; analysis and confusion, results, conclusions, external validity and applicability, and conflict of interest.

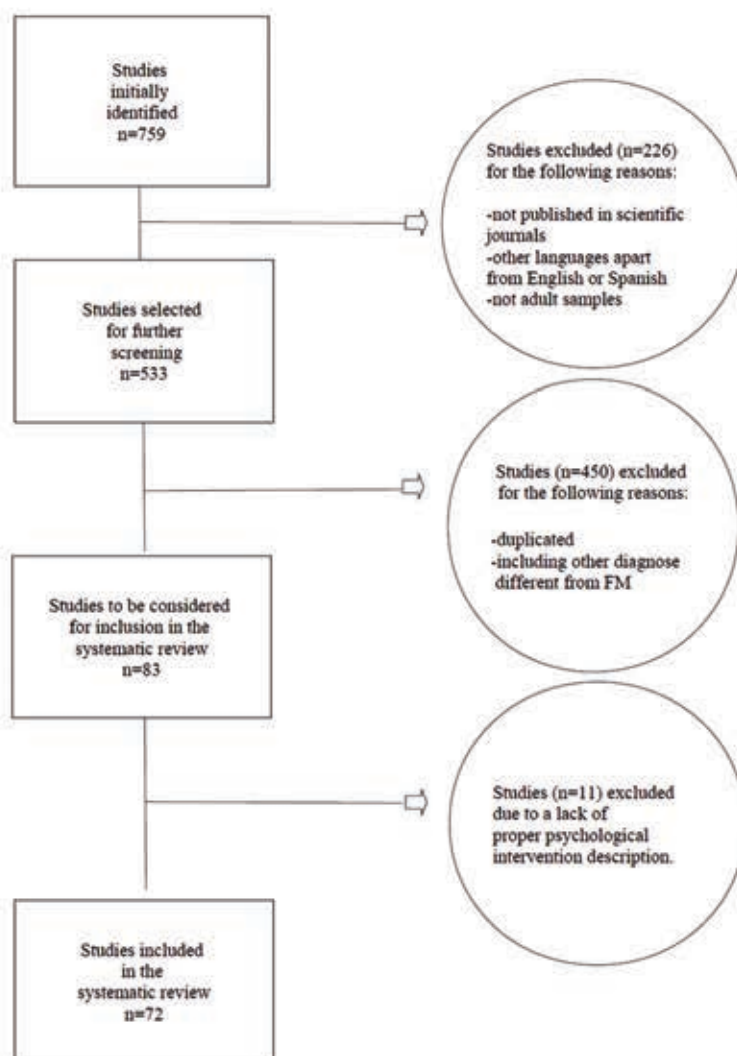


Figure 1. Flowchart of the study selection process

3. Results

Table 1 displays the 72 articles examined in this review. The studies are catalogued in alphabetical order under the name of the first author. The table also shows the characteristics of the study samples, interventions along with co-interventions, target variables, study quality analysis and results. Regarding results, short- and long-term assessments have been briefly described. In the event of presenting several long-term assessments, the table displays the longest available follow-up.

3.1 Participants

The number of participants of the records' samples in the present review, vary between $n=1$ and $n=583$, 88.6 being the mean. However, 80% of the articles present samples between $n=10$ and $n=190$. From among all the papers included, 49.3% consisted of mixed samples and 44.4% were only female samples. However, the majority of mixed samples include less than 20% of males. Only one study includes a proportional amount of males and females (13 and 15, respectively) intending to study gender differences for CBT in FM. The remaining 6.3% of all studies did not report the gender of the sample. The mean age of participants was 50.6 years and 25% incorporated a sample from 18 to approximately 65 years old.

3.2 Design

In relation to assessment, all studies carried out an evaluation before and immediately after intervention. Follow-up evaluations 6 months after intervention were performed in 20.8% of the studies. Moreover, 12-month follow-ups were included in 19.4% of the studies. In relation to control groups, 77% of the studies include a control group, of which 60.7% comprised a passive, waiting list or non-treatment control group, and 39.3% included an active control group.

3.3 Interventions

The review selected 72 studies, of which 24 evaluated Cognitive Behavioural Therapy (CBT) as a main treatment, 1 of them together with Biofeedback, and 11 included CBT in a multidisciplinary approach. Out of the 72 articles, 8 conducted mindfulness interventions, 6 performed Acceptance and Commitment Therapy (ACT), 1 compared and studied ACT and CBT in the same study, 5 were education-related approaches (together with psychological support), 1 psychodynamic psychotherapy, 1 constructivist therapy, 2 guided imagery, 1 relaxation intervention, and 1 training in autohypnosis. Another two multicomponent studies were incorporated. One encompassed Rational Emotive Therapy together with Transactional

Analysis as a main intervention, whereas the other one was described overall as a psychological therapy. The remaining 9 studies were specifically designed interventions. They included Emotional Expression Acknowledgment and Exposure (EEAE), Body Basic Awareness Therapy (BBAT), Group Music Imagery, Best Possible Self, Time In, Group Solving Therapy (2 studies), Forgiveness Education and psychotherapy together with spiritual care.

Relaxation training was performed as a stand-alone and primary treatment in 1 study; however, relaxation strategies seem to be present in a vast amount of studies (55%). Likewise, education was studied as a stand-alone treatment, but it is also broadly used as a part of other treatments. In particular, it was cited in 37 studies (51.4%) and it was mainly geared toward the descriptors of the biopsychosocial model of chronic pain and FM. These are psychological, biological and social factors influencing the experience of pain and other symptoms. Psychoeducation (education related to psychological aspects) was carried out by psychologists in 16 studies. Other healthcare professionals (physicians, nurses, occupational therapists and physiotherapists) are referenced in 5 studies.

Again, despite the fact that guided imagery was used as a main treatment to enhance coping skills and self-efficacy in 2 studies, it also emerges as part of other interventions in 2 other studies. This is described as the path to modify pain-related elements and to induce relaxing states of consciousness.

Specific treatment modalities have been analysed, such as smart-telephone intervention and internet-delivery. Telephone treatment was observed in 2.7% of the studies and 13.9% of interventions were performed and conducted on line. The remaining studies (83.4%) carried out standard on-site treatments. Also, virtual reality was used as a treatment modality in 6 studies (8.3%), half of which were implemented with an internet-delivery format and half with an on-site format. Finally, 6% of studies combined interventions with more than one format, such as group therapy and online techniques.

Treatment frequency varies among all selected studies; however, the majority of interventions implemented weekly sessions (52.2%). Mean treatment duration was 23 hours; however, these might be estimated data since some studies did not report this, and in another it depended on the patients' availability. The number of sessions of most interventions varied between 9 and 20. Mean duration of each session was 1.8 hours, being from 1h to 3 hours.

3.4 Outcome measures

Outcome measures among the studies are pain, pain-related variables, pain-related psychological variables, fatigue, quality of life, depression, anxiety, sleep variables, physiological variables and global score of some questionnaires. The questionnaires used to measure these outcomes are Visual Analogue Scale (VAS), Numeric Rating Scale (NRS), Brief Pain Inventory (BPI), Multidimensional Pain Inventory (MPI), McGill Pain Questionnaire (MPQ), Fibromyalgia Impact Questionnaire (FIQ), Widespread Pain Index (WPI), Multidimensional Fatigue Inventory (MFI), Brief Fatigue Inventory (BFI), Fatigue Severity Scale (FSS), Multidimensional Assessment of Fatigue (MAF), 36-Item Short Form Health Survey (SF-36), 12-Item Short Form Health Survey (SF-12), EuroQoL, COOP/WONCA Functional Assessment Charts, Hospital Anxiety and Depression Scale (HADS), State-Trait Anxiety Inventory (STAY), Beck Depression Inventory (BDI), Psychological Inflexibility in Pain Scale (PIPS), Acceptance and Action Questionnaire (AAQ-II), Chronic Pain Coping Inventory (CPCI), Coping Strategies Questionnaire (CSQ), Pain Catastrophising Scale (PCS), Chronic Pain Self-efficacy Scale (CPSS), Pittsburgh Sleep Quality Index (PSQI), Medical Outcomes Study (MOS), Chronic Pain Sleep Inventory (CPSI), Stanford Sleep Questionnaire, Epworth Sleepiness Scale (ESS), Prefrontal Symptoms Inventory (PSI), SCOPA, Patient Global Impression of Change (PGIC) and Perceived Stress Scale (PSS). The validation studies of all instruments are referenced in the papers included in the table.

Pain arises as the most evaluated outcome. Pain-related variables included pain perception, pain severity, pain symptoms, pain threshold and subjective pain. Approximately 65% of the papers studied pain as a primary outcome and approximately 41% of them studied pain outcomes in the long term. Pain was measured with the Visual Analogue Scale (VAS), the Numeric Rating Scale (NRS), the Brief Pain Inventory (BPI), the Multidimensional Pain Inventory (MPI), the McGill Pain Questionnaire (MPQ), the Fibromyalgia Impact Questionnaire (FIQ) and the Widespread Pain Index (WPI).

Fatigue was a primary outcome in 14 studies (19.4%) and was measured by the Multidimensional Fatigue Inventory (MFI), the Brief Fatigue Inventory (BFI), the Fatigue Severity Scale (FSS), and the Multidimensional Assessment of Fatigue (MAF).

Also, quality of life was often assessed as both primary and secondary outcome. This has included both quality of life and health-related quality of life. Although these terms are not equivalent, in some cases they have been used interchangeably in the literature being assessed with the same scale. There are 20 studies assessing (health-related) quality of life (27.7% of total

studies). The questionnaires used for this variable were SF-36, the reduced version SF-12, EuroQoL and COOP/WONCA.

Depression and anxiety are the two most evaluated psychological variables, mostly with HADS, STAY and/or BDI. In some cases, the terms depression and anxiety were referred to as psychological or emotional distress. From among all of the studies, 33 (45.8%) evaluated depression and 25 (34.7%) studies evaluated anxiety. Another psychological variable measured is psychological flexibility, which was reported in 4 studies (5.5%). This was measured with the Psychological Inflexibility in Pain Scale (PIPS), or with the Acceptance and Action Questionnaire (AAQ-II).

Regarding pain-related psychological variables, such as pain catastrophising, pain self-efficacy, pain anxiety and pain coping style variables, these are undervalued compared to other variables such as depression, anxiety or quality of life. Catastrophising was assessed in 11 (15.27%) studies, and coping skills and self-efficacy were assessed in 17 studies (23.6%). These variables were assessed mainly with the Chronic Pain Coping Inventory (CPCI), the Coping Strategies Questionnaire (CSQ), the Pain Catastrophising Scale (PCS), and the Chronic Pain Self-Efficacy Scale (CPSS).

Sleep variables were particularly studied after specific cognitive-behavioural treatments aimed at treating pain-related insomnia in several studies. Furthermore, some used sleep parameters and polysomnography measures. Overall, sleep-related variables were assessed in 21 studies (29.9%) and in several formats. The most common of these, included sleep quality, sleep latency, sleep duration, sleep efficiency, and sleep disturbance. The questionnaires most frequently used are PSQI, MOS, CPSI, Stanford Sleep Questionnaire, ESS, PSI, SCOPA, and VAS.

Some physiological variables were also measured after treatment. These included heart rate variability, pro-inflammatory cytokine levels and plasma SP level, each evaluated in one study.

In addition to assessing specific variables, the global score of some questionnaires was used as primary outcome measurement. The most common tool is the Fibromyalgia Impact Questionnaire (FIQ), which evaluates the impact of the disease on several variables (physical capacity, work, fatigue and others) and was evaluated in 28 (38.8%) studies. Also, the Patient Global Impression of Change (PGIC) and Perceived Stress Scale (PSS) were found in 4 (5.5%) studies each.

3.5 Effectiveness

Overall, 98.6% of the studies showed effectiveness of the treatment studied in at least 1 dependent variable. However, in order to draw more specific conclusions, an analysis of intervention effectiveness on each variable is presented.

Considering the 44 studies evaluating short-term outcomes in pain, approximately 59% showed positive results. Among studies with long-term pain-related assessments, 50% showed positive outcomes. Considering most common interventions in this review followed by pain assessment, the most pain-related successful interventions were ACT and CBT. Out of the 7 ACT studies, 4 carried out pain assessment after treatment and 3 (75%) provided beneficial reports. From among the 36 CBT studies, 25 assessed pain after treatment and 13 (52%) had positive outcomes. Mindfulness interventions were followed by pain assessment in 4 studies and only 1 (25%) reported positive outcomes. Although there are 5 studies related to educational approaches, only 1 assessed pain after treatment, reporting beneficial results. The 3 studies with relaxation and guided imagery interventions showed improvements in pain-related variables (100%).

Out of 14 articles that studied fatigue, 10 (71.4%) presented an improvement in the short term. From among studies assessing long-term effects on fatigue, 50% had positive results. Specifically, 60% of CBT interventions studying fatigue showed improvements. Another 4 interventions, ACT, mindfulness, relaxation and guided imagery, evaluated fatigue once each and all showed improvements.

Sixty-nine per cent of the 20 studies evaluating quality of life in the short term showed improvement after treatment. CBT interventions assessing quality of life (8 studies) demonstrated improvements in 50% of the studies. Four studies with ACT interventions evaluated this variable and all of them (100%) showed positive results.

In relation to psychological variables, from among 33 of the studies that evaluated depression 69.7% showed improvements in the short term. CBT had a 58% success rate; ACT 100%; Mindfulness 66.6% and educational approaches 50%. Some fewer usual interventions also showed positive outcomes in terms of depression, such as constructivist therapy, psychotherapy together with spiritual care, EEAT, Best Possible Self and Forgiveness Education.

Regarding the 25 studies reporting anxiety scores, 60% showed improvement in the short term. CBT interventions had 50% of improvements; ACT 100%; Mindfulness 66.6% and education 50%. Other studies that reported anxiety-related positive outcomes were EEAT and Forgiveness Education.

In relation to psychological flexibility, the 4 studies assessing this outcome suggested benefits in the short and long term after ACT (3 studies) and Mindfulness (1 study).

Regarding pain-related psychological variables, out of the 11 studies that reported catastrophising outcomes, short-term improvements were reported in 72.12% of the studies. These were after CBT, showing a 100% success rate, after mindfulness interventions (50%) and after educational approaches in one study.

Similarly, coping skills were reported in 17 studies, increasing positively in 76.4%. These effects were reported after CBT (75% of studies with positive outcomes), Mindfulness (100% of 2 studies) and after a single study related to ACT, education, relaxation, Best Possible Self and forgiveness education.

In relation to FIQ and PSIG scores, most of the studies showed improvements. Out of the 28 studies that assessed FIQ scores, 67.8% reported improvements in the short term. These were observed predominantly after CBT (80%), Mindfulness (100%) and ACT (66.6%). From among the 4 studies reporting PSIG scores, 75% demonstrated patient global impression of change in the short term. However, these results were found only after 2 studies related to CBT and to education.

In relation to sleep-related variables, 71.4% of the 21 studies assessing short-term effects reported improvement in sleep, these reports being detected after CBT (90.9%), Mindfulness (100%), and after 2 studies related to EEAT and to relaxation.

Summarising, we find that all variables show similar sensibility to overall psychological treatments. Effectiveness fluctuates between 59% and 76%. We also observe a non-existent treatment showing a major effectiveness in all variables. Effectiveness depends on the assessed variable.

Regarding effectiveness related to treatment modality, from among all the studies 46 were carried out with group treatments, 15 with individual treatments and 11 combined both modalities (individual and group interventions). When comparing effectiveness among these different treatment modalities, we found that short- or long-term positive outcomes occurred in 40% of individual treatments, 36.95% of group treatments and 45% of combined treatments. Although combined treatments show a higher percentage of effectiveness, differences among percentages are not relevant, it not therefore being possible to reach a firm conclusion.

In relation to the duration of each treatment, out of the 72 studies, 10 did not accurately report treatment extent. Among the studies reporting treatment duration, 47% conducted an intervention lasting a total of between 10 and 30 hours. Taking into account the studies in this

range of treatment duration, 56.5% showed pain improvement. On the other hand, 17.6% presented interventions with less than 10 hours, of which 11.8% showed success related to pain improvements. Finally, only 3 (4.4%) studies implemented more than 30 hours of treatment and only 1 (33%) revealed pain-related effectiveness.

3.6 Study Quality Analysis

The analysis of the studies encompassed in this review was performed with a quality evaluation tool developed by Berra et al. (2018). Considering the inclusion of experimental, quasi-experimental, single-case studies and abstracts of substantial research, fluctuant scores were predicted.

This tool to evaluate the quality of the studies compounds 27 items related to: research aim, participants, comparability, definition and measurement of variables, analysis and confusion, results, conclusions, internal and external validity, and implementation of the results. The final evaluation of each study can be found in table 1. Study quality analysis is provided according to its internal and external validity. Internal validity considers whether the investigator obtains a compelling difference between the treatment and control conditions, meaning that the study involves well-constructed, controlled and accurately measured experiments (Bernardy et al., 2018). In this review, 42 studies demonstrated high internal validity (from 3.5 to 4), 13 medium-high internal validity (from 3 to 3.5), 2 medium internal validity (from 2 to 3) and low quality (less than 2) was detected in 15 studies.

External validity refers to the generalisability of conclusions, that is the extent to which the findings can be related across different contexts or samples (Druckman et al., 2011). High external validity was found in 42 studies, medium-high internal validity in 13, medium internal validity in 3 and low quality in 14. However, low-quality results were found, in all cases, in studies presented in abstract format; therefore, most items could not be evaluated as a result of a lack of information. Consequently, these articles were qualified as NA (not available) in the table.

Berra et al. (2008) tool, which assesses the quality of the studies, enabled us to analyse strengths and weaknesses of fibromyalgia research by analysing each item. Regarding weaknesses, analysing the results of specific items, a low global score related to effect size and statistical power was identified in 30 studies (41.6%). This means that these studies did not estimate the size of the sample required to assess the frequency measurements with the accuracy (or the reliability or precision) that the investigator had expected. In relation to strengths, 57 (79.2%) studies did statistically estimate the significant differences between groups. Also, a similar number of studies (55) (76.4%) was found to use tool measurements or questionnaires with known and appropriate reliability and validity.

Table 1. Articles examined in the review

Author	Participants (n, age, gender)	Type of treatment	Sessions/frequency/total hours	Group p/In div	Control group	Target variables	Quality (0-4)	Results	
							IV	GV	
Aguilera et al 2018	n=20 33-60 years mean=50 Female	Constructivist therapy: welcoming and analysis of demand, feedback, construction of the self and future perspectives	16/weekly/16	1	Group Comparison (Multitreme at group - Non-maltreatment group).	FIQ variables. Anxiety (HAD) Depression (BDI). Cognitive outcomes (Repertory Grid Technique).	2.8	2.5	Short-term: Improvement in FM impact, anxiety and depression in maltreatment group compared to non-maltreatment group. Long-term: NA
Aminova et al 2017	n=191 37-69 years mean=49.1 Mixed (F=93.7%)	Online Self-administered Mitchell Method Relaxation (MMRT): written instructions and short audio recording of guided imagery.	30/daily/~2	G+1	Attention Control Waiting List	Pain severity (VAS), Sleep (MOSES), Fatigue and health-related quality of life (HRQoL), Impact of FM (FIQR), Depression and anxiety (HADS), Coping, Perceived Stress (PSS).	3.7	3.8	Short-term: Significant dose-effect of MMRT group improvement in pain levels. Long-term: Maintained improvement of group in fatigue.

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Arg et al. 2013	n=58 18-65 years mean=46.6 Mixed (F=93%)	(1) Telephone CBT: education, relaxation, visual imagery, automatic thoughts and pain, cognitive restructuring, stress management, time-based pacing, pleasant activities, anger management, sleep hygiene and relapse prevention + Milnacipran + Telephone Education	8/weekly/≈4.6	I	Group Comparison	Weekly average pain intensity (wrist watch pain monitor: ActiWatch). Physical function (SF-36).	3.9	3.9	NA	Significant improvement of group 1 in physical function and weekly average pain compared to group 3. Improvement of group 2 in physical functioning compared to group 3.	NA
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(2) Telephone CBT (Idem) + Placebo

(3) Milnacipran + Telephone education

Bosells et al. 2013	n=6 47-65 years mean=55 Female	CBT with Virtual Reality: Education, relaxation, activity pacing and behavioural therapy, cognitive restructuring, mindfulness, relapse prevention.	10/ biweekly/20	G	None	Functional status, (FIQ), Depression (BDI), Negative and positive affects (PANAS), Coping skills (Chronic Pain Coping Inventory).	NA	NA	NA	Improvement in functional status, positive affect	(6 months) Significant improvement in pain, depression, positive affect, coping strategies.
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Author et al. Year	n	Intervention	Waiting list	G	G	Pain severity (NRS), FM severity and impact, pain symptoms, functioning (FIQ), pain interference, sleep quality (CPSI), pain coping strategies (CSQ), depression (BDI), quality of life (SF-12v2), patient's global impression of change (PGIC), perceived pain relief (Perceived Relief Scale).	3.9	3.9	Significant improvement in PGHC measures, pain symptoms, functioning, quality of life and perceived pain relief compared to control group.	(12 months)	Significant improvement of PGHC scales, perceived pain relief, average pain intensity, impact of FM, pain catastrophizing, some coping strategies.	
Bougeza et al. 2015	n=58 ≥18 years mean=49.98 Mixed (F=92%)	Multicomponent interdisciplinary group intervention: PASSAGE Program: psycho-education tools and CBT-related techniques, + Tailored exercise activities	5	9/biweekly/72.	G	Waiting list	Pain severity (NRS), FM severity and impact, pain symptoms, functioning (FIQ), pain interference, sleep quality (CPSI), pain coping strategies (CSQ), depression (BDI), quality of life (SF-12v2), patient's global impression of change (PGIC), perceived pain relief (Perceived Relief Scale).	3.9	3.9	Significant improvement in PGHC measures, pain symptoms, functioning, quality of life and perceived pain relief compared to control group.	(12 months)	Significant improvement of PGHC scales, perceived pain relief, average pain intensity, impact of FM, pain catastrophizing, some coping strategies.
Bravo et al. 2019	n=39 18-65 years Mixed (F=97.4%)	Basic Body Awareness Therapy (BBAT) group sessions: breathing, awareness, new habits and sharing experiences with the group + BARS-MQ movements and dropy massage + TAU	12/biweekly/17	G+I	TAU	Pain (VAS), Movement quality (BARS-MQ), Psychological function (BDI, HAD, STAI), Quality of life (SF-36).	3.7	3.7	Significant improvement in pain and movement quality compared to control group.	(6 months)	Significant improvement in anxiety.	
Braze et al. 2016	n=100 ≥18 years mean=50 Mixed (F: Majority)	CBT in an interdisciplinary programme: cognitive behavioural therapy, relaxation training, exercise programme and strategies to address functioning and psychological distress + Exercise	NA	G	None	Functioning and distress (Questionnaire Revised).	NA	NA	Improvements in functioning and distress.	NA	NA	

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Camerin i et al. 2013	n=209 25-74 years mean=49 Mixed (F=95%)	Internet-based patient education ONESELF; self-management by increasing information and empowerment through social support.	It depends on the patient	I	None	Online questionnaire (frequency of use of website applications, health-related knowledge, self- management behaviour). Health outcomes (FIQ).	2.7	3.0	Improvement in self- management and health outcomes related to use of website applications.	NA
Cantero- Bajos et al. 2019	n=40 ≥18 years Female	Time lit: sensorimotor intervention that combines psychological strategies and other procedures + Biomechanical physiotherapeutic procedures.	5/weekly/15	G	Waiting list	Pain intensity, pain interference (BPI-S) Quality of life (SF-12), Psychological symptoms (SCL- 90-R), Well-being, problems, functioning, risk and behaviour (CORE-OM).	3.4	3.5	Significant improvement in pain intensity, pain interference, pain zones, quality of life, some psychological symptoms and behavioural changes compared to control group.	3 months Significant improvement in pain intensity, pain interference, pain zones, all psychological symptoms and behavioural changes compared to control group.
Cash et al. 2015	n=91 ≥18 years Female	Mindfulness-Based Stress Reduction (MBSR): instruction/discussion, attention-focusing technique, sitting meditation and relaxed and focused movement.	8/weekly/20	G	Waiting list	Perceived stress (PSS), Pain (VAS), Sleep quality (Stanford Sleep Questionnaire), Fatigue (Fatigue Symptom Inventory), Symptom severity (FIQ), Saftey control.	3.9	3.9	Significant improvement in perceived stress, sleep quality, fatigue and severity of fibromyalgia symptoms.	2 months Maintained perceived stress, fatigue and severity of fibromyalgia symptoms.

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Castro et al. 2015	n=130 18-60 years Female	Multidisciplinary FM treatment related to baseline body mass index (BMI): education, CBT, + TAU + Physical therapy.	24/twice/24	G	TAU	Pain intensity (NRS). Impact of FM (FIQ). Catastrophizing (CSQ). Psychological distress (HADS). Health-related quality of life (COOP-WONCA). Sleep problems index, sleep quantity (MOS).	3.7	3.8	Significant improvement in catastrophizing, psychological distress, FIQ, sleep quantity, sleep index problems and health-related quality of life regarding pre and post-treatment only in the intervention group.	(12 months) Maintained improvement in sleep index problems, number of hours slept and health-related quality of life.
Castro et al. 2013	n=150 18-60 years mean=48.9 Female	Multidisciplinary treatment: CBT: education, cognitive restructuring, skills training, life values and relapse prevention + TAU + Physical exercise.	24/twice/24	G	TAU	Pain intensity (NRS). Impact of FM (FIQ). Catastrophizing (CSQ). Psychological distress (HADS). Health-related quality of life (COOP-WONCA). Sleep disturbances (MOS).	3.6	3.7	Significant improvement in pain intensity, catastrophizing, psychological distress, FIQ, sleep disturbances.	(12 months) Maintained improvement in sleep disturbances, catastrophizing and psychological distress.
Castro et al. 2013	n=44 mean age=49.9 Female	Multidisciplinary treatment: CBT + Pharmacological treatment + Physiotherapy.	NA	G	Conventional pharmacological treatment (CphIT).	Pain intensity (NRS). Functionality (FIQ). Psychological distress (HADS). Quality of life and sleep problems (COOP-WONCA).	NA	NA	Significant improvement in pain intensity, functionality, quality of life and sleep problems.	(12 months) Maintained improvements in pain intensity, functionality, quality of life and sleep problems.

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Choudh ou et al. 2018	n=22 ≥18 years	1. CBT focused on pain. 2. CBT focused on sleep complaints	NA	I	Group Comparison	Parasympathetic activity (high frequency power). Sympathetic activity (low frequency power). Subjective sleep quality (Sleep Quality Assessment Index).	NA NA	NA NA	Significant improvement in subjective sleep quality related to an increase in high frequency power (parasympathetic activity).
Davis et al. 2013	n=79 22-81 years mean=46.14 Mixed (F=98%)	Online Mindful Sociomotional Regulation Intervention (MSERI): meditation, enhancing awareness and acceptance of emotions, and building strong social bonds	12/3weekly/≈ 3	I	Healthy lifestyle tips	Social functioning (SF- 36). Positive and negative affect (PANAS). Coping efficacy (Libert scale). Functional health (FIQ).	4.0	3.7	Significant improvement in coping efficacy, positive affect and social functioning compared to control group. Significant improvement in negative affect compared to baseline.
Garajon dobl et al. 2016	n=88 26-65 years Mixed (F=96.5%)	1) CBT (education, sleep hygiene, relaxation, coping strategies, self- esteem, acceptance of negative emotions) and EMG-FB (learning to control muscle tension and to relax) + EMG-FR 2) CBT (dcm).	10/weekly/12.5	G	No treatment	Hostility, interpersonal sensitivity, global severity index, positive symptom total and other symptoms (SCL- 90-R), state- anxiety and trait- anxiety (STAI). Depression (BDI). State- anger, trait-anger and anger expression index (STAXI-2).	3.2	3.4	Improvement of both intervention groups in hostility, interpersonal sensitivity, state-anxiety, trait- anxiety, depressive symptoms, trait-anger, expression of anger

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<p>García Palacios et al. 2015</p> <p>n=61</p> <p>23-70 years mean=50.4</p> <p>Female</p>	<p>CBT (education, activity management and relapse prevention) and Virtual reality (five predefined scenarios aimed at emotions, depending on the goal of the therapy session).</p>	<p>6/biweekly/12</p>	<p>G+1</p>	<p>TAU</p>	<p>Disability (FIQ), Pain intensity and interference (BPI), Coping (CPCI), Mood (BDI-II), Perceived quality of life (Quality Life Index), Acceptability and satisfaction (Satisfaction and Acceptability Scale).</p>	<p>3.5</p>	<p>3.7</p>	<p>NA</p>	<p>Significant improvement in disability, perceived quality of life, coping strategies in task persistence and exercise.</p>
<p>Garrido-Torres et al. 2016</p> <p>n=32</p> <p>≥18 years</p>	<p>1) Mindfulness sessions, education and advice related to the disease (online). 2) Onsite mindfulness sessions</p>	<p>NA</p>	<p>I</p>	<p>Group Comparison</p>	<p>Pain symptoms, anxiety (NA questionnaire).</p>	<p>NA</p>	<p>NA</p>	<p>Improvements in both groups in pain symptoms and anxiety.</p>	
<p>Harpree et al. 2014</p> <p>n=22</p> <p>NA age</p> <p>Mixed (F=86,36%)</p>	<p>CBT, relaxation training, activity regulation, facilitation of emotional awareness, cognitive restructuring, interpersonal communication training + Myofascial release techniques (MFR) and physiotherapy.</p>	<p>20/weekly/NA</p>	<p>G</p>	<p>MFR and physiotherapy</p>	<p>FIQR Score, Anxiety and depression (DASS), Sleep disturbance (Epworth Sleepiness Scale), VAS, Quality of life (FIM).</p>	<p>2.3</p>	<p>2.7</p>	<p>NA</p>	<p>Improvement in all variables studied in both intervention and control groups but no differences between groups. Significant improvement in FM symptoms compared to control group.</p>

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Hedman et al. 2019	n=140 14-77 years mean=50.3 Mixed (F=98%)	Internet-delivered exposure therapy (Exp): psychoeducation. Exposure to pain-related stimuli and mindfulness training	8/-/NA + 175 minutes total mean therapist time.	I	Waiting list	Cost-effectiveness (self-report questionnaire TIC-P). Treatment effectiveness (FIQ). Quality of life (EQ-5D).	3.7	3.7	Significant improvement in FIQ score compared to control group. Nonsignificant improvements. Significant difference in cost-effectiveness between groups favouring Exp.	(12 months)
Herrero et al. 2014	n=40 27-66 years mean=48.8 Female	Virtual reality (predefined scenarios to adjust each treatment and needs of each disorder) and CBT (psychoeducation and behavioural activation).	6/biweekly/12 (CBT) + 20min (Virtual reality)	G + I	None	Mood state (facial expression scale). Pain and fatigue (NRS). Motivation and self-efficacy (NRS). Intensity of emotions (Likert scale).	NA	NA	Significant improvement in mood state, self-efficacy, motivation and intensity of some emotions compared to baseline.	NA
Herrero et al. 2013	n=8 27-57 years mean=45.37 Female	Virtual reality (predefined scenarios to adjust each treatment and needs of each disorder) and CBT (psychoeducation and behavioural activation).	6/biweekly/12 (CBT) + 20min (Virtual reality)	G + I	None	Pain and fatigue (VAS). Mood state (facial expression scale). Motivation and self-efficacy (Likert Scale). Emotions (VAS). Sense of presence (SUS).	NA	NA	Significant improvement in pain intensity, perception of self-efficacy and motivation.	NA

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Author et al. Year	n	Intervention	Waiting list	G	Stress (VAS), Pain (MPI) (VAS), Vital exhaustion (Maastricht Questionnaire), Stress behaviour (Everyday Life Stress), Depression (MADRS-S), Plasma SP level	3.4	3.4	Outcomes
Karlsson et al. 2019	n=48 mean age=48.5 Female	CBT: knowledge, self-monitoring, behavioural exercises, cognitive restructuring, relaxation techniques and life value issues	20/weekly/60	G	Life control, support from spouses or significant others, life values, affective distress, interference (MPI-S)	3.8	3.9	Significant reduction of plasma SP level (33%) in treatment group associated with improved outcomes of "life values" and "support from spouses or significant others". Improvement in pain behaviour, vital exhaustion and everyday life stress.
Karlsson et al. 2015	n=48 18-64 years mean=49 Female	CBT: knowledge, self-monitoring, behavioural skills training, cognitive restructuring, and life value issues	20/weekly/60	G	Life control, affective distress, support from spouses or significant others and pain severity (MPI-1) General activity level (MPI-2), Vital exhaustion, stress behaviour, depression (MPI-3)	3.8	3.9	Improvements in life control, interference, affective distress, support from spouses or significant others, distracting responses, depression and pain severity compared to control group. Maintained and enhanced improvement in life control, interference, affective distress, support from spouses or significant others, distracting responses, depression, pain severity, vital exhaustion and stress behaviour.

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Kozl et al. 2014	n=60 24-65 years mean=51.4 Female	1) Cognitive restructuring instructions and writing exercises 2) Acceptance instructions and writing exercises	1/-/NA	I	Only writing exercises	Pain tolerance and pain intensity (VAS: heat/cold-pain).	3.7	3.7	NA	Significant improvements in both groups in heat pain tolerance compared to control group, but nonsignificant difference between both groups. Significant improvement in cognitive restructuring in cold pain tolerance compared to acceptance group and control group. Significant improvement in global assessment scale of change in TCBT, TCBT + Exercise programme and Exercise programme compared to TAU group.
Kroenke et al. 2013	n=442 ≥18 years mean=56.2 Mixed (F: 69.5%)	1) Telephone-delivered cognitive-behavioural therapy (TCBT). 2) TCBT + Exercise program.	8/weekly/≈7.5	I	1) TAU 2) Exercise programme	Score of global assessment scale of change. Pain, fatigue, sleep and psychological distress.	NA	NA	(9 months)	Maintained benefits.
Lami et al. 2016	n=28 25-60 years Mixed (F=53.6%)	CBT-I for insomnia: psychoeducational information, exercises, and topics to discuss during the session and homework + TAU	9/weekly/13.5	G	None	Sleep quality, sleep efficiency, sleep disturbances (PSQI). Pain intensity, functioning (MPQ-SF, FRQ), Fatigue (MFI), Emotional distress (HAD5, PASS-20), Catastrophizing (PCS). Gender differences.	2.9	3.3	(3 months)	Significant improvement in both genders in sleep quality, sleep efficiency, sleep disturbances, daytime functioning, pain intensity, mental fatigue, motivation and activity reduction, and FM impact. Significant improvement in male group in sleep disturbances and pain-related anxiety and catastrophizing. Significant improvement in female group in sleep latency, general fatigue and depression.

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Lami et al. 2018	n=113 25-65 years mean=50.19 Mixed	1) CBT-IP (for insomnia and pain): information, sleep hygiene restrictions, relaxation, planning activities, communication and relationships, cognitive therapy. 2) CBT-P (for pain): information, relaxation, identifying unpleasant emotional states, planning activities, cognitive therapy.	9/weekly/13.5	G	TAU	3.8	3.9	3 months	Significant improvement of CBT-IP in subjective sleep quality, sleep latency, sleep efficiency compared to baseline, CBT-I and control group. Significant improvement in interventions groups in self-efficacy and FM impact. Significant improvement of CBT-P in catastrophizing and pain acceptance compared to baseline.	Significant improvements of CBT-IP in pain intensity.
Lazarillo et al. 2015	n=62 NA age NA gender	1) CBT 2) Education	4weeks/NA	G	Group Comparison	NA	NA	6 months	Significant improvement of CBT group in catastrophizing compared to baseline. Significant reduction of CBT group in pain-evoked activation in the medial thalamus.	Significant improvement of CBT group in pain severity.
Laq-Jun et al. 2019	n=1 65 years Female	Psychotherapy and Spiritual Care: Behavioural techniques, relaxation training, biofeedback, guided imagery + physician, psychiatrist, physiatrist, pastoral counsel, pharmacist, social worker, nurse, and dietitian interventions.	NA	I	None	NA	2.1	NA	Improvements in pain interference and depressive mood.	NA

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<p>Ljésson et al. 2014</p> <p>n=41</p> <p>>18 years mean=52.0</p> <p>Female</p>	<p>Internet-delivered ACT (ICBT): acceptance, mindfulness, work with life-values, systematic exposure to FM symptoms and FM-related situations.</p>	<p>NA</p>	<p>I</p>	<p>None</p>	<p>FM aspects (FIQ), Interference (Pain Disability Index), Health-related quality of life (SF-12), Anxiety and depression (HADS), Impact & severity of fatigue (FSS), Psychological flexibility (PIPS), Social cost (Self-report test TIC-P).</p>	<p>3.0</p> <p>3.3</p>	<p>Significant improvement in FM symptoms and impact, disability, quality of life, anxiety, depression, fatigue and psychological flexibility.</p> <p>Social costs reduction that effectively offset the cost of the treatment intervention.</p>	<p>(6 months)</p> <p>Maintenance of all improvements.</p>
<p>Luciano et al. 2014</p> <p>n=156</p> <p>18-65 years mean=48</p> <p>Female</p>	<p>Group-based Acceptance and Commitment Therapy (GACT): exercises and topics within the context of ACT practice and training.</p>	<p>8/weekly/20</p>	<p>G</p>	<p>1)TAU 2)Waiting list</p>	<p>Functional status (FIQ), Pain catastrophizing (PCS), Pain acceptance (CPAQ), Anxiety and depression (HADS), Health-related quality of life (EQ-5D).</p>	<p>3.6</p> <p>3.7</p>	<p>Significant improvements in global functional status, pain catastrophizing, pain acceptance, subjective pain, quality of life, anxiety and depression.</p>	<p>(6 months)</p> <p>Maintained improvement in anxiety, depression and subjective pain.</p>
<p>Luciano et al. 2014</p> <p>n=168</p> <p>18-65 years mean=46.8</p> <p>Mixed (F=94.64%)</p>	<p>CBT: information, negative thoughts, nuclear beliefs, coping strategies, pain catastrophizing and assertive communication.</p>	<p>NA</p>	<p>G</p>	<p>1)TAU 2)Recomm. pharmacological treatment</p>	<p>Quality-Adjusted Life Years (QALYs), Health-related quality of life (EQ-VAS), Costs of health care (Client Service Receipt Inventory), Cost-effectiveness acceptability curves (CEACs).</p>	<p>4.0</p> <p>4.0</p>	<p>Improvement in health-related quality of life and quality-adjusted life years.</p>	<p>(6 months)</p> <p>Significant reduction in costs compared to control groups.</p> <p>Significant improvement in health-related quality of life compared to control groups.</p>

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Luciano et al. 2017	n=156 18-65 years mean=48.8 Mixed (F=96.1%)	Group-based Acceptance and Commitment Therapy (GACT): exercises and topics within the context of ACT practice and training	8/weekly/20	G	1)TAU 2)Waiting list	Direct and indirect cost differences. Health-related quality of life (EuroQoL). Health care use (Clean Service Receipt Inventory).	3.7	3.6	Significant improvement in quality of life and health care (overall) compared to control groups. Significant reduction in costs compared to control groups.
Lundley et al. 2017	n=230 ≥18 years mean=49.13 Female (F=93.9%)	1) Emotion awareness and expression therapy (EAET): experiential, intensive psychodynamic, prolonged exposure, expressive writing, therapeutic rescripting 2) CBT 3) FM education	8/weekly/12	G	Group Comparison	Pain severity index (BPI). Sleep problems (PSQI). Cognitive dysfunction (MASQ). Depressive symptoms (CES- D). Anxiety symptoms (GAD). Fatigue (PROMIS). Physical functioning (SF- 36). Positive and negative affect (PANAS). Life satisfaction (SWLS). Number of health profession visits. Patient global change (PGIC).	3.9	3.9	Significant improvements of EAET group in cognitive difficulties compared to CBT group. Significant improvement of EAET group in pain intensity and sleep problems compared to FM education group. Significant improvement of EAET group in widespread pain, cognitive difficulties, depression, anxiety, physical functioning, positive affect and life satisfaction compared to FM education group.

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		12/biweekly/12	G	TAU		3.3	3.5	(6 months)
Martin et al. 2014	n=153 ≥18 years mean=50.1 Mixed (F: 90.9%)	Interdisciplinary PSYMEPHY, CBT (cognitive, physiological and behavioural components) and education (nature of FM, course, treatments, daily activities, physician-patient relationship, psychology of pain) + Physiotherapeutic and medical interventions.	.75		Physical functioning, pain, impact of FM and HRQoL (FIQ).			Significans improvement in physical functioning, pain and impact of FM compared to control group.
Martin et al. 2014	n=93 ≥18 year mean=50.1 Mixed (F=93.4%)	Interdisciplinary PSYMEPHY, CBT (cognitive, physiological and behavioural components) and education (nature of FM, course, treatments, daily activities, physician-patient relationship, psychology of pain) + Physiotherapeutic and medical interventions.	12/biweekly/21	TAU	Pain, fatigue, morning tiredness, anxiety and impact of FM (FIQ). Perceived pain coping strategies (VAS).	3.7	3.8	Significans improvement in fatigue, anxiety and current pain compared to baseline. Maintained improvements in impact of FM and pain.

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Author(s) / Year	Intervention	Frequency	Group	Measures	Results	Duration
Martinez et al. 2014	1) CBT-1 (for insomnia): information, sleep restrictions and stimulus control, physiological deactivation procedures training, cognitive therapy, preventing relapses + TAU 2) Sleep Hygiene Education	6/weekly/9	G Comparison	Sleep variables (PSQI), Fatigue (MFI), Daily functioning (FIQ), Pain intensity (MPQ-SF), Catastrophizing (PCS), Self-efficacy (CRSS), Anxiety and depression (SCL-90-R)	3.9	3.9 (6 months)
						Significant improvement of group 1 in fatigue, daily functioning, pain catastrophizing, anxiety and depression compared to group 2. Significant improvement in both groups in subjective sleep quality compared to baseline. Significant improvement of group 1 in sleep latency, sleep duration, habitual sleep efficiency and sleep disturbance compared to group 2.
Martins et al. 2014	Weekly Interdisciplinary Programme (WIP): educational activities, cognitive behavioural strategies and approaches to psychosocial approaches + Physical therapy, stretching, ergonomics, posture guidance combined and occupational factors.	12/weekly/12	G Waiting list	FIQ variables (functional capacity, work absenteeism and others), Intensity of pain (VAS), Sleep quality (PSI), Quality of life (SF-12), Anxiety and depression (HADS).	3.1	3.2 NA
						Significant improvement in functional capacity and work absenteeism compared to control group.

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McCrac et al. 2019	n=130 ≥ 18 years mean=53 Mixed (F=97.7%)	1) CBT-I (insomnia): sleep education, sleep hygiene, relaxation, automatic thoughts and dysfunctional thoughts, recommendation and long-term maintenance skills. 2) CBT-P (for pain): pain education, diaphragmatic breathing, relaxation, autogenic relaxation, visual imagery, automatic and dysfunctional thoughts, balanced thinking, long-term maintenance skills	8/weekly/6.6	G	Waiting list	Self-reported sleep onset latency (SOL), Wake after sleep onset (WASO), Sleep efficiency (SE), Sleep quality (SQ), Pain ratings (VAS), Dysfunctional sleep-related beliefs (DRAS), Pain (PDI), MPQ, Depression (BDI-II), Anxiety (STAI-YI).	3.8	3.9	Significant improvement in insomnia in both intervention groups. Greater improvements of CBT-I group in sleep initiation and sleep maintenance difficulties. Improvement in immediate pain reduction in some patients of intervention groups.	(6 months)	Significant improvement in initiation and maintenance difficulties in both intervention groups compared to control groups.
Meñin et al. 2018	n=36 27-60 years mean=39 Mixed (F=81%)	Psychoeducation method The Affect School and Script Analysis (ASSA): increasing emotional awareness and expressiveness.	18/weekly/26	G + I	None	Depression and anxiety (HADS), Alexithymia (TAS-20), Medically unexplained physical symptoms (SCL-93), General health (VAS), Self-affirmation, self-love, self-blame, and self-hate (SASB).	2.5	2.9	Significant improvement in depression, anxiety, alexithymia, medically unexplained physical symptoms, general health, self-affirmation, self-love, self-blame, and self-hate.	(18 months)	Significant improvement in depression, alexithymia, medically unexplained physical symptoms, general health, self-affirmation, self-love, and self-hate.

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Meigs et al. 2014	n=56 ≥ 18 years mean=55 Mixed (F=88%)	1) Internet-based CBT MindGYM: cognitive restructuring, relaxation, pleasant events, assertiveness training, and problem solving. 2) TAU + online educational information about FM.	NA	G	Group Comparison	FIQ score: Changes in tender point scores (clinical assessment).	3.0	3.2	Significant improvement of group 1 in FIQ score and tender point scores compared to group 2.	(12 weeks) Significant improvement of group 1 in FIQ score and tender point scores compared to group 2.
Mezies et al. 2014	n=72 ≥18 years mean=46.9 Female	Guided imagery: guided relaxation, pleasant scene imagery, imagery journey through their immune system. Daily Weizen log of the guided imagery.	10/daily/≈23.5	I	TAU	Self-efficacy (ASES). Perceived stress (PSS). Fatigue (BFI). Pain (BPI). Depression (CES-D). Immune biomarkers	3.7	3.8	Significant improvement in fatigue and pain severity and fatigue.	(10 weeks) Significant improvement in self- efficacy, stress, fatigue, pain and depression.
Miles et al. 2013	n= 47 18-65 years Female	CBT: information, identification of dysfunctional thoughts, engaging in behavioural interventions.	8/weekly/20	G	Yoga	Mood. Fatigue (MAF). Sleep quality (PSIQ). Physical functioning (FHAQ). Pain (VAS, FIA- Pain). Anxiety (AIMS2). Depression (CES-D). Helplessness. Coping (PMI). Self-efficacy (ASES).	3.7	3.7	Significant improvement of yoga group in pain, fatigue, sleep, depression, helplessness, coping, self- efficacy, memory, certain measurements of HRV and respiration compared to intervention group.	NA

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		4/weekly/8	G	Group Composition	3.5	3.4	(3 months)
Moioli et al. 2017	n=80 ≥ 18 years mean=55.5 Mixed (F=95%)	1) Training in autolytic induction and induction techniques, deepening techniques, construction of autolytic pain management process, practice of autolytic process. 2) Psychological coping programme: Chronic pain education, self-esteem, relaxation, emotional regulation, attention skills, assertiveness and social skills, cognitive restructuring, exercise activation, social support.	G	Generalised pain (WPI), Pain intensity, symptom severity (SS), FM impact and interference (FIQ), Health-related outcomes (SF-12), Emotional variables (POMS), Depression (BDI), Pain quality, emotional and total discomfort (SFMPQ), PGIC score.	3.5	3.4	Improvement of autolytic group in symptom severity, pain interference, tension, depression, emotional variables, but non-significant improvement compared to control group. No maintenance of improvements.
Miro et al. 2017	n=10 31-62 years mean=46.5 Female	Mindfulness-based intervention: information, body exploration, mindfulness around insomnia, acceptance and emotions, self-compassion, mindfulness around thoughts, life values and prevention of relapse.	G	None	NA	NA	Significant improvement in PSQI score, subjective sleep quality, pain catastrophizing, chronic pain self-efficacy, fibromyalgia impact and habitual sleep efficiency compared to baseline.

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Moñani et al. 2018	n=71 23-71 years mean=51.1 Mixed	Online Best Possible Self (BPS) intervention: multimedia content related to aspects regarding personal, social, professional and health domains defined by the patient.	It depends on the patient	I	Daily Active control condition	Depression (BDI-II). Positive and Negative Affect (PANAS). Optimism (LOT-R). Future Expectations (SPT). Self-Efficacy (GSES-12). Quality of Life (QLI-Sp). Interference (FIQ-R). Catastrophizing (PCS).	3.5	3.6	Significant improvement in depression, positive affect, self-efficacy compared to baseline.	(3 months) Significant improvement in negative affect, optimism, pain functioning.
Montero-Marin et al. 2018	n=42 18-65 years mean=51.5 Female	1. Attachment-based compassion therapy (ABCT): mindfulness visualisation and homework assignments + TAU 2. Relaxation	8/weekly/22	G	Group Comparison	Health status (FIQ). Clinical Severity (CGI-S). Pain Catastrophizing (PCS). Anxiety and depression (HADS). Quality of life (EQ-5D). Psychological flexibility (AAQ-II).	3.9	4.0	Significant improvement of ABCT group in FIQ variables, clinical severity, anxiety, depression, quality of life and psychological flexibility compared to relaxation group.	(3 months) Significant improvement of ABCT group in FIQ variables, clinical severity, anxiety, depression, quality of life and psychological flexibility compared to relaxation group.
Montes-Curó et al. 2015	n=66 18-62 years mean=58.9 Mixed (F=96.9%)	1) Group Problem-Solving Therapy (GPST): identifying problems, solutions and negative feelings. 2) GPST + Cervical infiltration with botulinum toxin.	4/weekly/8	G	Cervical infiltration with botulinum toxin.	Health outcomes, anxiety and depression (EQ-5D). Suicidal risk (Painik suicide risk scale). Quality of pain experience (VAS). Nocturnal sleep and daytime drowsiness (SCOPA). Satisfaction.	NA	NA	Improvement in health status of all three groups compared to baseline. Significant improvement of group 2 in risk of suicide. Improvements in suicidal thoughts with the combination of the two therapies (infiltration + GPST) compared separately. Improvement in anxiety and depression in group 2.	NA

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Moontes-Carnó et al. 2018	n=44 mean age =61.1	Group Problem-Solving Therapy (GFST): identifying problems and solutions, negative feelings and effectiveness of GFST.	24-/weekly/48	G	None	Identification of problems and the solutions.	3.2	3.4	Relation to trauma in the past. Identification of the solutions.	NA
Misicki et al. 2019	n=583 mean age=52 Mixed (F=94%)	+ CBT-I: cognitive techniques and relaxation strategies to minimize the impact of night-time awakenings. + CBT for pain	NA	G	TAU	Acisographic: Total sleep time (TST); Sleep onset latency (SOL); Wake time after sleep onset (WASO); Lowest sleep efficiency (SE); Polysomnograph y (PSG), Sleep diaries. Questionnaires. Tender point testing.	3.2	3.4	Improvement of CBT-I group in objective measures in sleep were uniformly reflected by the different assessment methods. Significant improvements of CBT-I in all parameters of sleep diaries (subjective experience of poor sleep).	(6 months) Improvement of CBT-I in objective measures in sleep were uniformly reflected by the different assessment methods.
Misicki et al. 2019	n=583 mean age=52 Mixed (F=94%)	Educational manual-based programme: diagnosis and treatments of FMS, coping strategies for pain and stress, promotion of physical exercise, self-management and action planning + medical treatment, exercise therapy, health education, psychological support, relaxation and social counselling.	6/NA/9	G	TAU	Disease and treatment-specific knowledge (self-developed questionnaire). Self-management competencies and satisfaction (PerQ). Psychological distress (PHQ-4). Health impairment (FIQ-G).	3.5	3.7	Improvement in disease and knowledge compared to control group. Significant improvement in self-monitoring and insight, pain-related content, communication about the disease and action planning for physical activity.	(12 months) Significant improvement in knowledge, self-estimated knowledge and satisfaction with knowledge compared to control group.

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<p>Patra-Delegado et al. 2013</p> <p>n=31</p> <p>30-77 years mean=52.6</p> <p>Female</p>	<p>Mindfulness-based cognitive therapy (MBCT): medication and cognitive restructuring techniques.</p>	<p>8/biweekly/20</p>	<p>G</p>	<p>TAU</p>	<p>3.8</p>	<p>3.8</p>	<p>(3 months)</p> <p>Maintained improvements in FIQ score and depressive symptoms.</p>
<p>Perrez-Aranda et al. 2019</p> <p>n=204</p> <p>18-65 years mean=53.4</p> <p>Mixed (F:98%)</p>	<p>1) Mindfulness-Based Stress Reduction for Fibromyalgia (MBSR)</p> <p>1) TAU</p> <p>2) Multicomponent intervention (FibroQoL).</p>	<p>8/weekly/16</p>	<p>G</p>	<p>TAU</p>	<p>3.7</p>	<p>3.8</p>	<p>(12 months)</p> <p>Significant improvement in health-related quality of life of both groups MBSR and FibroQoL compared to TAU group.</p> <p>Significant reductions in costs of MBSR compared to FibroQoL and TAU groups.</p>
<p>Pires et al. 2016</p> <p>n=9</p> <p>38-64 years mean=53</p> <p>Female</p>	<p>Pain neuroscience education (PNE) programme: complex contents that do not take into account memory and concentration problems + Individualized exercise programme (aerobic exercise, motor control training and aquatic exercise).</p>	<p>NA</p>	<p>G</p>	<p>None</p>	<p>NA</p>	<p>NA</p>	<p>(6 months)</p> <p>Improvement in pain intensity (NRS) in 5 patients.</p> <p>Improvement in PGCS in 7 patients.</p>

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Racine et al. 2019	n=178 ≥ 18 years Mixed	Activity pacing CBT treatments: 1) Operant Learning: from pain-contingent to goal-directed behaviour + Exercise 2) Energy conservation: accomplishing day-to-day valued activities/goals and resting to reduce pain and fatigue + Exercise	11/weekly/22	G	No treatment	Pain (BPI), Fatigue (BFI), Pain and fatigue interference (BPI), Physical function and psychological function (SF-36), Sleep quality (MOS), Depression and anxiety (HADS).	3.5	3.4	3 months	Significant improvement of OI, group in depressive symptoms compared to EC group. Significant improvement of both groups in sleep quality and physical function, pacing and overtraining activity patterns. Maintained improvement of both groups in pain interference, fatigue and depressive symptoms. Maintained improvement of both groups in sleep quality and physical function.
Romeyk et al. 2018	n=1 64 years Female	Interdisciplinary assessment-oriented treatment. Psychotherapy: shifting attention, building up activity levels and providing information about pain. Pain management group: relaxation, cognitive behavioural therapy and management strategies + Physical therapy and physiotherapy, exercise, complementary medicine, detoxifying procedures, holistic massage and nutrition therapy.	17/daily/NA	I + G	None	Impairment of well-being, impairment of the body and sleep (VAS), Pain intensity and pain threshold (VAS average and max), Depression (PHQ-D), Physical function (FFMH), Subjective pain-related impairment (PDI).	NA	NA	(18 months)	Improvement in pain symptoms, sleep quality, pain intensity, impairment by general symptoms, functional capacity. Improvement in pain threshold, VAS average, VAS max and physical function.

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			G	TAU				
Szalai et al. 2016	n=66 25-60 years mean=41.7 Female	Interdisciplinary treatments: 1) Long-term (LG) treatment: short CBT, education, exercise training 2) Short-term (SG) treatment: long CBT, education, exercise training	1) LG: 10/weekly/30 + 1 educational day 2) SG: 2/once/NA (intensive)	TAU	Pain, fatigue and sleep (VAS). Number of tender points, pressure pain threshold, physical functioning and general health assessment (FIQ). Depression (BDI), Health-related quality of life (SF-36).	3.9	3.9	NA Significant improvement in pain intensity, tender point numbers, increasing pressure pain threshold levels, controlling disease activity. Significant improvement of LG group in fatigue and physical components (HRQL).
Scheidt et al. 2013	n=46 18-70 years mean=48.7 Female	Individual short-term psychodynamic psychotherapy (ASTPP); dysregulation model of psychosomatic illness attachment styles and affect regulation in somatoform disorder.	25/weekly/≈25	TAU	FIQ score. Depression (HADS). Psychological distress (SCL-27-plus). General symptom score (GSI). Pain Disability Index (PDI). Health-related QoL (SF-36).	3.9	3.9	Improvements in FIQ score, depression, anxiety, pain-related quality of life and somatoform symptoms compared to baseline. Improvement in FIQ score.

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Simister et al. 2018	n=67 18-64 years mean=39.7 Mixed (F=95%)	Online ACT: written unit readings, mp3 audio recordings, videos and experimental homework exercises + TAU	7/NA/NA	I	TAU	3.8	3.8	Significant improvement in FM impact compared to control group. Significant improvement in pain interference, pain-related psychological inflexibility, pain acceptance, depression, pain and kinesiophobia.	(3 months) Significant improvement in FM impact and cognitive fusion compared to control group. Maintained improvement in pain acceptance.
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Steiner et al. 2013	n=28 18-65 years mean=49.4 Female	1) ACT: conceptualisation, unwanted emotions, cognitive defusion, values and commitment. 2) FM education	8/weekly/8	G	Group Comparison	3.3	3.2	Significant improvements of both groups in family compared to baseline. Significant improvement of ACT group in intimate relations compared to baseline.	(12 weeks) Significant improvement of both groups in family compared to baseline.
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Thieme et al. 2016	n=145 21-67 years mean=47 Female	1)OBT: Operant behavioural therapy: video feedback and contingent positive reinforcement of pain behaviours. 2)CBT: patient's thinking, problem-solving, stress, coping strategies and spouse response.	15/weekly/30	G+I	1)Whole-body infrared heat (IH). 2)Pain-free controls	Surface electro-myogram (EMG). Diastolic blood pressure (DBP). Systolic blood pressure (SBP). Heart rate (HR). Skin conductance levels (SCL).	3.8	3.8	Significant improvement of OBT and CBT groups in EMG compared to control groups. Significant improvement of CBT group in HR and SCL compared to all the other groups. Significant improvement of OBT group in DBP.	(12 months) Significant improvement of OBT and CBT groups in EMG compared to control groups and post-treatment results. Significant improvement of CBT group in HR and SCL compared to all the other groups. Significant improvement of OBT group in DBP.
Torres et al. 2018	n=56 35-65 years mean=51.3 Female	Group Music and Imagery Intervention GpMI: verbal dialogue, relaxation and induction, active music listening, creative drawing, verbal reflection.	12/weekly/24	G	No treatment	Psychological well-being (PWS). Functional capacity and health (FIQ). Pain (MPQ). Anxiety (STAI). Depression (SI/DEIP).	3.9	3.9	Significant improvement in psychological well-being, functional capacity, health, pain perception, anxiety and depression compared to baseline.	Significant improvement of OBT group in DBP. Significant improvement in psychological well-being, functional capacity, health, pain perception, anxiety and depression compared to baseline. Maintained improvement in functional capacity, health, pain perception, anxiety and depression compared to baseline and control group.
Toussaint et al. 2014	n=13 30-55 years mean=47 Female	Forgiveness education: definition and discussion of forgiveness, emotion-focused coping strategies brief exercises of letting go, deeper breathing, feeling gratitude and a question-and-answer session.	2/NA/25	G	Note	Psychological distress, participant engagement, observed emotion (fearfulness, use of facial tissues), and overall energy in the room (sense of passivity participating) (Observational Scale).	NA	NA	Beneficial behavioural observations in relation to psychological distress. Comfort, satisfaction and benefits of learned coping strategies and information related to chronic pain (reported by the patients).	NA

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Vallejo et al. 2015	n=60 ≥ 18 years mean=55.5 Female	1) Internet-delivered CBT (iCBT): written and graphic content, suggested activities, relaxation exercises, individual and feedback messages 1) TAU 2) Conventional face-to-face CBT.	10/weekly/NA	I	Waiting List	Daily functioning (FIQ). Psychological distress and cognitive variables (PCS). Depression. Self-efficacy and coping strategies (CPSS).	3.9	3.9	Significant improvement of CBT group in FM impact compared to all the other groups. Significant improvement of iCBT and CBT groups in psychological distress, depression, catastrophizing, relaxation coping strategies compared to waiting list.	(12 months) Improvement of iCBT group in FM impact and catastrophizing compared to post-treatment scores.
Van Den Hoona et al. 2017	n=153 Mixed (F=88.2%)	Multidisciplinary group programme: psychoeducation (interactions between psychological and social factors and physical complaints) and psychomotor therapy (regaining trust in the body) + Physiotherapy and occupational therapy.	12/3-weekly/92	G	None	Pain disability (PDI), Physical functioning (SF-36), Pain severity and functional interference (MDI-DIV), Anxiety and depression (HADS), Kinesiophobia (Tampa Scale of Kinesiophobia).	2.8	3.1	Significant improvement of iCBT group in self-efficacy compared to control groups. Moderate improvement in pain disability, physical function, pain severity and functional interference.	(12 weeks) Maintained moderate improvement in pain disability, physical functioning, pain severity and functional interference.
Van Eijk-Hoisinga et al. 2013	n=203 18-65 years Mixed (F=86.29%)	Multidisciplinary Intervention. Information, rational emotive therapy, transactional analysis + Socioterapy, physiotherapy and arts therapy.	48/-/-/≈122.5	G + I	1) Aerobic exercise 2) TAU	Health-related quality of life (EQ-5D), Impact of fibromyalgia (FIQ).	3.6	3.6	Significant improvement in health-related quality of life.	(24 months) Nonsignificant group differences.

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Author	n	Intervention	Frequency	Group	Comparison	Overall impact	Duration	Outcomes
Van Groenou et al. 2017	n=128 18-65 years mean=46.8 Mixed (F=62%)	1) Second generation mindfulness-based intervention (SG-MBI): taught presentations, guided meditations, group discussions, guided meditation and/or mindfulness exercises, and one-to-one sessions. 2) Cognitive Behavioural Theory for groups (CBTG).	8/weekly/16	G+I	Group Comparison	Overall impact (FIQ), Pain (SF-MQP), Psychological distress (DASS), Sleep quality (PSQI), Attachment to (NAS).	3.7	3.7 Significant improvement of SG-MBI group in pain perception, sleep quality, psychological distress, non-attachment, civic engagement. Maintained results (and in some cases slightly augmented).
Verhaak et al. 2014	n=65 22-76 years mean=47.4 Mixed (F=98.5%)	1) Guided Imagery: relaxation techniques, music, positive imagery and specific pain-related elements 2) Only group discussion	2//NA/≈3.5	G	Group Comparison	Pain (NAS), Functional status (FIQ), Self-efficacy (CPSS).	3.9	3.9 Nonsignificant improvements. Nonsignificant improvements.
Vincent et al. 2013	n=7 38-72 years mean=55.5 Mixed (F=85.7%)	Multidisciplinary fibromyalgia clinical programme: cognitive behavioural therapy, activity pacing, graded exercise therapy.	NA	G	None	Pain (FIQ, SF-36), Mental and physical components (SF-36), Fatigue (MFSI-SF), Self-efficacy (CPSS).	2.6	2.9 Improvements of 6 patients in self-efficacy, fatigue and physical component. Improvement in 6 patients in self-efficacy, fatigue and physical component. Improvement in all patients in mental component.

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Wicksell et al. 2013	n=40 18-55 years mean=45.1 Female	ACT: discussing and preparing for behavioural change, shifting perspective from personal values, values-oriented behaviour activation, activation and cognitive defusion.	12/weekly/18	G	Waiting List	Pain disability (PDI), FM impact (FIQ), Health-related quality of life (SF-36), Self-efficacy (SES), Depression (BDI), Anxiety (STAI), Pain intensity (NRS), Psychological inflexibility (PIPS).	3.6	3.8	Significant improvement in pain disability, FM impact, mental health, quality of life, self-efficacy, depression, psychological inflexibility and anxiety.	(3 months) Significant improvement in pain disability, FM impact, mental health, quality of life, self-efficacy, depression, psychological inflexibility and anxiety.
Zabihye gneh et al. 2019	n=33 18-64 years mean=46.4 Female	CBT: identification of troublesome situations, interactions, thoughts, emotions and behaviours, identification of irrational beliefs and patterns, restructuring irrational beliefs.	20/biweekly/40	G	Waiting list	Pro-inflammatory cytokine levels (circulating IL-6, IL-8, and TNF- α level), FM impact (FIQ), Widespread pain (WPI), Depression (BDI-II), Anxiety (BAI-II).	3.7	3.8	Significant changes of pro-inflammatory cytokine levels (serum concentration of IL-6, and IL-8). Improvements in FM impact, widespread pain.	NA

4. Discussion

This work allowed us to know in detail the characteristics of the research aimed at verifying the effectiveness of different psychological techniques in patients with fibromyalgia carried out from 2013 to 2019 inclusive.

These new data allow us to shed light on strengths and weaknesses regarding research methodology. This also provides evidence in relation to applied techniques and how they are implemented. Finally, it contributes to knowing the effectiveness of the interventions. Likewise, when comparing our results with those of the last review, our results allow us to observe whether there is any change in research topic trends.

4.1 Participants

Samples of the review studied present a majority of females and a mean age of 50.6 years, all of them being between 18 and 65 years old. This tendency coincided with similar characteristics included in other reviews regarding psychological treatments and FM (Glombiewski et al., 2010; Lami et al., 2013). In particular, Glombiewski et al. (2010) found that 92% of the sample was female. FM is more common in women and frequently appears to start between 32 and 55 years old. Overall, FM characteristics endure over time. Therefore, the studies presented in this review considered samples representative of the study population.

4.2 Design

This review presents a higher number of experimental designs compared to the previous review (Lami et al., 2013) (78.8% and 46.4%, respectively). This therefore seems to be an improvement in terms of methodology.

In relation to follow-up frequency and duration, we found that approximately 20.8% of the studies included 6-month follow-up, whilst Lami et al. (2013) found 6-month follow-up in 28% of the studies. Long-term evaluations (12-month follow-up) remain similar in comparison to Lami et al. (2013) review (19% and 18%, respectively). More long-term assessments are required in order to obtain substantial results.

4.3 Outcome measures

Our results seem to be in line with Lami et al. (2013) conclusions. Most interventions in the present review focused on pain outcomes (65%), concurring with Lami et al. (63.8%). Depression (45.8%) and anxiety (34.7%) also seem to be the most analysed psychological variables, similar to depression (41.4%) and anxiety (25.9%) in the previous review. In relation to pain-related psychological variables, catastrophising was assessed in 15.3% of the studies

(compared to 10%), and both coping skills and self-efficacy in 23.6% (compared to 13.8% and 5.17%). Lami et al. (2013) reported that assessment of these variables was insufficient. According to our findings, it seems that assessment of pain-related psychological variables is steadily increasing, albeit at a slow pace. Taking into account the influence of these variables on chronic pain recovery (Söderlund et al., 2017) further research regarding pain-related psychological variables is required.

4.4 Interventions

CBT was the most implemented treatment (50%), equivalent to the previous review which found that 48% of the studies implemented CBT interventions (Lami et al., 2013). Multicomponent programmes also remain similar in our review: 18% of the studies compared to 19% of the studies with multimodal interventions found in Lami et al. (2013). ACT and mindfulness-based interventions significantly increased in number. ACT was found in 8.3% of the studies compared to 1.7% in the previous review. Likewise, Mindfulness-based interventions were found in 11% of the studies compared to 5.17% in the previous review. Therefore, while there is no significant increasing tendency in CBT and multicomponent programmes, it does appear to be a rising trend in ACT and mindfulness-based interventions.

Relaxation interventions as the main intervention were found in 1 study. However, relaxation was part of the intervention in 55% of the studies. This high percentage is similar to Lami et al. (2013) review in which relaxation techniques can be found in 53.4% of the studies. These numbers show the importance attributed to relaxation procedures since long ago and the continued use over the last few years, probably due to their effectiveness.

Another 13 studies were conducted with other types of interventions. For instance, a psychodynamic intervention was carried out in one study but was not present in Lami et al. (2013). Also, the present review found 5 studies described as psycho-education interventions, whilst Lami et al. (2013) cite 3. On the other hand, the past review included 7 studies with Biofeedback, whereas the present review presented one only biofeedback intervention together with CBT.

Finally, when comparing our review with Lami et al. (2013) review, alternative approaches for FM treatment related to emotional aspects seem to have emerged over the past six years. These include Emotional Expression Acknowledgment and Exposure (EEAE), Best Possible Self, Time In, Rational Emotive Therapy together with Transactional Analysis, Forgiveness Education and psychotherapy together with spiritual care.

In the present review, education was cited in 37 studies. This differs from the past review which indicates the specific presence of psychoeducation in almost all studies. This could be due to a

lack of citation and description rather than to a lack of education-related aspects in the current studies.

In relation to the modality of the interventions, 79% of the studies presented in the review involve a group treatment, of which a few were combined with individual intervention. When comparing this with Lami et al. (2013) review, which presented 65.5% of the interventions with a group modality, the growing trend of group interventions can be observed. This past review does not describe mixed modalities, with individual and group treatments, whereas we found some studies which presented mixed interventions (13.9%).

In relation to mean total treatment duration, this is 20.30 hours and is similar to Lami et al. (2013), who estimated 24.61 hours in their review. Regarding frequency of treatment, 52.28% of the studies performed weekly sessions, also a very similar percentage to Lami et al. (2013), who counted 55.17% of studies performing weekly sessions.

Regarding intervention setup, 4 studies administered virtual reality together with group therapy or online configuration. On the other hand, Lami et al. (2013) do not describe any study using virtual reality. This review found that 1.4% of studies described telephone treatments and 9.7% of the studies implemented online interventions, while Lami et al. (2013) found telephone treatment in 1.7% and online interventions in 5.1% of the studies. Online treatment seems to target the population with logistic barriers, such as timing, travel or access inconveniences in rural areas, and it is steadily increasing with encouraging results. Bernardy et al. (2018) carried out a systematic review and meta-analysis of internet-based cognitive behavioural therapies for FM patients and concluded that these therapies could be useful in graded implementation for mild to moderately affected patients.

4.5 Effectiveness

In this review, we found that CBT was followed with a high percentage of beneficial outcomes related to pain, similarly to Lami et al. (2013). Also, our results are in line with other recent systematic reviews related to CBT in FM, which conclude that CBTs were superior to controls (treatment as usual, other active non-pharmacological treatments, waiting list) in pain relief (Bernardy et al., 2018).

There were 7 studies related to mindfulness interventions; however, several variables were not frequently measured. This makes the task of comparing results complicated. Pain-related psychological variables (coping skills and catastrophising) were assessed in 2 studies. Despite an overall lack of values for a conclusive verdict, our results suggest that mindfulness might be beneficial in sleep-related problems, improving the impact of the disease, depression and anxiety

symptoms, and quality of life. Lakhan & Schofield (2013) carried out a meta-analysis regarding somatisation disorders (included FM), in which they concluded that mindfulness interventions showed a small to moderate positive effect on pain, depression, anxiety and quality of life. Our results also agree with Lauche et al. (2013) who highlighted the need for further high-quality RTCs for a compelling conclusion. The authors also pointed out the need to select custom outcomes such as awareness, acceptance or coping.

Concerning guided imagery therapies, Meeus et al. (2015) carried out a systematic review which found that most of these techniques demonstrated moderate evidence for pain effects. This differs from our results from two guided imagery studies which indicated successful pain outcomes. However, the authors pointed out the need for re-evaluation of relaxation formats and visualisation content.

We found ACT to be a promising intervention for several variables such as fatigue, quality of life, depression, anxiety and psychological flexibility. Pain improved in 75% of the studies assessing the variable (4 studies). In accordance with our results, other recent reviews such as Simpson et al. (2017) also concluded that ACT was promising as a therapeutic treatment for non-malignant chronic pain.

In accordance with Merlo (2019), all this data represents a significant progress in the role of psychological approaches in the integration of clinical practice. However, it seems difficult to state that one intervention is more effective than others. In fact, among the studies included in this review, when comparing outcome differences between two different psychological interventions, most studies do not conclude the superiority of one over another (Chouchou et al., 2018; Kohl et al., 2014; Lumley et al., 2017; Miles, 2013; Moiola, 2017).

Difficulties in determining the effectiveness of each therapy are also due to the fact that the composition of each intervention presented in this review does not seem to be entirely independent from the others. For instance, CBT incorporated a variety of elements (mindfulness techniques, or life and values components, among others), mindfulness generally involved acceptance among other exercises, and most multidisciplinary programmes are commonly made up of several other types of interventions besides CBT (e.g., stress management). Therefore, we think that attributing the effectiveness to one intervention model might be inaccurate.

4.6 Common factors and mediator variables

The present review allowed us to carry out a panoramic overview of the type of psychological interventions implemented in fibromyalgia and the benefits obtained from them. This panoramic view displays a greater amount of heterogeneity. That is to say that diverse

psychological interventions are implemented and the results do not seem to depend directly on the type of intervention. In other words, it does not seem to be a superior technique in terms of effectiveness. This is along the same lines as the APA conclusions (2013) after comparing different psychotherapeutic models. *"In contrast to large differences in outcome between those treated with psychotherapy and those not treated, different forms of psychotherapy typically produce relatively similar outcomes"*.

When trying to bring order, it is perceivable that overall intervention groups achieve greater improvements than passive control groups, regardless of the intervention implemented. This leads us to conclude that different therapies, although coming from different theoretical frameworks, share factors in common and that these are closely related to patient improvement. As a matter of fact, there is an increasing amount of evidence analysing these common factors (Laska et al., 2014). Therapeutic alliance, expectations and empathy are possible variables that can be found transversely in any technique analysed in our review and might be responsible for effectiveness. Unfortunately, due to the difficulty in operating and quantifying these variables, they are not usually studied.

A similar concept to common factor is mediator variable. As we know, this refers to those variables that act as a "bridge" and lead to benefits. In this case, they would be variables manipulated through the intervention that leads to pain relief. There are therefore more hypotheses than results. Several authors point to behavioural and/or cognitive variables as important mediators in pain management (Söderlund et al., 2017). Karlson et al. (2015) identified developing individual coping strategies as an essential part of pain improvement with CBT. Cash et al. (2015) suggested that mindfulness may improve perception of symptom control. Montesó-Curto et al. (2018) highlighted the importance of enhancing adaptive behaviours leading to improvements in self-management through a group problem-solving therapy. However, these hypothetical mediator variables depend on a specific theoretical frame which prevents a common theory from being reached explaining how therapies obtain their benefits.

When analysing the interventions from the present review, we found two transversal elements across several treatments: relaxation and education. This led us to think that, beyond the specific theoretical frame, there are two mediator variables: relaxation as a state, and patients' pain-related knowledge. In other words, relaxation and pain-related knowledge might induce cognitive and behavioural changes.

With regard to relaxation, this seems to be associated with different labels. Several authors state that they implement relaxation techniques; however, these are described with different, specific terms. Regardless of the label, as mentioned above, relaxation strategies seem to be present in a

vast amount of studies in our review (55%). Also, Lami et al. (2013) pointed out that 53.4% of the studies included in their review incorporated relaxation components. The fact that relaxation is one of the most frequently used techniques led us to corroborate that relaxation as a state might be a possible mediator variable.

Regarding education, Lami et al. (2013) mentioned psychoeducation as one of the main common components in all interventions, being present in almost all treatments. In the present review, psychoeducation is present in a large proportion of interventions, but was not described in all treatments. Overall, psychoeducation aimed to inform the patient regarding psychological processes implicated in maintaining or aggravating pain experiences.

In terms of general patient education, 51.4% of the studies included some type of educational component. Some studies focused the research on specific educational barriers. These showed that cognitive aspects might lead to difficulties in understanding parts of the treatment and, consequently, might lead to impeding improvements in health outcomes. For instance, Castel et al. (2013) implemented an adapted multidisciplinary programme for low educational levels and demonstrated a reduction in key FM symptoms. Pires et al. (2016) pointed out memory and concentration problems as possible barriers for significant health changes in FM patients. In this last research, after implementing an adapted programme for patients with cognitive deficits, results proved the need for and success of an adjusted educational programme.

Other studies highlight the importance of pain-related educational aspects in order to achieve health improvements. These include not only educational components related to psychological processes (psychoeducation), but also education related to the syndrome's characteristics and physiology. Camerini et al. (2013) associated self-management and health outcomes with increased knowledge acquisition through a personalised, especially designed internet-based treatment. The authors found that increased knowledge about FM modified patients' amount of exercise; at the same time, it increased self-management and positively impacted patients' health status. Along the same lines, Butler & Moseley (2003) pointed out that learning about pain physiology reduces the threat value of pain, and consequently decreases the activation of protective systems diminishing pain triggers.

The divergent approaches and therapies that we analysed in our review are a mere reflection of the complexity of both the pain phenomenon and FM syndrome. We believe that emphasising transversal factors might help us to unify different perspectives.

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APPENDIX 2:
Cognitive restructuring and mindfulness training
combination effectiveness

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Effectiveness of two video-based multicomponent treatments for fibromyalgia: The added value of cognitive restructuring and mindfulness in a three-arm randomised controlled trial

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ABSTRACT

Background/objectives: The aim of this study was to examine the effectiveness of two video-based multicomponent programs (FIBROWALK) and the Multicomponent Physiotherapy Program (MPP) for patients with fibromyalgia (FM) compared to treatment-as-usual (TAU) only. We posit that FIBROWALK, due to inclusion of specific psychological ingredients (cognitive restructuring and mindfulness), can produce additional clinical benefits when compared to TAU or MPP alone.

Methods: A total of 330 patients with FM were recruited and randomly allocated (1:1:1) to TAU only, TAU + FIBROWALK, or TAU + MPP. FIBROWALK and MPP consisted of weekly videos on pain neuroscience education, therapeutic exercise and self-management patient education, but only the FIBROWALK intervention provided cognitive restructuring and mindfulness. Both programs were structurally equivalent. Between-group differences in functional impairment, pain, kinesiophobia, anxious-depressive symptoms and physical functioning were evaluated at post-treatment following Intention-To-Treat and complete-case approaches.

Results: Compared to TAU only, individuals in the FIBROWALK arm showed larger improvements in all clinical outcomes; similarly, participants in the MPP program also showed greater improvements in functional impairment, perceived pain, kinesiophobia, depressive symptoms compared to TAU only. The FIBROWALK intervention showed superior effects in improving pain, anxiety and depressive symptoms and physical functioning compared to MPP.

Conclusions: This RCT supports the short-term effectiveness of the video-based multicomponent programs FIBROWALK and MPP for FM and provides evidence that cognitive-behavioural and mindfulness-based techniques can be clinically useful in the context of physiotherapeutic multicomponent treatment programs.

Trial registration number: NCT04571528.

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1. Introduction

Fibromyalgia (FM) is a complex and highly prevalent disease (2–4% in the general population) characterized by widespread musculoskeletal pain, and often accompanied by symptoms of fatigue, sleep disturbance, cognitive problems, and psychological distress, which is usually diagnosed in women between the ages of 20 and 50 years (Häuser et al., 2015). People with FM typically present with comorbid psychiatric disorders, particularly major depressive disorder (63% of FM patients with lifetime depression) but also bipolar disorder, panic disorder, or post-traumatic stress disorder (Kleykamp et al., 2021; Lichtenstein, Tiosano, & Amital, 2018). These comorbidities, in turn, can aggravate the negative influence of pain on health-related quality of life (Galvez-Sánchez, Duschek, & Reyes Del Paso, 2019).

FM represents a great challenge for national health services because of the lack of curative treatment options. The efficacy of pharmacological approaches alone is generally limited, and more generalized clinical effects have been found for non-pharmacological interventions (Perrot & Russell, 2014). In response to the increased evidence of efficacy of non-pharmacological modalities, the 2016 revised European League of Association of Rheumatology recommendations point to the need to increase the implementation of non-pharmacological interventions gradually and sequentially in the treatment of FM (Macfarlane et al., 2017; Okifuji & Hare, 2010).

In this regard, education is a fundamental ingredient of many treatment programs for managing FM symptoms and is typically used as a first-line therapeutic option (Cunningham & Kashikar-Zuck, 2013). Increased knowledge about pain mechanisms and the FM diagnosis itself through education has been associated with positive effects in self-management skills and health outcomes in FM subjects (Camerini, Camerini, & Schulz, 2013; Mosekamp et al., 2019). Patients who are well-informed regarding their disease, prognosis and symptom-management strategies are better prepared to cope with the disease and thereby reduce its consequences (De Miquel et al., 2010). Furthermore, when comparing different types of pain education, there are clear differences between classical biomedical education (i.e., contents related to pathophysiology and biomechanics) and Pain Neuroscience Education (PNE) (i.e., contents related to pain neurobiology and pain processing). PNE is based on the reconceptualization of pain-related cognitive factors, within a biopsychosocial model, emphasizing that any evidence of danger or safety can increase or decrease the patient's pain experience (Moseley & Butler, 2015). A recent systematic review has supported the efficacy of PNE in people with chronic musculoskeletal pain in terms of improvements in pain catastrophizing, pain-related disability, inactivity, and avoidance behaviours (Lowe, Puentedura, Zimney, & Schmidt, 2016). Due to the mounting evidence of the beneficial effects of PNE in people with FM, it is progressively becoming a standard treatment modality for this population (Amer-Cuenca et al., 2020; Moseley, 2003).

It is also important to note that PNE might be more effective when combined with other techniques such as therapeutic exercise or cognitive behavioural therapy (CBT; Moseley et al., 2017). There is solid evidence that therapeutic exercise can result in significant improvements in core FM symptoms such as pain, depressive symptomatology, sleep, fatigue, global well-being, and health-related quality of life (Kundakci et al., 2021; Sosa-Reina et al., 2017). Frequently recommended exercises for FM include low-impact aerobic exercises, stretching, balance training, posture correction, and gentle strengthening exercises adapted to a patient's current physical state (e.g., Serrat, Almirall, et al., 2020).

Psychotherapeutic approaches have also been used for treating FM. A systematic review and meta-analysis found that psychological therapies for FM were associated with improvements in depression symptoms, catastrophizing, sleep disturbance, functional status, and short- and long-term pain reduction (Glombiewski et al., 2010). These outcomes were determined to be comparable to traditional FM treatment modalities, including pharmacological treatments. CBT demonstrated the

greatest effect sizes in this meta-analysis. A separate systematic review determined that CBT is the most common psychological intervention used for treating FM, both standalone and within multidisciplinary programs (Albajes & Moix, 2021). The efficacy of CBT has been demonstrated in many studies, resulting in treatment improvements in many core FM symptoms, including pain, fatigue, depression, psychological well-being, and physical functioning (Albajes & Moix, 2021; Bernardy, Klose, Welsch, & Häuser, 2018; Glombiewski et al., 2010; Kundakci et al., 2021; Macfarlane et al., 2017; Sosa-Reina et al., 2017). The American Psychological Association division 12 (Society of Clinical Psychology division of the APA) rated CBT interventions for FM as having strong research support (<https://div12.org/diagnosis/fibromyalgia/>).

In addition to CBT-based approaches, mindfulness training has been shown to be effective in people with FM (Haugmark, Hagen, Smedslund, & Zangi, 2019; Pérez-Aranda, Andrés-Rodríguez, et al., 2019). For instance, Mindfulness-Based Stress Reduction has demonstrated treatment improvements in functional impairment, anxiety and depressive symptoms in FM subjects (Pérez-Aranda, Feliu-Soler, et al., 2019). Mechanisms of this intervention seem to be related to a decreased pain catastrophizing and increased self-efficacy, pain acceptance and psychological flexibility (Pardos-Gascón, Narambuena, Leal-Costa, & van-der Hofstadt-Román, 2021; Pérez-Aranda, Feliu-Soler, et al., 2019; Turner et al., 2016). Though these treatments are traditionally provided face-to-face, these psychological approaches have shown positive results in online formats in individuals with FM (Bernardy, Klose, Welsch, & Häuser, 2019; Davis & Zautra, 2013).

In light of the above, PNE, therapeutic exercises, CBT-based techniques, and mindfulness training are the four non-pharmacological therapy approaches that have the most published evidence for FM management (Aman, Jason Yong, Kaye, & Urman, 2018). While the first two approaches are more in the area of physiotherapy, the others tend to belong to the field of psychotherapy. There is burgeoning interest in the scientific literature in integrating these therapies and evaluating the specific contribution of each one within chronic pain treatment programs (Conversano & Di Giuseppe, 2021; Merlo, 2019). In this regard, an interdisciplinary treatment approach, using multicomponent empirically validated therapeutic techniques within a biopsychosocial perspective, is considered the best treatment model for FM (De Miquel et al., 2010; Häuser, Bernardy, Arnold, Offenbächer, & Schiltenswolf, 2009; Macfarlane et al., 2017; Rivera et al., 2006). Multicomponent treatment approaches are recommended by most of national and international FM treatment guidelines (Rivera et al., 2006; Thieme, Mathys, & Turk, 2017). Although there is evidence that multidisciplinary approaches that integrate physiotherapy and psychology components can be superior to physiotherapy alone for subjects with general chronic pain conditions, this has not yet been fully evaluated in subjects with FM (Kemper et al., 2015; Wilson & Cramp, 2018).

FIBROWALK is a multicomponent treatment program, involving 2-h weekly sessions over 12 weeks, that was specifically designed for, and tested with, individuals with FM (Serrat et al., 2020a, 2021b). It involves five components, including PNE (sessions 1–10), therapeutic exercise (sessions 2–9), self-management patient education (sessions 2–9; 11–12), CBT techniques (cognitive restructuring; sessions 8–9; 11–12), and mindfulness training (sessions 2–9; 11–12) in a group-based format. Traditionally, physiotherapists have been responsible for PNE, therapeutic exercise, and self-management patient education and psychologists have been responsible for teaching CBT and mindfulness techniques. A previous randomised controlled trial (RCT) has shown that the FIBROWALK program (vs. usual care) was effective (with medium-to-large effect sizes) for significantly improving functional impairment, pain, kinesiophobia, physical function, fatigue, anxiety, and depressive symptoms in a sample of patients with FM (Serrat, Sanabria-Mnzo, et al., 2021).

Recently, a video-based version, including all FIBROWALK components, was adapted into a home-based format and tested in a pilot RCT

during the first Spanish COVID-19 lockdown (Serrat, Coll-Omaña, et al., 2021). The goal of this online version was to provide clinical support to patients with FM who were unable to attend face-to-face treatment. The online FIBROWALK program was found to be effective (with small-to-moderate effect sizes) for improving patient-reported functional impairment and other relevant FM symptoms (Serrat, Coll-Omaña, et al., 2021; Serrat, Sanabria-Mazo, et al., 2021). It is well known that efficacious online interventions have several advantages over face-to-face interventions, including cost, convenience, and availability for those patients with limited mobility and transportation options (Andersson, 2018; Andersson & Titov, 2014).

Determining the effects of specific physiotherapy and psychotherapeutic modalities can provide new clues for refining and improving treatment efficacy. Therefore, the primary aim of this RCT was to evaluate the effectiveness of two video-based multicomponent treatment programs for FM, one that integrated physiotherapy and psychotherapeutic modalities (i.e., FIBROWALK) and one that only used physiotherapy techniques (i.e., Multicomponent Physiotherapy Program; MPP), and to compare them to treatment-as-usual (TAU) only. Treatment effectiveness of the two programs was determined by improvements in patient-reported functional impairment (primary outcome), pain, anxious-depressive symptoms, kinesiophobia, and physical function. Our hypotheses were as follows: It was expected that both FIBROWALK and MPP arms, which were equivalent in terms of treatment dosage, would show greater improvements in primary and secondary outcomes when compared to TAU alone (hypothesis 1). Furthermore, it was expected that FIBROWALK would result in better improvement in anxiety and depressive symptoms compared to MPP because CBT and mindfulness techniques have been shown to have significant effects on these variables (Etzelmueller et al., 2020; Spijkerman, Pots, & Bohlmeijer, 2016) (hypothesis 2). In addition to assessing statistical significance, the number-needed to treat (NNT) index was computed to allow findings from this study to be more meaningful to clinicians. We expected a lower NNT in both active treatment arms when compared to TAU alone (hypothesis 3) as well as a lower NNT for FIBROWALK when compared to MPP (hypothesis 4). As far as we know, this was the first study to assess the unique contribution of cognitive restructuring and mindfulness training in a multicomponent treatment program for the management of FM.

2. Methods

2.1. Design

A three-arm randomised controlled trial (RCT) was carried out, with assessments at pre- and post-treatment. This RCT was approved by the Ethics Committee of Clinical Investigation (PR(AG)249/2020), posted and registered in [Clinicaltrials.gov](https://clinicaltrials.gov) (NCT04571528) and was conducted in accordance with the guidelines issued by the Consolidated Standards of Reporting Trials (CONSORT; Moher et al., 2012).

2.2. Sample size

The required sample size was estimated to be $n = 51$ participants per study arm, considering a moderate effect size (Cohen's $d = 0.50$) for the between-group differences at post-treatment for the primary outcome (i.e., Revised Fibromyalgia Impact Questionnaire total score) with an $\alpha = .05$ and power $1 - \beta = 0.80$. Expecting an attrition of at least 20%, the required sample size was nearly doubled so that small differences could be detected between the active treatment arms.

2.3. Participants

A total of 337 patients with FM participated in the study from September 2020 to January 2021. All participants were consecutively recruited from the Vall d'Hebron University Hospital - Central

Sensitivity Syndromes Specialised Unit and were assessed by a rheumatologist and a physical therapist to ensure they met the selection criteria. The inclusion criteria were as follows: (a) 18–75 years of age; (b) fulfilment the FM classification criteria according to 2010/2011 American College of Rheumatology (Wolfe et al., 2010), i.e., widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale score ≥ 5 or WPI 3–6 and SS scale score ≥ 9 , symptoms have been present at a similar level for at least 3 months, and the patient does not have a disorder that would otherwise explain the pain; (c) being able to understand Spanish; and (d) written informed consent. Individuals participating in concurrent or past RCTs (during the previous year) or suffering any comorbidity such as severe mental disorders (i.e., psychosis) or neurodegenerative diseases (i.e., Alzheimer) that would have limited the ability of the patient to participate in the RCT were excluded.

2.4. Procedure

The study was carried out in the context of routine clinical practice at the Vall d'Hebron University Hospital - Central Sensitivity Syndromes Specialised Unit. That is, all participants were provided by their rheumatologist with an overview of the study aims when they visited the hospital. COVID safety measures were followed. Participants were told that they would receive a potentially effective treatment in addition to the usual one that the Unit usually provides. Those interested in participating signed informed consent and were told that their data would be used in this study. Participants were informed about their right to withdraw from the research at any time, with the assurance that they could continue to receive usual care. They were asked to complete an online questionnaire, gathering sociodemographic and clinical information, and all study outcome measures. The online measures were completed both at pre- and at post-treatment.

Participants who voluntarily agreed to participate in the study were assigned to an alphanumeric code list and were randomised (1:1:1 ratio) using SPSS v25 to receive either TAU only, TAU + video-based FIBROWALK or TAU + video-based MPP. Numbered sealed envelopes which included information sheets related to participant allocation were used within the randomization process. The envelopes were distributed by a nurse from the Vall d'Hebron University Hospital - Central Sensitivity Syndromes Specialised Unit. Neither the participants nor the therapist responsible for the treatments were blinded to the participants' allocated intervention. However, the nursing staff who coordinated the online assessments were blinded to the participants' treatment allocation.

2.5. Treatment interventions

Both FIBROWALK and MPP were delivered as add-ons to TAU. Subjects participated in no additional treatments during the study. TAU care in the Vall d'Hebron University Hospital - Central Sensitivity Syndromes Specialised Unit included: (a) prescribed medications for FM (i.e., amitriptyline, duloxetine, pregabalin and/or tramadol at low doses) adapted to each patient's needs and (b) written advice on PNE and aerobic exercise adapted to the physical capacities of the patients. Subjects in the TAU group were offered the opportunity to participate in the FIBROWALK program upon study completion.

The video-based FIBROWALK program consisted of weekly 60-min videos that were presented over the course of 12 weeks. Subjects participated in the virtual training from home. Each video was comprised of different components of the program. The FIBROWALK intervention included PNE, therapeutic physical exercise, Self-management Patient Education, CBT techniques (mainly cognitive restructuring), and mindfulness training. PNE was based on the book "Explain Pain" (Moseley & Butler, 2017) and was the essential constituent that directed the approach taken by all the procedures involved in FIBROWALK. Therapeutic physical exercise interventions were designed from the recommendations of the American College of Sports Medicine

and were taught from the same procedures described elsewhere (Serrat, Sanabria-Mazo, et al., 2020). The Self-management Patient Education was comprised of different educational components aimed at teaching patients how psychosocial stressors can impact pain perception and ways of managing symptoms and improving health and well-being. Specifically, patients were taught strategies for increasing activity, improving sleep quality, increasing autonomy, coping better with stress and other FM symptoms, enhancing treatment adherence, preventing relapses/aggravations, and developing a greater ability to live a meaningful life despite pain. CBT techniques, mainly cognitive restructuring, were introduced for improving mood, reducing anxiety, enhancing adaptive emotional regulation responses, reducing catastrophic thinking about pain, and promoting positive behaviour changes towards a healthier lifestyle. Patients were taught how to identify automatic negative thoughts and to challenge them with more rational responses, including recognizing and removing cognitive biases and correcting false beliefs and assumptions. Mindfulness training included meditation practices based on Mindfulness-Based Stress Reduction (Kabat-Zinn, 2013). This training was aimed at changing the relationship with one's thoughts (to accept thoughts nonjudgmentally without trying to change their content) in order to foster alternative and healthier ways of relating and responding to personal life challenges, including chronic pain. For a more detailed description of the FIBROWALK contents, see the supplementary tables (Supplementary Tables S1 and S3).

Participants allocated to the video-based MPP training received all aspects of the FIBROWALK arm except for cognitive restructuring and mindfulness training. The length of time spent on each component of the MPP training (including PNE, therapeutic physical exercise therapy, and self-management patient education) was slightly longer compared to those in the FIBROWALK in order to match the overall treatment doses of 1 h per week for 12 weeks between the two active arms. See Supplementary Tables S2 and S3 for more details.

To verify that participants adhered to FIBROWALK and MPP interventions, participants were asked to complete a brief online questionnaire (5–10 items) every week. This questionnaire asked for verification of follow-through with homework exercises (e.g., meditation practices, guided relaxation exercises, therapeutic exercise recommendations) and for one's understanding of very basic concepts explained in the videos (e.g., "Please, provide a short example of a catastrophic thought"). These weekly questionnaires were used for the early detection of potential adherence issues (e.g., not watching the videos, not doing the homework) as well as to prevent potential dropouts. The first author (MS) supervised all participants and provided remote guidance. She is both a physical therapist (>17 years of experience) and a health psychologist (>8 years of experience). In addition, she has also been trained in CBT and mindfulness. Every week, the therapist (MS) contacted (via SMS and/or telephone calls) those participants who did not answer the questionnaire or reported issues with participation (e.g., not being able to do the homework, watch the videos, answer the questionnaire, etc.) and helped them develop solutions for enhancing adherence. If necessary, individuals who were unable to view or answer the questionnaire in a specific week could request an extension of the date. There was no therapeutic interaction with the participants, but participants were invited to contact the therapist by email if they experienced any problems. Approximately 24 h of clinician time was spent on the guidance of both interventions (i.e., FIBROWALK and MPP).

2.6. Study measures

A sociodemographic and clinical ad-hoc questionnaire was used. It collected information about age, gender, educational level, employment situation, living arrangement (alone/accompanied), civil status, height and current weight (for calculating body mass index), illness self-perceived start/duration, incapacity certificate (indicating level of incapacity if affirmative), and diagnosis of chronic fatigue syndrome by a rheumatologist (yes/no).

2.6.1. Primary outcome

The *Fibromyalgia Impact Questionnaire Revised* (FIQR; Bennett et al., 2009) was used to assess the functional impairment experienced by participants during the previous week. The FIQR includes a total of 21 items, scored on a 0–10 numerical scale, which are distributed into three dimensions: physical dysfunction (ranging from 0 to 30), overall impact (ranging from 0 to 20), and intensity of symptoms (ranging from 0 to 50) with a total possible score of 100. Higher scores indicate greater functional impairment. The Spanish version of the FIQR has demonstrated satisfactory internal consistency (Luciano, Aguado, Serrano-Blanco, Calandre, & Rodríguez-Lopez, 2013; Cronbach's $\alpha = 0.91$); in our sample, the internal consistency of the FIQR was found to be excellent ($\alpha = 0.94$).

2.6.2. Secondary outcomes

The *Visual Analog Scale* (VAS) for pain (i.e., intensity of perceived pain during last week, from 0 = "no pain", to 10 = "unbearable pain") from the FIQR was used to assess pain intensity (Bennett et al., 2009).

The *Tampa Scale for Kinesiophobia* (TSK; Miller, Kori, & Todd, 1991) was used to assess fear of movement. This scale comprises 11 items which are scored with a 4-point Likert scale (total score ranging from 11 to 44). Higher scores are indicative of greater pain and fear of movement. The Spanish version of the TSK has demonstrated satisfactory internal consistency ($\alpha = 0.79$; Gómez-Pérez, López-Martínez, & Ruiz-Párraga, 2011). The α for the TSK was 0.89 in our sample.

The *Hospital Anxiety and Depression Scale* (HADS; Zigmond & Snaith, 1983). It includes two main dimensions (anxiety and depression), with 7 items each, which are scored with a 4-point Likert scale. The scores of the HADS subscales range from 0 to 21 with higher scores reflecting higher symptom severity. The Spanish version of the HADS has demonstrated satisfactory internal consistency for anxiety ($\alpha = 0.83$) and depression ($\alpha = 0.87$) subscales (Luciano, Barrada, Aguado, Osma, & García-Campayo, 2014). In this work, the α was 0.84 and 0.86 for HADS-A and HADS-D, respectively.

The *Physical Function subscale from the 36-Item Short Form Survey* (SF-36; Ware & Sherbourne, 1992) assessed perceived level of physical functioning. This subscale includes 10 items, each scored with a 3-point Likert scale. Total scores are transformed to obtain scores that can range from 0 to 100, with higher scores indicate better physical functioning. The Spanish version of the physical function SF-36 subscale has shown satisfactory internal consistency ($\alpha = 0.94$; Alonso, Prieto, & Antó, 1995). The α in our sample was .84.

2.7. Statistical analysis

All study outcomes were analyzed with descriptive statistics and expressed as means and standard deviations (SD) for quantitative variables, and percentages (%) and frequencies (f) for categorical variables. The Levene test was used to evaluate the equality of variances of continuous variables, and Kolmogorov-Smirnov was used to verify sample normality and distribution.

Baseline between-group differences were calculated for both continuous and categorical variables. MANOVA was used to assess baseline differences in continuous variables, whereas the χ^2 test was applied for categorical variables.

An analysis of covariance (ANCOVA), considering baseline values as a covariate, was conducted to analyse between-group differences at post-treatment in all study outcomes. The ANCOVA has shown greater power to discern changes than analyses of variance (ANOVA) in randomised study designs (Van Breukelen, 2006).

Taking an Intention-To-Treat (ITT) approach as reference, all outcomes were analyzed using Multiple Imputation (Jakobsen, Gluud, Wetterslev, & Winkel, 2017). Five imputations of all outcome variables were computed, from which pooled post-treatment means and standard deviations were calculated. The pooling of ANCOVA statistics is not available in SPSS. Therefore, the tables report inferential statistics (F , p ,

Cohen's *d*) for the most "pessimistic" analytic scenario, i.e., the imputation iteration that yielded the highest *p*-value, to prevent an inflation of false positives (Type I error). In addition, a sensitivity analysis was conducted with the complete-case sample. The effect size (Cohen's *d*) for each pairwise comparison, using the pooled baseline SD to analyse the differences in the baseline-post intervention mean values and correct these values for the estimated population, was also computed for the complete-case sample (Morris, 2008). For the imputed dataset, the *d* was calculated by subtracting the means and dividing the results by the pooled standard deviation. Effect sizes were considered small (*d* = .20), medium (*d* = 0.50), and large (*d* = 0.80) according to classical cut-offs (Cohen, 1988).

A ≥ 20% reduction in the total FIQR score at post-treatment compared to pre-treatment was considered a clinically relevant treatment response (Bennett et al., 2009). This classification in responders vs non-responders was used to compute the Number Needed to Treat (NNT) of each intervention arm. The NNT is an index aimed at make results from RCTs more meaningful to clinicians. It refers to the estimated number of individuals who need to be treated with a novel proposed treatment (i.e., FIBROWALK or MPP) instead of the usual care for one additional patient to benefit (i.e., vs. TAU or MPP). An NNT between 2 and 5 is indicative of a clinically effective treatment in pharmaceutical research (Cook & Sackett, 1995). Furthermore, in order to identify baseline characteristics potentially associated with being a "responder" in each evaluated treatments, baseline differences among sociodemographic and clinical variables between "responders" and

"non-responders" were evaluated with a Student's *t*-test (for quantitative variables) and χ^2 -test (for categorical variables). All statistical analyses were computed with the SPSS v25.

3. Results

3.1. Participant's flow and treatment adherence

As shown in Fig. 1, a total of 387 patients with FM were assessed for eligibility. Fifty-seven did not meet the eligibility criteria, and therefore, a total of 330 patients were finally included and randomised [TAU (*n* = 110), TAU + FIBROWALK (*n* = 110) and TAU + MPP (*n* = 110)]. The participants' mean age was approximately 53 years old (SD = 9.11; range: 20–77). The mean body mass index (BMI) of 27.27 kg/cm² (SD = 5.56) indicated that the subject group was overweight. The mean FM duration was 15.6 years (SD = 9.12). Approximately 24% of the participants were employed, 57% married/in a stable relationship, 83% lived with someone, 60% reported having secondary education level or higher, 70% reported some degree of disability, and 86% had a comorbid chronic fatigue syndrome diagnosis (Table 1). Retention rate was high in the three intervention arms (around 10% dropped out of treatment in each arm). No differences were found in the retention rate at post-treatment (FIBROWALK: 90.9%; MPP: 89.1%; TAU: 90.9%; $\chi^2(2) = 0.277, p = .87$). All participants in the FIBROWALK and MPP arms attended all 12 sessions of the programs, watched the videos, and completed the weekly questionnaires.

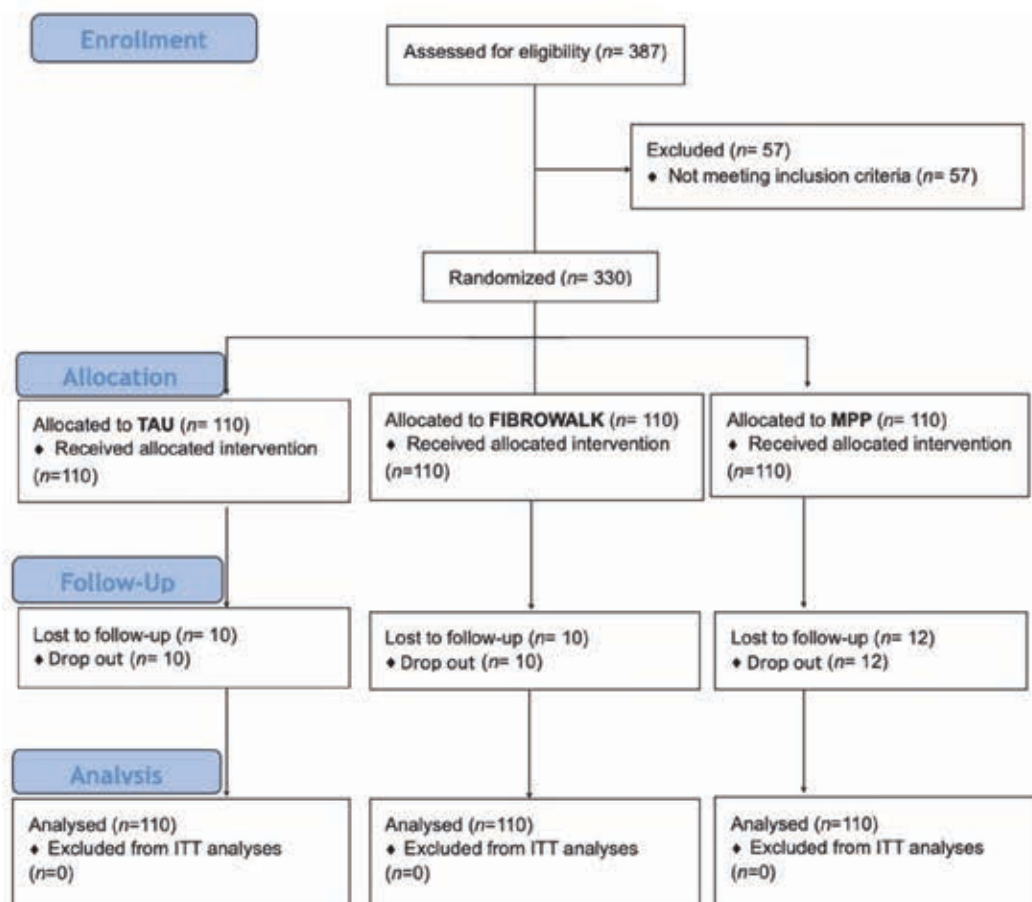


Fig. 1. CONSORT Flow diagram of participants throughout the randomised controlled trial.

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3.2. Baseline differences between study arms

There were no statistically significant differences between treatment arms in demographic or baseline clinical characteristics (see Table 1).

3.3. Between-group differences in the primary and secondary outcomes

3.3.1. Primary outcome

Individuals allocated to both active treatment arms showed greater reductions in FIQR scores when compared to those allocated to TAU only ($p < .001$; FIBROWALK, $d = 0.80$; MPP, $d = .53$). No differences in FIQR scores were found between the FIBROWALK and the MPP groups ($p = .163$; $d = 0.26$). Mean differences and SDs between pre- and post-treatment for each study arm are detailed in Table 2 (ITT approach). Similar results were found in the complete-case sample (Table 3).

3.4. Secondary outcomes

Patients allocated to FIBROWALK showed greater reductions in perceived pain intensity, kinesiophobia, anxiety and depressive symptoms and increased physical functioning compared to the TAU only group (all $p < .001$), with medium-to-large effect sizes ($d = 0.51$ – 1.48). Similarly, significant treatment effects ($p < .05$) in favor of the MPP arm were found when compared to TAU in perceived pain intensity ($d = .39$), kinesiophobia ($d = 1.13$), and depressive symptoms ($d = 0.37$) (all $p < .05$). No differences between MPP and TAU were found in the other outcomes. When comparing FIBROWALK and MPP arms, statistically significant effects in favor of the former were found in pain intensity, depression, and physical functioning (all $p < .05$), with small-to-medium effect sizes ($d = 0.24$ – 0.49).

Similar results were found when looking at the complete-case dataset, except for the differences between FIBROWALK and MPP arms in anxiety and depressive symptoms. As shown in Table 3, FIBROWALK was significantly more effective than MPP for reducing anxiety symptoms ($p = .036$, $d = 0.50$). In the case of depressive symptoms, the differences were marginally significant in favor of FIBROWALK ($p = .053$, $d = 0.22$).

3.5. Baseline differences between "Responders" and "Non-Responders" to treatment

In the FIBROWALK arm, individuals classified as responders indicated less anxiety ($p = .02$), depressive symptoms ($p = .02$) and better physical functioning ($p = .03$) prior to treatment compared to non-responders. MPP responders were older ($p = .05$), men (100% men vs. 94% of women; $p = .05$), reported less pain ($p < .001$), had less functional impairment ($p = .03$), and better physical functioning ($p = .01$) than "non-responders." All details are shown in Table 4.

3.6. Number Needed to Treat (NNT)

Forty-two subjects (42%) in the FIBROWALK arm and 33 subjects in the MPP arm (34%) showed a clinically significant improvement in their FIQR total score at post-treatment (i.e., $\geq 20\%$) so were considered responders, whereas only four subjects (4%) from the TAU only arm achieved the status of responder. The absolute risk reduction in the FIBROWALK arm in comparison with TAU only was 38% (95% CI = 27.59–48.41%), with an NNT = 3 (95% CI = 2.1 to 3.6). The absolute risk reduction obtained in the MPP versus TAU only was 29.67% (95% CI = 19.56–39.79%), with an NNT = 4. The absolute risk reduction obtained in the FIBROWALK versus the MPP arm was 8.33% (95% CI = -5.13 to 21.78%) with an NNT = 13. As in this latter case, the 95%CI for the absolute risk reduction extended from a negative number (FIBROWALK may not benefit) to a positive number (FIBROWALK may benefit), the NNT result had no interpretable meaning.

Table 1

Demographic and baseline clinical characteristics by treatment groups.

	TAU (n = 110)	TAU + FIBROWALK (n = 110)	TAU + MPP (n = 110)	F/ χ^2 (df)	p
Age (years), M \pm SD	53.48 \pm 8.93	52.78 \pm 8.64	52.54 \pm 9.78	.318 (2)	.73
Women, n (%)	103 (96.7)	109 (99.1)	107 (97.3)	5.27 (2)	.07
Civil Status, n (%)				9.61 (6)	.14
Single	24 (21.8)	22 (20.0)	13 (12.7)		
Married	52 (47.3)	62 (56.4)	73 (66.4)		
Divorced	27 (24.5)	21 (19.1)	16 (14.5)		
Widow	7 (6.4)	5 (4.5)	7 (6.4)		
Not living Alone, n (%)	84 (76.4)	93 (84.5)	97 (88.2)	5.72 (2)	.06
Educational Level, n (%)				14.86 (10)	.14
Without Studies	3 (2.7)	2 (1.8)	0 (0.0)		
Primary Education not completed	9 (8.2)	10 (9.2)	6 (5.5)		
Primary Education	40 (36.4)	28 (25.5)	25 (22.7)		
Secondary Education	31 (28.2)	47 (42.7)	54 (49.1)		
Higher Education	24 (21.8)	20 (18.2)	23 (20.9)		
Other	3 (2.7)	3 (2.7)	2 (1.8)		
Employment Situation, n (%)				14.71 (14)	.40
Housekeeper	13 (11.8)	10 (9.1)	9 (8.2)		
Active	22 (20.0)	26 (23.6)	30 (27.3)		
On leave	22 (20.0)	25 (22.7)	24 (21.8)		
Unemployed with allowance	6 (5.5)	13 (11.8)	5 (4.5)		
Unemployed without allowance	10 (9.1)	7 (6.4)	4 (3.6)		
Retired	15 (13.6)	10 (9.1)	10 (9.1)		
Temporary work disability	12 (10.9)	8 (7.3)	10 (9.1)		
Other	10 (9.1)	11 (10.0)	18 (16.4)		
Incapacity certificate, n (%)				4.382 (4)	.36
No	31 (28.2)	24 (21.8)	35 (31.8)		
Between 33% and 66%	65 (59.1)	73 (66.4)	58 (52.7)		
More than 66%	14 (12.7)	13 (11.8)	17 (15.5)		
BMI, M \pm SD	27.62 \pm 5.41	27.31 \pm 6.17	26.89 \pm 5.06	.477 (2)	.62
ISPS, M \pm SD	15.79 \pm 9.12	16.21 \pm 9.24	14.80 \pm 8.72	.692 (2)	.50
With CFS, n (%)	94 (85.5)	100 (90.9)	88 (80.0)	5.27 (2)	.07
FIQR, M \pm SD		74.72 \pm 14.71		.043	.96

(continued on next page)

Table 1 (continued)

	TAU (n = 110)	TAU + FIBROWALK (n = 110)	TAU + MPP (n = 110)	F/ χ^2 (df)	p
	74.57 ± 15.63		75.16 ± 16.00		
Pain (VAS), M ± SD	7.99 ± 1.44	8.02 ± 1.28	8.11 ± 1.57	.204	.82
TSK, M ± SD	30.56 ± 7.99	30.16 ± 7.98	31.67 ± 7.46	1.100	.33
HADS Anxiety, M ± SD	13.70 ± 4.31	12.93 ± 4.42	13.69 ± 4.12	1.314	.27
HADS Depression, M ± SD	12.69 ± 4.31	12.06 ± 4.38	12.01 ± 4.83	.838	.43
SF36-PF, M ± SD	32.59 ± 17.36	35.14 ± 20.15	34.81 ± 20.42	.565	.57

Note: TAU = Treatment-as-usual; MPP = Multicomponent Physiotherapeutic Program; BMI: Body Mass Index; CFS: Chronic Fatigue Syndrome; FIQR: Revised Fibromyalgia Impact Questionnaire; HADS: Hospital Anxiety and Depression Scale; ISPS: Illness Self-Perceived Start; SF-PF: Physical Functioning component of the 36-Item Short Form Survey; TSK: Tampa Scale for Kinesiophobia.

4. Discussion

Both the video-based FIBROWALK and MPP multicomponent treatments were found to be more efficacious than TAU only, with small-to-large clinical effects. The superiority of these two programs over TAU only was corroborated by the low NNT values. Furthermore, FIBROWALK produced additional clinical benefits when compared to MPP. Our findings provide additional evidence of the effectiveness of video-based FIBROWALK, which was initially obtained in a pilot study during the first lockdown due to COVID-19 pandemic in Spain (Serrat, Coll-Omaña et al., 2021) and confirmed existing evidence of the efficacy of PNE combined with therapeutic exercise in people with FM (Ibarrenegoa-Cuadra et al., 2021; Ceballos-Laita et al., 2020; Louw, Puentedura, et al., 2016).

Interestingly, although both FIBROWALK and MPP were effective in improving the primary outcome of perceived functional impairment, only FIBROWALK showed statistically significant effects on all the study outcomes. Though the MPP program was also effective in reducing perceived pain intensity, kinesiophobia, and depressive symptoms it did not result in improved anxiety symptoms and perceived level of physical function compared to TAU only. Furthermore, though the effect sizes were small-to-medium, FIBROWALK achieved statistically larger improvements in the secondary outcomes of pain intensity, anxiety (only in the complete-case dataset) and depressive symptoms and physical function compared to MPP. These findings suggest a broader and stronger therapeutic effect by combining psychological ingredients with physiotherapy interventions based on PNE and therapeutic exercise. These results are in line with other studies evaluating the effects of physiotherapy plus psychological interventions compared with physiotherapy alone in other chronic pain samples (Wilson & Cramp, 2018). These findings are remarkably important, as they support the inclusion of evidence-based psychotherapeutic approaches in ongoing multicomponent physiotherapy programs for people with FM.

The efficacy of the two treatments, in part, rely on the shared components of PNE and therapeutic exercise. Many studies have separately supported the efficacy of both PNE and therapeutic exercise (e.g., adapted aerobic and muscle strengthening exercises) in reducing pain, affective symptoms, kinesiophobia, and perceived disability and in improving global well-being and health-related quality of life in people with musculoskeletal pain (Sosa-Reina et al., 2017; Watson et al., 2019). It is known that PNE and therapeutic exercise can be even more effective when combined (Louw, Zimney, Puentedura, & Diener, 2016; Malfliet

Table 2 Descriptive statistics and between-group analyses for primary and secondary outcomes from an ITT approach (with multiple imputation of missing data).

	TAU (n = 110)		TAU + FIBROWALK (n = 110)		TAU + MPP (n = 110)		TAU vs FIBROWALK		TAU vs TAU + MPP		TAU + FIBROWALK vs TAU + MPP	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F	p	d	p	d	p	d	p
FIQR												
Baseline	74.57 ± 15.63	74.72 ± 14.71	75.16 ± 16.00	75.16 ± 16.00								
Post-Treatment	74.92 ± 14.58	60.68 ± 20.56	65.84 ± 19.34	65.84 ± 19.34	27.58	<.001	.80	<.001	.53	<.001	(4.59-13.28)	.26
Pain (VAS)												
Baseline	7.99 ± 1.44	8.02 ± 1.28	8.11 ± 1.57	8.11 ± 1.57								
Post-Treatment	8.12 ± 1.50	6.73 ± 2.12	7.43 ± 2.01	7.43 ± 2.01	20.97	<.001	.76	<.001	.39	.002	(.22-1.23)	.34
TSK												
Baseline	30.56 ± 7.99	30.16 ± 7.98	31.67 ± 7.46	31.67 ± 7.46								
Post-Treatment	32.11 ± 6.44	22.52 ± 6.55	24.40 ± 7.24	24.40 ± 7.24	90.08	<.001	1.48	<.001	1.13	<.001	(6.26-9.84)	.27
HADS Anxiety												
Baseline	13.70 ± 4.31	12.93 ± 4.42	13.69 ± 4.12	13.69 ± 4.12								
Post-Treatment	13.66 ± 4.37	11.35 ± 4.74	13.11 ± 4.59	13.11 ± 4.59	7.75	.001	.51	<.001	.12	1.000	(-.62 to 1.35)	.38
HADS Depression												
Baseline	12.69 ± 4.31	12.06 ± 4.38	12.01 ± 4.83	12.01 ± 4.83								
Post-Treatment	13.12 ± 4.53	10.15 ± 4.93	11.36 ± 5.05	11.36 ± 5.05	13.38	<.001	.63	<.001	.37	.037	(.053-2.28)	.24
SF-PF												
Baseline	32.59 ± 17.36	35.14 ± 20.15	34.81 ± 20.42	34.81 ± 20.42								
Post-Treatment	30.47 ± 14.09	45.14 ± 20.80	35.22 ± 20.02	35.22 ± 20.02	22.68	<.001	.83	<.001	.27	.389	(-7.29 to 1.65)	.49

Note: Statistically significant effects are shown in bold ($p \leq 0.05$). Pooled post-treatment means and standard deviations are shown. Bonferroni-adjusted post hoc tests were conducted for pairwise comparisons. The table reports inferential statistics (F , p , Cohen's d) for the imputation iteration that yielded the highest p -value, to prevent an inflation of false positives (Type I error), 95%CI for the between-groups difference adjusted means at post are shown. TAU = Treatment-as-usual; MPP = Multicomponent Physiotherapeutic Program; FIQR: Revised Fibromyalgia Impact Questionnaire; TSK: Tampa Scale for Kinesiophobia; HADS: Hospital Anxiety and Depression Scale; ISPS: Illness Self-Perceived Start; SF-PF: Physical Functioning component of the 36-Item Short Form Survey.

Table 3
Descriptive statistics and between-group analyses for primary and secondary outcomes (only with completers).

	TAU (n = 100)		TAU + FIBROWALK (n = 100)		TAU + MPP (n = 98)		TAU vs TAU + FIBROWALK		TAU vs TAU + MPP		TAU + FIBROWALK vs TAU + MPP	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F	p	d	p	d	p	d	p
FQR												
Baseline	74.12 ± 15.92	74.26 ± 14.91	74.77 ± 16.64									
Post-Treatment	74.49 ± 13.93	60.66 ± 20.93	65.28 ± 19.80		27.84	<.001	-.92	<.001	-.62	<.001	-.26	.088
Pain (VAS)												
Baseline	7.97 ± 1.45	7.99 ± 1.27	8.08 ± 1.62									
Post-Treatment	8.08 ± 1.43	6.73 ± 2.16	7.39 ± 2.08		19.38	<.001	1.01	<.001	.54	.002	.40	.025
TSK												
Baseline	30.43 ± 7.99	29.73 ± 8.02	31.67 ± 7.19									
Post-Treatment	31.96 ± 6.31	22.43 ± 6.64	22.29 ± 7.35		85.17	<.001	-1.14	<.001	-1.39	<.001	-.21	.829
HADS Anxiety												
Baseline	13.43 ± 4.26	12.80 ± 4.53	13.51 ± 4.16									
Post-Treatment	13.47 ± 4.33	11.27 ± 4.85	12.93 ± 4.60		7.87	<.001	-.33	<.001	-.33	.521	.50	.036
HADS Depression												
Baseline	12.74 ± 4.41	12.07 ± 4.54	11.87 ± 4.67									
Post-Treatment	13.05 ± 4.55	10.23 ± 5.01	11.20 ± 5.103		11.78	<.001	-.50	<.001	-.26	.045	.22	.053
SF-36												
Baseline	32.80 ± 17.35	35.15 ± 20.46	35 ± 21.26									
Post-Treatment	30.70 ± 13.74	44.73 ± 21.09	35.92 ± 20.39		22.00	<.001	.61	<.001	.61	.156	.42	<.001

Note: Statistically significant effects are shown in bold (p ≤ 0.05). Unadjusted means are shown. Bonferroni-adjusted post hoc tests were conducted for pairwise comparisons. When the Benjamini-Hochberg correction was applied to correct for multiple comparisons, all significant effects remained significant. 95%CI for the between-groups difference adjusted means at post are shown. TAU = Treatment-as-usual; MPP = Multicomponent Physiotherapy Program; FQR: Revised Fibromyalgia Impact Questionnaire; HADS: Hospital Anxiety and Depression Scale; SF-36: Physical Functioning component of the 36-Item Short Form Survey; TSK: Tampa Scale for Kinesiophobia.

et al., 2017). Furthermore, FIBROWALK and MPP shared other self-management and patient education components, which were found in a recent systematic review in FM to be effective in improving pain intensity, fatigue, sleep quality, depression, anxiety, functional ability, cognitive impairment, and quality of life (Gómez-de-Regil, 2021).

While superior improvements in anxiety and depressive symptoms were expected outcomes for the FIBROWALK arm, participants allocated to this intervention also showed greater pain ameliorations and physical functioning when compared to those allocated to MPP. Similar results have also been found in other studies assessing the effects of CBT or mindfulness-based interventions in subjects with FM (Bennett & Nelson, 2006; Kundakci et al., 2021; Williams et al., 2002). Moreover, larger improvements in physical function after multidisciplinary interventions, including both psychotherapeutic and physiotherapeutic components compared to physiotherapy interventions alone were also reported in a systematic review and meta-analysis including different chronic pain samples (Wilson & Cramp, 2018). In this regard, it is known that patients suffering from chronic pain tend to exhibit maladaptive beliefs regarding physical exercise (Harding & Williams, 1995), which can lead to a sedentary lifestyle and non-compliance with physical therapy recommendations (Dysvik, Vinsnes, & Eikeland, 2004). Avoidance of physical activity is often a barrier to recovery and can contribute to reduced physical function, deconditioning, and increased pain. The psychological components included in FIBROWALK were aimed at helping patients overcome such barriers by modifying maladaptive pain beliefs and cognitive biases and fostering adaptive emotional regulation in order to reduce pain catastrophizing, increase psychological flexibility, and promote positive behavioural changes. Addressing these barriers to function are essential steps for escaping from the vicious circle of fear and avoidance of physical activity in musculoskeletal pain (Vlaeyen, Crombez, & Linton, 2016; Wright & Gatchel, 2002). Similarly, mindfulness can play an important role in breaking this vicious circle by reducing negative rumination, increasing pain acceptance, and improving one's ability to stay focused on the present moment with a non-judgemental attitude (Curtin & Norris, 2017; McCracken & Keogh, 2009; Pérez-Aranda, Feliu-Soler, et al., 2019). Both cognitive restructuring and mindfulness, combined with PNE, can contribute to reduce fear of pain and fear of movement (Jay et al., 2016). In this way, CBT, Mindfulness, therapeutic exercise and PNE might present a synergistic effect (Heller et al., 2021) in which all components have a greater effect when combined than the sum of their separate effects. Furthermore, given the known bidirectional relationship between pain-related distress and physical function (e.g., Stegenga et al., 2012; Talaei-Khoel et al., 2018; Wegener et al., 2011), the additional CBT and mindfulness approaches for reducing pain-related distress in FIBROWALK may have contributed to the stronger therapeutic effects compared to MPP and TAU only.

When looking specifically at the impact on kinesiophobia, both active groups showed similar improvements (large effect sizes) compared to TAU. In this regard, adding CBT and mindfulness training did not increase the effects of the MPP on this variable, which probably reached a therapeutic ceiling. Previous research has suggested that changes in cognitive biases and behavioural factors in chronic pain conditions might not occur exclusively by means of psychological approaches but also by providing subjects with comprehensive information about the biopsychosocial essence of chronic pain as is done in PNE (Burns, Van Dyke, Newman, Morais, & Thorn, 2020). PNE is aimed at reconceptualizing pain in order to break the cycle of fear of movement and avoidance. Previous studies have reported that PNE is high effectiveness in reducing kinesiophobia in FM and other musculoskeletal pain conditions (Louw, Diener, Butler, & Puentedura, 2011; Luque-Suarez, Martinez-Calderon, & Falla, 2019; Siddall et al., 2022; Watson et al., 2019).

Although both FIBROWALK and MPP were clearly superior to TAU alone, it is important to highlight that only 42% and 34% of the participants, respectively, showed a clinically significant improvement (i.e.,

Table 4
Baseline differences between responders (FIQR \geq 20%) and non-responders from the FIBROWALK and MPP.

	FIBROWALK (n = 100)				MPP (n = 98)			
	Non-Responders (n = 58)	Responders (n = 42)	t/x2	p	Non-Responders (n = 65)	Responders (n = 33)	t/x2	p
Age (years), M \pm SD	52.59 \pm 7.84	54.40 \pm 9.28	-1.031	.306	51.42 \pm 9.81	55.12 \pm 7.78	-2.035	.045
Women, n (%)	58 (100.0)	41 (97.6)	1.395	.238	65 (100)	31 (93.9)	4.021	.045
Civil Status, n (%)			2.326	.508			.109	.991
Single	14 (24.1)	8 (19.0)			8 (12.3)	4 (12.1)		
Married	28 (48.3)	26 (61.9)			43 (66.2)	22 (66.7)		
Divorced	12 (20.7)	7 (16.7)			9 (13.8)	5 (15.2)		
Widow	4 (6.9)	1 (2.4)			5 (7.7)	2 (6.1)		
Not living Alone, n (%)	50 (86.2)	34 (81.0)	.500	.479	60 (92.3)	27 (81.8)	2.417	.120
Educational Level, n (%)			6.977	.222			1.996	.736
Without Studies	2 (3.4)	0 (0.0)						
Primary Education not completed	8 (13.8)	1 (2.4)			4 (6.2)	1 (3.0)		
Primary Education	13 (22.4)	14 (33.3)			14 (21.5)	8 (24.2)		
Secondary Education	25 (43.1)	19 (45.2)			34 (52.3)	15 (45.5)		
Higher Education	9 (15.5)	8 (19.0)			12 (18.5)	9 (27.3)		
Other	1 (1.7)	0 (0.0)			1 (1.5)	0(0.0)		
Employment Situation, n (%)			4.279	.747			6.002	.539
Housekeeper	4 (6.9)	3 (7.1)			5 (7.7)	3 (9.1)		
Active	13 (22.4)	9 (21.4)			18 (27.7)	10 (30.3)		
On leave	16 (27.6)	8 (19.0)			18 (27.7)	5 (15.2)		
Unemployed with allowance	8 (13.8)	5 (11.9)			4 (6.2)	1 (3.0)		
Unemployed without allowance	4 (6.9)	3 (7.1)			1 (1.5)	1 (3.0)		
Retired	3 (5.2)	7 (16.7)			3 (4.6)	5 (15.2)		
Temporary work disability	4 (6.9)	2 (4.8)			7 (10.8)	2 (6.1)		
Other	6 (10.3)	5 (11.9)			9 (13.8)	6 (18.2)		
Incapacity certificate, n (%)			6.665	.155			1.220	.748
No	12 (20.7)	8 (19.0)			19 (29.2)	12 (36.4)		
Between 33% and 66%	40 (69.0)	23 (54.8)			32 (49.2)	15 (45.5)		
More than 66%	5 (8.6)	5 (11.9)			9 (13.8)	5 (15.2)		
BMI, M \pm SD	27.28 \pm 5.86	27.77 \pm 6.88	-.371	.711	26.84 \pm 5.38	27.11 \pm 4.97	-.248	.805
ISPS, years, M \pm SD	16.62 \pm 10.14	15.48 \pm 8.09	.627	.532	14.83 \pm 8.41	14.27 \pm 9.09	.294	.769
With CFS, n (%)	55 (94.8)	37 (88.1)	1.500	.221	53 (81.5)	25 (75.8)	.450	.502
FIQR, M \pm SD	75.59 \pm 15.34	72.43 \pm 14.28	1.056	.294	77.46 \pm 15.48	69.47 \pm 17.79	2.193	.032
Pain (VAS), M \pm SD	8.09 \pm 1.27	7.86 \pm 1.26	.891	.375	8.46 \pm 1.44	7.33 \pm 1.73	3.429	.001
TSK, M \pm SD	30.07 \pm 7.55	20.26 \pm 8.70	.484	.630	31.92 \pm 6.89	31.18 \pm 7.84	.460	.647
HADS Anxiety, M \pm SD	13.71 \pm 4.01	11.55 \pm 4.95	2.328	.023	14.26 \pm 3.79	12.03 \pm 4.52	2.436	.018
HADS Depression, M \pm SD	12.98 \pm 4.05	10.81 \pm 4.91	2.349	.021	12.42 \pm 5.00	10.79 \pm 3.76	1.646	.103
SF36-PF, M \pm SD	31.29 \pm 18.79	40.47 \pm 21.66	-2.210	.030	31.15 \pm 21.02	42.58 \pm 19.93	-2.632	.011

Note: Statistically significant effects appear in bold ($p \leq 0.05$). MPP = Multicomponent Physiotherapeutic Program; BMI: Body Mass Index; CFS: Chronic Fatigue Syndrome; FIQR: Revised Fibromyalgia Impact Questionnaire; TSK: Tampa Scale for Kinesiophobia; HADS: Hospital Anxiety and Depression Scale; ISPS: Illness Self-Perceived Start; SF-PF: Physical Functioning component of the 36-Item Short Form Survey.

20% between pre- and post-treatment) in the primary outcome measure of perceived functional impairment, as determined by FIQR scores. Though FIBROWALK in the present study yielded a higher rate of responders (43%) than the initial pilot RCT (30%), which was conducted during the Spanish lockdown (Serrat, Coll-Omaña, et al., 2021), there is room for considerable improvement. Moreover, greater clinical effects in FIQR scores (Cohen's d of 0.83 vs 1.13; NNT = 3 vs 2) and a larger proportion of treatment "responders" were found in the face-to-face FIBROWALK format (Serrat, Sanabria-Mazo, et al., 2021) compared to the video-based version in the present study (42% vs 51.85%). It is also important to note that, although online approaches may be less effective than equivalent face-to-face options, these video-based programs are highly scalable and have the potential to provide treatment availability for FM patients who are unable to attend face-to-face sessions.

Furthermore, these telemedicine programs may help reduce healthcare costs and decongest health system services which are experiencing huge workload burdens as a result of the current COVID-19 pandemic (Moman et al., 2019).

Although comparisons in effectiveness between the virtual and face-to-face formats of FIBROWALK should be evaluated in future RCTs, many factors may contribute to these apparent differences, including the feeling of belonging to a group and having regular contact with a therapist, which both have potentially therapeutic benefits. Furthermore, we cannot rule out that our results would have been better in a patient sample with less severe symptoms. In this regard, compared to non-responders in the present study, the responders reported lower pre-treatment symptom severity. In general, the patients in our sample reported a relatively high degree of pre-treatment functional impairment,

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low degree of perceived physical function, high perceived pain intensity and a moderate degree of depressive and anxiety symptomatology. Future studies should evaluate if additional treatment time or tailored adaptations of FIBROWALK (e.g., adding individual therapy or extra CBT virtual sessions for those individuals scoring high in anxiety and/or depression) may work better for those patients with a higher risk of non-responsiveness. In this regard, evidence-based care has started to move toward process-based therapies to target core mediators and moderators based on testable theories, to identify what treatments are most effective, for whom, why and under what set of circumstances (Hofmann & Hayes, 2019; McCracken, 2020). This change of perspective from “one size fits all” to more individualised treatment may better suit the high level of complexity that chronic pain conditions, and particularly FM, present.

Finally, FIBROWALK and MPP showed a relatively low attrition rate (around 10%). This low rate of dropouts supports the feasibility of these virtual interventions. A range between 4% and 54% of attrition has been found with other online interventions in patients with chronic pain (Buhrman, Gordh, & Andersson, 2016). The attrition rate in FIBROWALK was also lower than in the pilot RCT conducted during the COVID-19 outbreak (38.7%; Serrat, Coll-Omaña, et al., 2021) and even lower than the reported in the face-to-face version of the program (9% vs 24%) (Serrat, Sanabria-Mazo, et al., 2021). This finding may suggest a superior ability of the virtual format of the FIBROWALK for engaging participants who were not able to attend a 12-week face-to-face intervention. The increased adherence and low attrition rate of participants in the present study could have been due to the high flexibility of the video-based format, participation through the hospital system from which they were receiving TAU care, the emphasis at the beginning of the study about the importance of actively participating in the intervention, and therapist support during the program. Results from the present study suggest that the virtual interventions of FIBROWALK and MPP can be effective therapeutic alternatives to classical face-to-face treatments in times of pandemics and beyond when it comes to specific logistic barriers, such as timing, difficulties in access to treatment in remote areas, or other perceived barriers, such as individual's fatigue or family conciliation issues.

This RCT had several strengths, such as the inclusion of two innovative video-based active treatments that were structurally equivalent, the relatively large sample size and the reduced number of dropouts. However, there were several limitations. First, comparisons between the two intervention groups (FIBROWALK vs MPP) may have been underpowered. Second, this study was carried out in daily clinical practice in a specialised tertiary care hospital. Therefore, stricter eligibility criteria could not be applied. Subjects with certified disability were included in our sample. The sample was composed of people with FM with high impact on daily functioning and relatively long duration of the disease. Future studies could explore the role of multicomponent interventions in other settings (e.g. primary care) including less severe patients. Third, no long-term follow-ups were done, due the fact that the present study was carried out within usual clinical practice. Future studies should include long-term follow-ups for assessing the stability of the observed clinical effects. Fourth, it cannot be confirmed that all subjects viewed all the videos and performed all the homework, even though they reported compliance in a weekly questionnaire format. Fifth, all outcome data were patient-reported. No objective functional data were measured. Though it is common to use patient-reported data to evaluate FM symptom domains (Outcome Measures in Rheumatology Clinical Trials; Mease et al., 2009), future studies should include complementary objective measures. Future studies should also include weekly patient-reported state measures to examine the evolution of participants throughout the study instead of only at the end of the intervention (e.g., Navarrete, García-Salvador, Cebolla, & Baños, 2022). Sixth, future studies should evaluate potential sampling bias, which are inherent to any study, including online interventions. Participants with a perceived low digital competency may have been self-excluded themselves when

initially being told about the virtual nature of the intervention, which may have undermined the generalizability of our findings. Finally, this trial was conducted under de COVID-19 pandemic context and after termination of national lockdowns. Given the well-known negative effects of these circumstances on mental health and treatment adherence (e.g., López-Medina et al., 2021), further studies conducted beyond current pandemic context should be done to evaluate the generalizability of our findings.

5. Conclusions

This study showed that two video-based multicomponent treatments including PNE, therapeutic exercise and self-management patient education, were clinically effective in improving functional disability, pain and kinesiophobia compared to TAU only for people with FM. Furthermore, FIBROWALK, which combined all therapeutic components of MPP with cognitive restructuring and mindfulness training, was more effective in reducing anxiety, depressive symptoms and in improving physical function than MPP or TAU only. The results of this RCT support the clinical effectiveness of both video-based treatments over usual care in FM and provide more scientific evidence regarding the increased benefits of combining physical therapy and psychological techniques in the management of this highly prevalent and limiting disease.

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Mayte Serrat: Conceptualization, Methodology, Resources, Software, Data curation, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Klara Albajes:** Conceptualization, Methodology, Resources, Software, Data curation, Validation, Formal analysis, Writing – original draft, Writing – review & editing, Supervision. **Jaime Navarrete:** Formal analysis, Writing – review & editing. **Miriam Almirall:** Writing – review & editing, Supervision. **Enrique Lluch Girbés:** Writing – review & editing. **Randy Neblett:** Writing – review & editing. **Juan V. Luciano:** Conceptualization, Writing – review & editing, Supervision. **Jenny Moix:** Writing – review & editing, Supervision. **Albert Feliu-Soler:** Conceptualization, Methodology, Resources, Software, Data curation, Validation, Formal analysis, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brat.2022.104188>,

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APPENDIX 3:
PNE Effectiveness

Increasing pain neuroscience knowledge by using brief fact sheets: a mixed methods study

0. Abstract

Background/Objectives. Pain Neuroscience Education (PNE) is an effective educational strategy that incorporates the multidimensionality of pain experience and aids individuals to reconceptualise pain by understanding the biological and processing mechanisms involved in the phenomenon of pain. The use of PNE has been associated to reductions in pain, improved function, decreased fear of movement, and less catastrophising, and is currently an essential element in any treatment for fibromyalgia. This study aims 1) to evaluate the usefulness of 9 fact sheets on the neuroscience of pain translated to Spanish and 2) to analyse the correlation of patients' pain-related knowledge and their health status. **Methods.** This study encompasses both quantitative and qualitative research carried out in three parts. The first part aims at analysing the quality of the fact sheets based on collected qualitative feedback from 10 patients with fibromyalgia; the second part aims at evaluating the effectiveness of a new pain neuroscience tool in two formats, written and video-based among 337 patients with fibromyalgia; and the third part aims at analysing the correlation between participants' pain neuroscience knowledge and health status. **Results.** The qualitative results of the fact sheets suggest a progressive meaningful learning, along with a change of beliefs in pain-related concepts. The fact sheets have also proven to be effective in providing adequate knowledge in both written and video-based formats. Finally, there is a correlation between pain neuroscience knowledge and health status (functional impairment, physical functioning, anxiety, depression symptoms and kinesiophobia). **Conclusions.** This study validates a very valuable tool of PNE and confirms the importance of pain neuroscience knowledge in the health status of fibromyalgia patients. **Keywords.** Pain Neuroscience Education, PNE, Fibromyalgia, Qualitative Research.

1. Introduction

Pain neuroscience knowledge refers to the understanding of the physiological and processing mechanisms involved in the phenomenon of pain. Helping patients to comprehend what is happening in their own body, provides a base for enhanced self-informed intervention choices, self-management, self-monitoring (Moseley & Butler, 2015) and better health outcomes (Camerini et al., 2013; Musekamp et al., 2019). Due to this reported contribution, pain education is progressively included in psychological interventions (Albajes & Moix, 2021), physical therapy interventions (Marris et al., 2018) and in multicomponent treatments (Serrat et al., 2020; Serrat et al., 2021a; Serrat et al., 2021b) for chronic pain.

Education related to pain biology appeared approximately in the early 2000s as a therapeutic approach after randomised control trials (RCT) demonstrated it to be of clinical benefit (Moseley & Butler, 2017). This therapeutic approach was based on pathological model aimed at explaining why someone is undergoing pain experience. With the advancement of scientific studies, a new approach framed within the biopsychosocial model known as PNE began to gain ground and scientific evidence (Moseley & Butler, 2017; Ziegler et al., 2021).

PNE incorporates the multidimensionality of pain experience and aids individuals reconceptualise pain by understanding the multiple neurophysiological, neurobiological, physical and sociological components that might underpin individual pain experience (Moseley 2007; Moseley & Butler 2015). This approach utilises several metaphors to elucidate the neurophysiological processes and other multidimensional aspects of pain contributing to individuals' pain experience. The use of PNE has been associated to reductions in pain, improved function, decreased fear of movement, and less catastrophizing (Meeus et al. 2010; Moseley 2002, 2003a; Téllez-García et al. 2014; Van Oosterwijck et al. 2013; Vibe Fersum et al. 2013), and it has proven to be an effective educational

strategy as a complement of an all-inclusive multidisciplinary programme compatible with a biopsychosocial model (Louw et al. 2016). In this line, Saracoglu et al. (2020) found that the combination of PNE, manual therapy (physical therapy delivered with hands) and home exercises led to significant improvements compared to manual therapy and home exercises together or only home exercises.

In a qualitative study (Wijma et al., 2016) that delves into the constructs that contribute to a better patient experience, the alliance with the caregiver, listening, taking time, and providing a clear explanation were highlighted. New ways of providing education in pain neuroscience are emerging. These need not always be exclusive of the above aspects but complementary. When looking back at studies on types of health literacy interventions in general (Bader et al., 2022), it was found that most of them were video-based, but also written and face-to-face formats. All these forms yielded optimal results (although to a different degree) and were recommended to be provided in multiple formats. Heathcote et al. (2019) found numerous sources of PNE on the internet through the platform Youtube. Although many publications came from medical professionals, only a 10% came from a reliable scientific source or medical institution, and only 9 of 17 videos found were considered to be engaging. A study aimed at evaluating written education about pain neuroscience outcomes (van Ittersum et al., 2014) found that this did not change perceived symptoms of patients with FM, catastrophizing or daily life impact of FM. It did show only improvements in beliefs in a chronic timeline of FM.

With very few language and cultural adaptations available until now (e.g., Muhtr et al., 2021), PNE materials are scarce, and adequate analyses of these materials seem to be almost nonexistent. One recent PNE work is the book 'Explain Pain', a guide that has gained increasing popularity among pain experts. The guide, developed by the Australian researchers Butler and Moseley (2013) after almost 30 years of experience on PNE tools, was created with the purpose of delivering "self through neuroscience knowledge" and it has been studied in approximately 20 RCTs in a population with chronic pain, most often as a component of a multimodal activity-based rehabilitation (Moseley & Butler, 2017). Following the same line of action of 'Explain Pain', The 'Pain Revolution' non-profit movement (founded by Professor Lorimer Moseley) has recently created 9 fact sheets with the purpose of summarising essential concepts of PNE for pain patients to comprehend autonomously with a didactic approach (Butler & Moseley, 2017). This new educational tool represents the work of several years of performance and improvement and, if useful for increasing pain knowledge among chronic pain patients, may be a suitable easily transferable tool to be added to existent therapeutic approaches.

Pain education is currently an essential element in any treatment for Fibromyalgia (FM) (Cunningham & Kashikar-Zuck, 2013), a chronic and complex non-degenerative disease related mainly to pain, fatigue and sleep afflictions (Bellato et al., 2012).

Developing linguistically adapted materials and assessing their usefulness in specific conditions is essential before assessing their effect on health status. In this sense, this study aims to evaluate the usefulness of this compound of 9 fact sheets translated into Spanish among patients with fibromyalgia. To this end, this work pursues three specific objectives: 1) to analyse patients' experience of understanding and perceived usefulness of these sheets by patients to increasing pain knowledge; 2) to evaluate the effects on pain knowledge of two formats or presentation of these 9 sheets (with/without the support of additional professional explanations); 3) to analyse the correlation between pain knowledge and health status.

2. Methods and Material

2.1 Participants

A total of 347 participants were recruited from Vall d'Hebron University Hospital - Central Sensitivity Syndromes Specialised Unit for the quantitative and qualitative research. The inclusion criteria were: (a) adults ≤ 18 years old, (b) to meet the 2010–2011 American College of Rheumatology (ACR) diagnostic criteria for FM (Segura-Jiménez et al., 2014; Wolfe et al., 2011; Wolfe et al., 2016) and (c) to be able to understand and agree to participate in the study. The exclusion criteria were: (a) participating in concurrent or past RCTs (previous year) and (b) exhibiting comorbidity with severe mental disorders (e.g., psychosis) or neurodegenerative diseases (e.g., Alzheimer's) that would limit the patient's ability to participate in the study. Among the 347 recruited participants, 337 participated in the quantitative and 10 in the qualitative phase.

2.2. Procedure

In an early interview, an outline of the study was provided to FM patients interested in taking part who meet inclusion and exclusion criteria. Prior to being randomly allocated to treatments, informed agreement forms were collected, which contained a detailed description of the features of the interventions. The participants were allocated to the active groups or control group, using a SPSS v25 randomisation list. The protocol for the RCT was designed using SPIRIT recommendations and recorded in a clinical studies database (ClinicalTrials.gov) in accordance with CONSORT guidelines. This study was posted and registered at Clinicaltrials.gov (NCT04571528).

2.3 Ethical aspects

Patients were informed that their involvement was voluntary and that they were able to disengage at any time. The study was carried out in agreement with the ethical standards set forth in the 1964 Declaration of Helsinki and approved by the hospital's Ethics Committee (PR(AG)249/2020). Patient data was treated in confidence, guaranteeing that only the research team has access to this data after recording the name and personal identity number. The principal investigator has exclusive access to the patient code key, which, in accordance with current data protection legislation in Spain, was stored in a safe place.

2.4 Methods

This study is composed of three phases: the qualitative and the quantitative phases and a single correlation study.

1. First, a qualitative and descriptive analysis in a sample of 10 individuals with FM was conducted to assess the quality of the fact sheets based on qualitative feedback.
2. Second, a quantitative methodology was used to study the usefulness of pain neuroscience knowledge of the 9 fact sheets assessing 337 individuals with FM, and to compare patients' understanding of the fact sheets in the two formats: written and video-based.
3. Third, a correlation analysis was carried out between patients' pain neuroscience knowledge and their health status.

2.4.1 Phase I: Qualitative analysis of the quality of the fact sheets

The aim of this phase was to assess the quality of the fact sheets based on qualitative feedback.

2.4.1.1. Specific Objectives

- To obtain feedback regarding the structure and content of each fact sheet
- To assess whether the subjects attain adequate knowledge and also have the perception

of learning.

2.4.1.2 Design

The educational procedure of this phase comprised 11 video sessions. The first and last sessions were introductory and closure sessions explaining and concluding the purpose of the research. The following 9 sessions were focused on the fact sheets. Each accorded day, the educational therapist conducted an online session with each of the 10 subjects individually. In each session the subject was provided with one fact sheet and given the task of reading while being connected online with the educational therapist. Following this, the therapist interviewed the subject to obtain the required feedback and information about each fact sheet.

The PNE tool, as previously mentioned, consists of 9 fact sheets. Each fact sheet contains two pages relating to one main concept. The first page introduces the concept, and the second one cites and summarises important ideas that emerge from the main concept. The 9 main concepts and consequent ideas presented in the fact sheets are based on current scientific research in pain science and have been selected and structured specifically for PNE education for chronic pain patients. The fact sheets have been fully developed and designed by the group Pain Revolution, a pain educator network founded by Professor Lorimer Moseley, group leader in Body in Mind Research Group from University of South Australia. Subsequently, the fact sheets have been translated to Spanish by using the Round-trip translation.

These 9 fact sheets are introduced as follows:

1. Pain is always real.
2. Learn more about your pain.
3. Pain does not equal tissue damage.
4. Pain equals protection.
5. Pain depends on context.
6. Pain and your Protectometer.
7. Your overprotective pain system.
8. Retrain your pain system.
9. Being proactive about your pain.

2.4.1.3. Qualitative Analysis

The 10 subjects responded to the semi-structured interview about the fact sheets which provided data for the final interpretation. Questions and answers were clustered in four categories: 1) format and presentation; 2) personal contribution of the content; 3) perception of learning; 4) content-related questions. The first category is related to any aspect related to the design of the fact sheets: the appearance and format of the text, the illustrations and the layout. The second category included four questions referring to the contribution of the content: new concepts, already known concepts, most important concepts and concepts that have not been understood. The third category incorporated four straightforward questions regarding perception of learning, perception of changing pain-related beliefs, perceptions of possible change in pain-related behaviours, and whether they would recommend each fact sheet. Finally, in the fourth category, subjects were asked to answer the questions of the KNAP-S that corresponded to each fact sheet. These questions were answered again in the final session using the KNAP-S.

During the online sessions, a verbatim transcription was conducted. Based on this, the collected data was carried out via the following steps: a) identification of relevant aspects in the interviews; b) classification and analysis from the four different categories: format and presentation, contribution of the content, perception of learning and content-related questions c) analysis of each category and comparison of participants' answers.

2.4.1.4 Results

In the midst of the 10 participants recruited for this qualitative analysis, two were men and eight women, and they were between 40 and 63 years old (the average age was 56.6). Educational level ranged from secondary to higher education. Time of diagnose ranged from 4 to 20 years. Only 2 of the 10 subjects presented comorbidity with other conditions, only 3 people had at some stage received specialised treatment for FM and only 1 person had previously received some kind of PNE.

The average registered time taken to read the fact sheets during the online session was 4 minutes for each fact sheet (ranging from 3 to 5 minutes). The qualitative analysis follows the four categories above mentioned to record participants' feedback: format and presentation, perception of personal contribution, perception of learning, content-related questions.

Regarding format and presentation (first category), all participants found the configuration of the PNE in sheets very useful and entertaining. Overall, the design and layout was described as helpful and the illustrations made the readings more enjoyable; only two participants found them confusing or unnecessary most of them.

When researching whether a personal contribution of the content was perceived (second category), at some stage all participants detected a shift of paradigm and a conceptual change in pain. A few of them verbalised being surprised by the statement "it even help you make a full recovery over time" on the second sheet, and confessed feeling more hopeful after reading the eighth sheet along with the "retrain your pain system". Only one subject maintained a sceptical position regarding the possibility of being able to reduce pain through the fact sheets suggestions.

Several doubts arose about the content during the sessions, but these were not answered at that moment to perceive their actual learning process, but were discussed at the last session of closure. Participants solved some questions they had themselves during the sessions, but repeated some others after completing the KNAP-S in the final session. These were related to concepts such as bioplasticity, non-tissue factors, protectometre and nociceptive. In addition, most of the subjects manifested disagreement with the mention of working with a health professional as their "pain coach" as they all felt that most doctors had not understood their pain. When the subjects were asked for possible behavioural changes after reading the content, most common answers were maintaining or increasing movement, keeping updated about scientific pain-related findings, looking for factors that reduce or aggravate danger perception, and looking for a professional able to help them and understand their pain.

In relation to participants' perception of learning (third category), when we asked in relation to each sheet whether they had learned something new or whether the sheet had led them to think differently about their pain, discordant responses arose among the subjects: 6 of them assented overall in all fact sheets, and 4 subjects denied learning anything new for the first two or three fact sheets. However, three subjects did state that

although the information was not at all new for them, it was helpful to confirm what they already knew. Furthermore, these subjects changed their mind over the course of the sessions, and they did perceive new learnings as the sessions progressed. Overall, all participants stated that they would recommend all the sheets to other people in the same health situation, although they did suggest some clarifications in specific aspects.

Considering the general impressions of each sheet according to the 10 participants, it seems that the 7th sheet, which refers to the overprotective, pain system, would be the most difficult and confusing one, due to a greater amount of information. The 5th sheet would be the easiest and most understandable sheet (biological, psychological and social aspects of pain), and the 4th and 6th sheets were perceived as the most interesting. These two last sheets refer both to the concept of protection. Overall, it would seem that subjects do understand and perceive that psychological and social aspects also influence pain, the concept of a system that works as a protection would be perceived as an interesting explanation, and they find it more complex to comprehend that persistent pain equals to overprotection.

Regarding specific content-related questions (4th category), these were asked twice; first the questions corresponding to each sheet were asked after the sheet had been read, and the whole questionnaire was answered again on the last day. Only two participants failed to answer more accurately, while the remaining eight responded equally well or better. There were fewer 'I don't know' answers the second time the S-KNAP was done, although all of them then gave at least two wrong answers. Finally, at the end of the fact sheets, 4 participants gave 3 or fewer wrong answers, 3 participants gave 7 or 8 wrong answers and 2 participants gave 12 out of 26 wrong answers.

When comparing perception of learning to actual learning, a relation between perceived change of beliefs and KNAP-S results was found. Participants that expressed having learned or changed specific contents scored higher in the KNAP-S at the final session.

2.4.1.5 Discussion

This study aimed at deepening into providing a qualitative and descriptive analysis based on 10 different participants' feedback. The results of the study are significantly robust: the feedback received from the participants has been generally positive and their actual learning corresponds to their perception of learning.

Studying and analysing PNE tools through quantitative and qualitative research contribute to standardising PNE tools. Identifying specific elements by which patients can achieve significant shift in beliefs, behavioural changes and overall pain-related symptoms management is essential to meet an agreement of required and essential PNE content. A qualitative analysis provides personal feedback but also the possibility of analysing whether the patients' perception of learning after reading the tool is consistent with actual learning. Certainly, the present qualitative results suggest a progressive (perceptual and actual) meaningful learning, along with a change of beliefs in pain-related aspects. Meaningful learning refers to the learned knowledge that is completely understood by the person, and the person understands how to relate this new information to old information, thus enabling further comprehension (Ausubel, 2000). Meaningful learning is an indispensable element to pursue when developing new PNE tools and, for this reason, this study might offer insight (through feedback) on how to improve this tool: several suggestions that arose among participants might be very useful for this task. With this in mind, a quantitative evaluation with 337 subjects validates the tool and confirms its effectiveness in a large and representative sample.

2.4.2 Phase II: Quantitative Study

This phase was conducted using a three-arm controlled design: one control group (without receiving any PNE tool) and two active groups that were provided with the fact sheets in two different formats. Both active groups were assessed to measure pain neuroscience knowledge after having had access to the fact sheets.

2.4.2.1 Specific Objectives

- To compare pain neuroscience knowledge among two active groups that were provided with the 9 fact sheets and a control group that was not provided with any material.
- To compare pain neuroscience knowledge between two different formats (written and video-based).

2.4.2.2 Design

The two separated active groups received the PNE content of the fact sheets in two different formats: written and video-based. One group received the 9 fact sheets by email (written) and the other group received by email a link to an explanatory video of the fact sheets (video-based).

The written group that received the fact sheets via email were also provided with instructions regarding the content and the procedure on how to read the content. Instructions suggested reading the fact sheets at their own pace and conscientiously to fully understand the content. The participants in the video-based group were explained the fact sheets via an informative video. The video lasted one hour approximately and consisted of a presentation with a view and explanation of the fact sheets. Both groups were given one week to understand their content and were provided with a link to access the KNAP-S based on the fact sheets to measure pain neuroscience knowledge. For access to the fact sheets, please contact the authors of the original version.

2.4.2.3 Control Group (CG)

Participants allocated to the control group did not receive any PNE content but had basic information and usual pharmacological treatment and were asked to answer the KNAP-S at the same time as both the two active groups.

2.4.2.4 Measure

The Knowledge and Attitudes of Pain Questionnaire Spanish version (KNAP-S) (Beetsma et al., 2020) was used to assess pain neuroscience knowledge. This questionnaire comprises two main sections: the first section is related to the knowledge acquired after reading and explaining the fact sheets, and the second section consists of 4 questions aimed at providing feedback about the learning process. The first section encompasses 26 items which are used to measure acquired knowledge by the subjects after being provided with the 9 fact sheets content. The 26 multiple choice questions are answered with: *true*, *false* and *I don't know*. Total scores can range from 0 to 26. Some of the items respond to reverse score, such as 1, 5, 7, 8, 10, 12, 14, 20, 22, 25, 26. This tool has been recently developed and has been translated for use in this study. Therefore, the Spanish version was for the first time evaluated in the present study.

2.4.2.5 Statical Analysis

A comparative study was conducted with the Student t test for the results of the three groups.

2.4.2.6 Results

Significant differences in pain neuroscience knowledge of both PNE groups were found compared to the control group. When comparing both PNE groups, differences were not significant (Table 1).

	CG Mean (SD)	video-based (SD)	Written (SD)	F (p)	CG vs video-based			CG vs Written			video-based vs Written		
					d	p	(95%CI)	d	p	(95%CI)	d	p	(95%CI)
KNAPS	11.85 ± 4.82	16.90 ± 5.13	16.24 ± 5.52	29.58 (.000)	5.05	.000	3.331 to 6.776	4.04	.000	2.660 to 6.122	.662	1.000	-1.086 to 2.410

Table 1. Differences between written, video-based and control groups.

2.4.2.7 Discussion

This study aimed at analysing the usefulness of the 9 fact sheets based on PNE in two different formats (written and video-based) among 337 participants. The results of the study are significantly robust: the fact sheets have proven to be effective in providing adequate knowledge in both written and video-based formats.

The effective comprehension of the fact sheets achieved by all subjects is consistent with favourable results in FM patients from other studies (Van Oosterwijck et al., 2013). Regarding studies related to specific PNE formats, the results of the present study show discordance. In contrast to the study around scientifically based videos found on the online platform Youtube (Heathcote et al., 2019), the video-based format through a video in the present study does show an engaging effect among subjects. In relation to the written format, a favourable change in the subjects' learning was also perceived after reading the material. Considering the learning obtained, its relationship with a change in clinical aspects such as perceived symptoms, catastrophizing or improvement of the impact of FM could be subsequently evaluated for comparison with other studies (van Ittersum et al., 2013)

The effective use of this tool in two formats opens many options for implementing PNE in the clinical field. The written format can be a suitable tool for specific circumstances where the accessibility to information is difficult. For example, circumstances where access to technology or the Internet is not possible. The video-based format can be a helpful tool for virtual and/or face-to-face programs, or in general as a support tool for clinicians. Moreover, in both cases, having a validated PNE tool adapted to the specific population in terms of culture and language is a key element in clinical contexts where professionals' knowledge of pain neuroscience is limited. Another possible function attributable to the fact sheets is its usefulness in preventive medicine. Offering this tool to promote pain health among patients could lead to a reduction in disease impact and even clinical improvements. Along these lines, other studies have also evaluated and validated the effectiveness of medical educational materials for patients (Hirsh et al., 2009).

The validation of the fact sheets in terms of usefulness, also contributes to the scientific field. Having an effective pain neuroscience education tool opens the possibility for studies in relation to clinical knowledge and clinical improvement. Based on the present validation, correlation studies between the level of knowledge acquired and cognitive or behavioural changes could also be carried out.

2.4.2.8 Conclusions

The results of the study are significantly robust: the fact sheets have proven to be effective in providing adequate knowledge in both written and video-based formats.

2.4.3 Phase III: Correlation between patients' pain neuroscience knowledge and health status

This work aims at analysing the relationship between participants' pain neuroscience knowledge and health status after completing the multicomponent treatment for FM FIBROWALK.

2.4.3.1 Study objectives

-Correlation between patients' pain neuroscience knowledge and health status.

2.4.3.2 Participants

The data collected through the 337 participants recruited in the Phase I were used for this part.

2.4.3.3 Design

All 337 participants from the Phase I, after being provided with the fact sheets (in both formats written and video-based) participated in the multicomponent treatment for FM FIBROWALK (PNE, Therapeutic Exercise and Cognitive-behavioural Therapy) and completed questionnaires to measure functional impairment, physical functioning, anxiety, depression symptoms and kinesiophobia, and the KNAP-S to measure patients' pain neuroscience knowledge.

2.4.3.4 Study measures

The Knowledge and Attitudes of Pain Questionnaire Spanish version (KNAP-S) was used to measure pain neuroscience knowledge.

The Revised Fibromyalgia Impact Questionnaire (FIQR) assesses three dimensions: physical functioning, overall impact and intensity of the symptoms. The tool gathers information regarding the previous week from patient reports, clinical observations and functional status instruments and it encompasses 21 items with a numerical rating scale (from 0 to 10). Total scores fluctuate from 0 to 100, with a score of 100 indicating greater impact of FM. The Spanish version has been proven to have a satisfactory internal consistency ($\alpha = 0.93$) and acceptable test-retest reliability ($r = 0.84$) (Luciano et al., 2013).

The Hospital Anxiety and Depression Scale (HADS) measures levels of anxiety and depression. Despite the fact there are many questionnaires for assessing depression and anxiety, the HADS has been considered useful in evaluating fibromyalgia (Pascual López et al., 2004). This tool encompasses seven items related to both dimensions (depression and anxiety), from which each responds on a Likert scale (0-4). Total scores fluctuate from 0 to 21, with a score of 21 indicating greater severity of symptoms. The Spanish version has a satisfactory internal consistency for anxiety ($\alpha = 0.83$) and for depression ($\alpha = 0.87$) (Vallejo et al., 2014).

The Tampa Scale for Kinesiophobia (TSK) measures kinesiophobia (Miller et al., 1991). This scale is compounded by 11 items that can be responded with a 4-point Likert scale (from 0 to 11). Total scores of this questionnaire can range from 11 to 44: higher scores

indicate greater fear of movement and pain. The Spanish version shows presents internal consistency (alfa=0.79) (Gómez et al., 2011); in our sample, alfa= 0.90.

The physical functioning element of the 36-Item Short Survey (SF-PF) (Ware & Sherbourne, 1992) measures physical functioning. The subscale incorporates a total of 10 items, with a 3-point Likert scale answer format. Total scores are converted in order that score range from 0 to 100: higher scores indicate superior physical functioning. The Spanish version presents adequate internal consistency (alfa =0.94) (Alonso et al., 1995); in our sample, alfa =0.86.

2.4.3.5 Statistical Analyses

The Pearson correlation coefficient was used to measure the linear correlation between patients' pain neuroscience knowledge and patients' health status (functional impairment, physical functioning, anxiety, depression symptoms and kinesiophobia.).

2.4.3.6 Results

In Table 2 the correlation analysis between pain neuroscience knowledge and health outcomes is presented. Health outcomes are measures with functional impairment, physical functioning, anxiety, depression symptoms and kinesiophobia.

		Functional Impairment	Anxiety	Depression Symptoms	Physical Functioning	Kinesiophobia
KNAP-S	C Pearson	-.344	-.223	-.303	.340	-.573
	p	.000	.000	.000	.000	.000

Table 2. Correlational analysis for pain neuroscience knowledge and health status.

There is a significant correlation between pain neuroscience knowledge and health outcomes: functional impairment, physical functioning, anxiety, depression symptoms and kinesiophobia (Table 2).

2.4.3.7 Discussion

This study aimed at analysing the relationship between participants' pain neuroscience knowledge and health status. The results of the study are significantly robust: there is a correlation between pain neuroscience knowledge and *all* the study outcomes.

In terms of the significant influence of PNE on health status in FM, these results are consistent with previous research. The significant relationship between cognitive aspects and pain shown in this study is consistent with the bidirectionality between these two elements shown in another research (Lazaridou et al., 2017; Villemure and Bushnell, 2002). Furthermore, this is not only present when participants were provided with PNE but also with the CG. Therefore, this study contributes towards the progress in the study of pain understanding's influence on several pain-related variables.

5.5.7 Limitations

Limitations of this research include the fact that this is the first time the KNAP-S has been used. Therefore, a validation of the KNAP-S is suggested in order to be able to use it also in both clinical and research settings. Also, more research of the fact sheets in other languages should be carried out to extrapolate results. Another limitation is that evaluation of previous

participants' pain neuroscience knowledge was not collected, therefore previous knowledge might influence the KNAP-S results after being provided with the fact sheets. Nevertheless, this was computed through the control group that was not provided with any PNE content.

3. General Conclusions

- 1) The feedback received from the 10 FM subjects was positive and perception of learning corresponded with actual learning.
- 2) This study provides the Spanish validation of a new PNE tool with two different formats: written and video-based for clinicians working with FM patients.
- 3) A significant correlation between patients' pain neuroscience knowledge and health status was found.

Further quantitative and qualitative research is required to enhance PNE for research and all clinical settings and contexts.

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