Conceptualization of poor sleep quality in the context of fibromyalgia: from patient experience to management

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CONCEPTUALIZATION OF POOR SLEEP QUALITY IN THE CONTEXT OF FIBROMYALGIA: FROM PATIENT EXPERIENCE TO MANAGEMENT

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TESI DOCTORAL

CONCEPTUALIZATION OF POOR SLEEP QUALITY IN THE CONTEXT OF FIBROMYALGIA: FROM PATIENT EXPERIENCE TO MANAGEMENT

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The night is only a sort of carbon paper,
Blueblack, with the much-poked periods of stars
Letting in the light, peephole after peephole —
A bonewhite light, like death, behind all things.
Under the eyes of the stars and the moon's rictus
He suffers his desert pillow, sleeplessness
Stretching its fine, irritating sand in all directions.

Over and over the old, granular movie
Exposes embarrassments–the mizzling days
Of childhood and adolescence, sticky with dreams,
Parental faces on tall stalks, alternately stern and tearful,
A garden of buggy rose that made him cry.
His forehead is bumpy as a sack of rocks.
Memories jostle each other for face-room like obsolete film stars.

He is immune to pills: red, purple, blue —
How they lit the tedium of the protracted evening!
Those sugary planets whose influence won for him
A life baptized in no-life for a while,
And the sweet, drugged waking of a forgetful baby.
Now the pills are worn-out and silly, like classical gods.
Their poppy-sleepy colors do him no good.

His head is a little interior of grey mirrors.
Each gesture flees immediately down an alley
Of diminishing perspectives, and its significance
Drains like water out the hole at the far end.
He lives without privacy in a lidless room,
The bald slots of his eyes stiffened wide-open
On the incessant heat-lightning flicker of situations.

Nightlong, in the granite yard, invisible cats
Have been howling like women, or damaged instruments.
Already he can feel daylight, his white disease,
Creeping up with her hatful of trivial repetitions.
The city is a map of cheerful twitters now,
And everywhere people, eyes mica-silver and blank,
Are riding to work in rows, as if recently brainwashed.

Insomniac. Crossing the Water. Sylvia Plath

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Abstract

The general objective of this doctoral thesis was to conceptualize poor sleep quality in the context of fibromyalgia taking the Symptom Management Theory as a biopsychosocial conceptual framework. The specific objectives were: i) To develop a protocol for a Web-Based Therapeutic Education Intervention about sleep and pain for women diagnosed with Fibromyalgia (study I), ii) To identify and synthesize the available qualitative literature on the experience of poor sleep quality in the context of Fibromyalgia (study II), iii) To explore how Spanish adult women diagnosed with Fibromyalgia experience and manage poor sleep quality (study III), iv) To describe and analyze the psychometric properties of the validated Self-Reported Outcome Measures for assessing sleep quality in Fibromyalgia (study IV). Each of the studies included in this doctoral thesis was developed using different methodological approaches. Study I was a mixed methodology protocol with a sequential exploratory design. With study II, a meta-synthesis of qualitative studies was performed. In study III, a qualitative approach was implemented, conducting semi-structured personal interviews with 21 adult women from the Lleida region diagnosed with fibromyalgia. Finally, study IV was a COSMIN systematic review. Taken together, the results of studies II and III showed that poor sleep quality is perceived as a severe symptom of fibromyalgia and the most common problems are those related to the initiation and maintenance of sleep, and dissatisfaction with the amount of daily sleep. Women diagnosed with fibromyalgia respond to poor sleep quality by developing catastrophic thoughts and feeling helplessness and frustration at not being able to sleep. They perceive that their self-management strategies are ineffective because they do not receive enough information from health care professionals, whose therapeutic focus is mainly pharmacological. Women with fibromyalgia claim as a basic need to have a greater knowledge about sleep in their health condition and to be educated on how to develop effective management strategies that allow them to have a good quality of sleep. Study IV showed that there are five self-reported outcome measures to assess the quality of sleep validated in people with fibromyalgia, although the psychometric measures of the Fibromyalgia Sleep Diary, which is the only measure developed specifically for fibromyalgia, have not been investigated. In conclusion, poor sleep quality is perceived as one of the symptoms of greater severity and impact in fibromyalgia. In addition, it is necessary to develop therapeutic approaches from a biopsychosocial perspective that include education programs focused on people's needs and that contribute to modifying maladaptive cognitions related to sleep and, in turn, facilitate the development of effective self-management strategies.

Keywords: Fibromyalgia; Poor Sleep Quality; Symptom Management Theory; Symptom Experience; Patient-Centered Care.

Resumen

El objetivo general de esta tesis doctoral fue el de conceptualizar la baja calidad del sueño en la fibromialgia tomando la Teoría de Manejo Sintomático como marco conceptual desde una perspectiva biopsicosocial. Los objetivos específicos fueron: i) Desarrollar un protocolo para una intervención educativa terapéutica basada en la web sobre el sueño y el dolor para mujeres diagnosticadas con fibromialgia (estudio I), ii) Identificar y sintetizar la literatura cualitativa disponible sobre la experiencia de la baja calidad del sueño en el contexto de la fibromialgia (estudio II), iii) Explorar cómo las mujeres adultas españolas diagnosticadas con fibromialgia experimentan y manejan la mala calidad del sueño (estudio III), iv) Describir y analizar las propiedades psicométricas de las medidas de resultado autoinformadas validadas para evaluar la calidad del sueño en la fibromialgia (estudio IV). Cada uno de los estudios incluidos en esta tesis doctoral se abordó utilizando diferentes enfoques metodológicos. El estudio I es un protocolo de metodología mixta con diseño exploratorio secuencial. En el caso del estudio II, se realizó una meta-síntesis de estudios cualitativos. En el estudio III se implementó un enfoque cualitativo, realizando entrevistas personales semi-estructuradas a 21 mujeres adultas de la región de Lleida diagnosticadas con fibromialgia. Finalmente, el estudio IV fue una revisión sistemática COSMIN. En conjunto, los resultados de los estudios II y III mostraron que la baja calidad del sueño es percibida como un síntoma severo de la fibromialgia y los problemas más comunes son los relacionados con el inicio y mantenimiento del sueño, así como insatisfacción con la cantidad de sueño diaria. Las mujeres con fibromialgia responden a la baja calidad del sueño desarrollando pensamientos catastróficos y sienten impotencia y frustración por no poder dormir. Perciben que sus estrategias de automanejo son inefectivas porque no reciben suficiente información por parte de los profesionales sanitarios, cuyo enfoque terapéutico es principalmente farmacológico. Las mujeres con fibromialgia reclaman como una necesidad básica tener un mayor conocimiento sobre el sueño en el contexto de su condición de salud y ser educadas en cómo desarrollar estrategias de manejo. El estudio IV evidenció que existen cinco medidas de resultado autoinformadas para valorar la calidad del sueño en personas con fibromialgia. En conclusión, la baja calidad del sueño es percibida como uno de los síntomas de mayor severidad e impacto en el contexto de la fibromialgia. Además, es necesario el desarrollo de enfoques terapéuticos desde una perspectiva biopsicosocial que incluyan programas de educación centrados en las necesidades de las personas y que contribuyan a modificar cogniciones maladaptativas relacionadas con el sueño y, a su vez, faciliten el desarrollo de estrategias efectivas de automanejo.

Palabras clave: Fibromialgia; Baja Calidad del Sueño; Teoría de Manejo Sintomático; Experiencia Sintomática, Cuidado Centrado en el Paciente

Resum

L'objectiu general d'aquesta tesi doctoral va ser el de conceptualitzar la baixa qualitat del son en el context de la fibromiàlgia prenent la Teoria de Maneig Simptomàtic com a marc conceptual des d'una perspectiva biopsicosocial. Els objectius específics van ser: i) Desenvolupar un protocol per a una intervenció educativa terapèutica basada en la web sobre el son i el dolor per a dones diagnosticades amb fibromiàlgia (estudi I), ii) Identificar i sintetitzar la literatura qualitativa disponible sobre l'experiència de la baixa qualitat del son en el context de la fibromiàlgia (estudi II), iii) Explorar com les dones adultes espanyoles diagnosticades amb fibromiàlgia experimenten i manegen la baixa qualitat del son (estudi III), iv) Descriure i analitzar les propietats psicomètriques de les mesures de resultat autoinformades validades per avaluar la qualitat del son en la fibromiàlgia (estudi IV). Els estudis inclosos en aquesta tesi doctoral es varen abordar utilitzant diferents enfocaments metodològics. L'estudi I és un protocol de metodologia mixta amb disseny exploratori seqüencial. En el cas de l'estudi II, es va realitzar una meta-síntesi d'estudis qualitatius. En l'estudi III es va implementar un enfocament qualitatiu, realitzant entrevistes personals semiestructurades a 21 dones adultes de la regió de Lleida diagnosticades amb fibromiàlgia. Finalment, l'estudi IV va ser una revisió sistemàtica COSMIN. En conjunt, els resultats dels estudis II i III van mostrar que la baixa qualitat del son és percebuda com un símptoma sever de la fibromiàlgia i els problemes més comuns són els relacionats amb l'inici i manteniment del son, així com insatisfacció amb la quantitat de son diària. Les dones amb fibromiàlgia responen a la baixa qualitat del son desenvolupant pensaments catastròfics i senten impotència i frustració per no poder dormir. Perceben que les seves estratègies d'automaneig són inefectives perquè no reben suficient informació per part dels professionals sanitaris, donat que l'enfocament terapèutic és principalment farmacològic. Les dones amb fibromiàlgia reclamen com una necessitat bàsica tenir un major coneixement sobre el son en el context de la seva condició de salut i ser educades en com desenvolupar estratègies de maneig efectives. L'estudi IV va evidenciar que hi ha cinc mesures de resultat autoinformades validades per valorar la qualitat del son en persones amb fibromiàlgia. En conclusió, la baixa qualitat del son és percebuda com un dels símptomes de major severitat i impacte en el context de la fibromiàlgia. A més, és necessari el desenvolupament d'enfocaments terapèutics des d'una perspectiva biopsicosocial que incloguin programes d'educació centrats en les necessitats de les persones i que contribueixin a modificar cognicions maladaptatives relacionades amb el son i, al seu torn, facilitin el desenvolupament d'estratègies efectives d'automaneig.

Paraules clau: Fibromiàlgia; Baixa Qualitat del Son; Teoria de Maneig Simptomàtic; Experiència Simptomàtica; Atenció Centrada en el Pacient.

INTRODUCTION AND OVERVIEW OF THE THESIS

Introduction

Fibromyalgia (FM) is a central sensitivity syndrome that affects up to 2.10% of people worldwide with a prevalence in Spain of 2.4% of the general population over 20 years of age. FM is predominantly diagnosed in women with a female to male ratio of 21:1 (1,2), and representing the 90% of the cases (3).

Although FM does not have a notorious prevalence compared to other rheumatologic conditions, its economic impact in Spain is estimated at around 13 billion euros per year (1). About 75% of this economic burden is mainly related to indirect costs due to the loss of productivity. Current scientific evidence indicates that there is a positive correlation between the severity of FM and the costs associated with it, with a cost difference of more than 200% between people with moderate and severe symptoms (4).

People diagnosed with FM also show an increased use of health services and, in terms of medical consultation, it represents approximately the 5,7% of the total in the primary care setting and the 20% in the secondary or specialized care setting (1).

This syndrome is one of the most common causes of widespread musculoskeletal pain in adults (5) and poor sleep quality is a prominent factor affecting between 65 and 99% of people diagnosed with FM (6–8). Other authors (9) state that 63% of these patients report 2 or more symptoms of difficulty sleeping, while only 11.2% report having no problem sleeping. A recent meta-analysis of case-control studies indicated that, in comparison with healthy controls, people with FM show significant lower sleep efficiency and sleep quality, shorter sleep duration, longer wake time after sleep onset and more percentage of light sleep stages when assessed with polysomnography. Subjective assessment showed that patients with FM have more difficulties falling asleep and worse sleep efficiency. Therefore, and although there are no conclusive data regarding the prevalence of poor sleep quality in FM, the results presented reveal that it is a recurrent and a concerning symptom among these patients (10). Furthermore, poor sleep quality has been shown to be related with increases in the intensity of pain, and it is an aggravating factor of other FM symptoms such as fatigue, cognitive problems and poor quality of life (8,11).

As to date no curative treatments are available, efforts of health providers should be focused on providing treatment approaches that facilitate the development of effective self-management strategies to their FM patients (12). Treatments and recommendations should be patient-centered, adapted to the specific needs of patients with FM.

Overview of the thesis

This Doctoral Thesis is a research document on the conceptualization of poor sleep quality in FM, exploring how people diagnosed with FM evaluate and respond to poor sleep quality and their experience with prescribed and self-management strategies to cope with it. This research document also presents the validity and reliability of the available self-reported outcome measures validated in patients with FM for the assessment of poor sleep quality. In addition, a protocol for a web-based therapeutic educational intervention for the treatment of pain and poor sleep quality in women diagnosed with FM is presented.

The present doctoral thesis is organized into the following sections: 1) Introduction and overview of the thesis, 2) Fibromyalgia in context: Clinical construct, 3) Conceptual framework, 4) Objectives, 5) Methodology, 6) Results, 7) Discussion, 8) Conclusions, 9) References, 10) Appendices. The structure of each section it is outlined below:

Fibromyalgia in context: Clinical construct

This section aims to provide an overview of FM from a clinical perspective. The current scientific evidence regarding the etiology and pathophysiology of FM, the nociceptive and pain processing alterations both at the peripheral and the central nervous system, the existent relationship between poor sleep quality and pain, and the current treatment approaches for FM were reviewed and summarized.

Conceptual Framework

The Symptom Management Theory (SMT) was taken as a conceptual framework. The SMT is a middle range theory that can be applied to both the clinical practice and research in order to guide the assessment of the experience of symptom/s and to develop management strategies. The theory is based on the assumption that the symptom management process is dynamic and multidimensional, and it is organized into three interconnected dimensions: 1) Symptom Experience, 2) Symptom Management Strategies, and 3) Outcomes. To comprehensively explore the symptom/s experience domain, the three factors nested within said domain should be assessed: perception, evaluation and response; the dimension of symptom management strategies explores how the symptom/s are treated and/or managed; and the outcomes dimension recommends assessing functional and emotional status, quality of life, self-care, costs, mortality and morbidity to analyze the effects of the management strategies. This section includes a brief overview of the SMT and how it was integrated into this doctoral thesis.

Objectives

In this section, we define the general and specific objectives of the present research document.

Methodology

This section describes the methods implemented for the development of each of the scientific papers that are part of this doctoral thesis. A combination of qualitative and quantitative approaches was applied to respond to the objectives of this research, including a mixed methods research protocol (study I), a qualitative metasynthesis (study II), a qualitative inquiry (study III), and a COSMIN systematic review of patient-reported outcomes measures (study IV).

Results

In this section are presented the results of the studies II, III, and IV. Studies II and III attempted to provide a comprehensive account of poor sleep quality in FM in terms of patients' experience and self-management of the symptom, and their perceptions about the treatments prescribed by healthcare professionals. In study IV patient-reported outcomes measures validated in people diagnosed with FM for the assessment of poor sleep quality were described and their psychometric properties analyzed.

Discussion

This section summarizes the findings of the studies II, III, and IV placing them in the context of the previous and most relevant scientific literature investigating poor sleep quality in patients with FM.

Conclusions

The general conclusions of this doctoral thesis are presented in this section, including recommendations for future research.

FIBROMYALGIA IN CONTEXT: CLINICAL CONSTRUCT

Fibromyalgia: syndrome or disease?

The recognition of a health disorder has historically been based on the manifestation of certain signs and symptoms that, when they occur simultaneously, characterize a specific pathological entity. Likewise, these pathological entities can be classified according to a basic criterion, whether their etiology is known or not. When the etiology is clearly described and the cause identified, that pathological entity is called disease. However, when there is over one possible cause or it is unknown, it is called syndrome (13).

In the case of FM, and after the celebration in Copenhagen of the 2nd World Congress on Myofascial Pain and Fibromyalgia, the so-called Declaration of Copenhagen was drafted and FM was established as a distinctive diagnosis (14). In addition, the ACR developed and validated specific diagnostic criteria for FM two years earlier (6). These two facts contributed to the WHO's inclusion of FM in the International Statistical Classification of Diseases and Related Health Problems (ICD-10) in Chapter 13 "Musculoskeletal System Disease and Connective Tissue Disease" as a soft tissue disorder neither specified nor classified under another concept (15). Thus, FM is recognized as a disease by the WHO since it was incorporated into the ICD-10 in 1992. Taken together, these events served to legitimize people diagnosed with FM and to recognize FM as a cause of disability and early retirement (14).

In the most current version of the ICD, the ICD-11, FM can be found in the Chapter 21 "Symptoms, signs or clinical findings, not elsewhere classified" as a "General symptom" and classified as Chronic Widespread Pain (MG30.01). Therefore, and although FM is included in the ICD-11 and recognized as a distinct health condition, it is not classified as a disease *per se.*

Recently, the IASP Working Group in collaboration with the WHO (16) developed a new classification of chronic pain with the aim of incorporating it into the ICD-11. In this classification, two top level diagnoses were established for chronic pain: 1) chronic primary pain and 2) chronic secondary pain syndromes. Chronic primary pain is defined as "pain in one or more anatomical regions that persists or recurs for longer than 3 months and is associated with significant emotional distress or functional disability and that cannot be better accounted for by another chronic pain condition" and chronic secondary pain syndromes "are linked to other diseases as the underlying cause, for which pain may initially be regarded as a symptom". Conceptually, in chronic primary pain syndromes, pain is understood as a health condition in itself, while in chronic secondary pain syndromes pain is understood as a symptom derived from another disease. FM is established as a first level diagnosis identified as "chronic widespread pain" and nested within the chronic primary pain classification (Figure 1: IASP chronic pain classification).

Therefore, taking into account the data presented above, FM must be understood as a legitimate health condition. However, given the criteria that differentiate disease from syndrome, and that the underlying etiology and physiopathology of FM continue to be a subject of current scientific debate, throughout this doctoral thesis I will refer to FM as a syndrome.

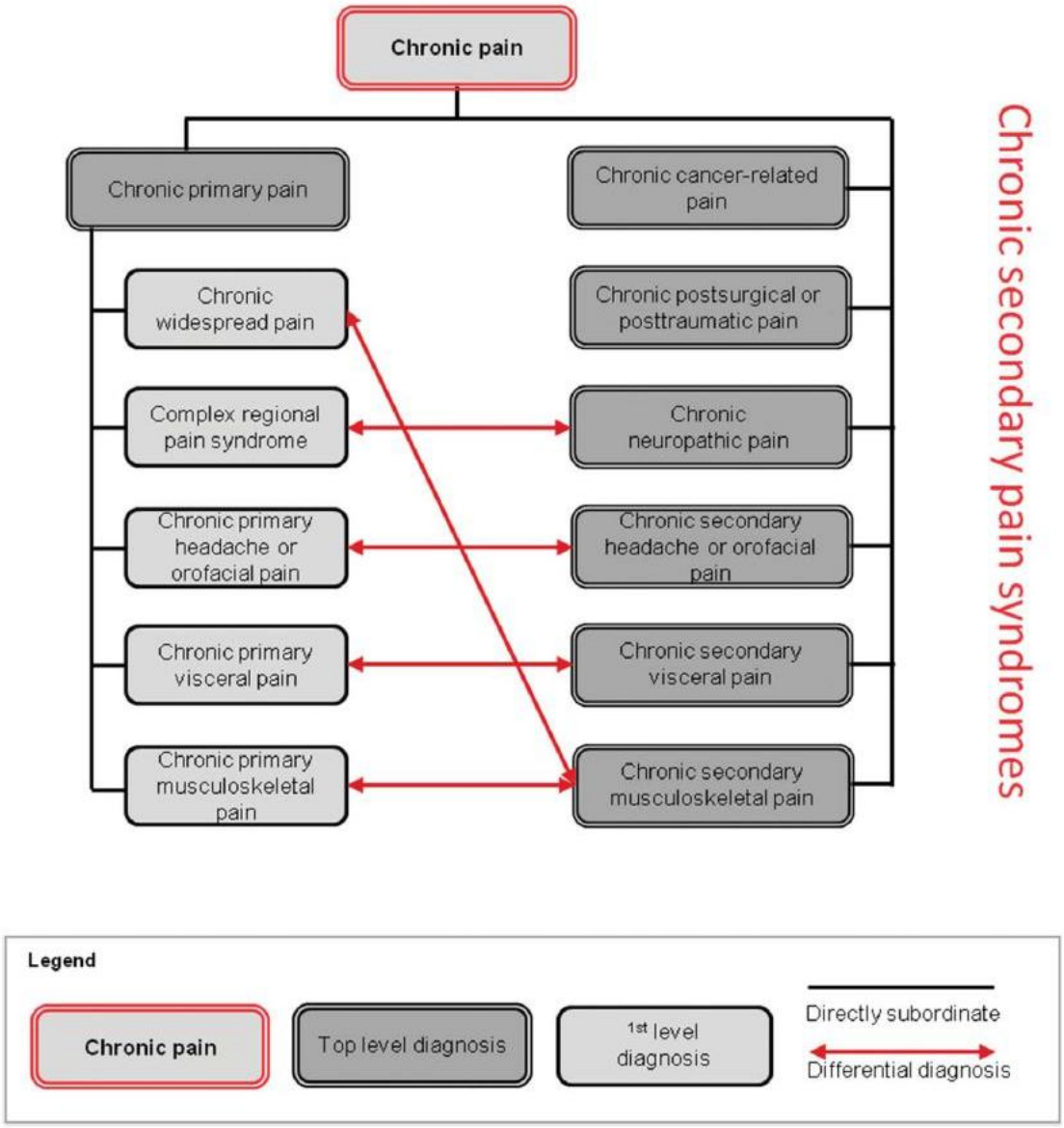

Figure 1. IASP chronic pain classification. From Treede et al. (16).

Epidemiology

Between 10 and 30% of the world's population suffers from chronic widespread pain (17) and FM is one of its most common causes (18). According to the results of the "Worldwide Epidemiology of Fibromyalgia" study (18) including data from 26 studies, a global prevalence of 2.7% was estimated. However, the data on the prevalence are very variable among countries, being a rare diagnosis in countries like Venezuela, where the prevalence of FM is around 0.2% (19,20) to 6.4% in the United States of America (20,21). In

Spain there is an estimated prevalence of 2.4% among the adult population over 20 years of age (1). In terms of gender, FM is mainly diagnosed in women with a prevalence range of 2.4-6.8% (20,22–24) and representing more than 90% of the cases (3). In relation to age, although FM can also appear during childhood, adolescence (25) or old age (20), it seems that this health condition appears for the first time mostly in middle-aged adults (18). Also, studies comparing the prevalence of FM in rural and urban areas showed that people living in rural areas are more likely to be diagnosed with FM (20,26–30). Other identified risk factor for the development of FM are low education and low socioeconomic status (31–34).

Under the results of a US National Health Interview Survey study (35), in which they included a representative sample of 8446 persons, there are some differences in the prevalence of FM based on ethnicity. The lowest prevalence was found in Asian people with a percentage of 0.20%; while those classified as "all other races" by the authors (including multiracial people, Other Pacific Islander, Asian and Native Hawaiian) showed a prevalence of 7,35%. However, there were no prevalence differences among Hispanics, non-Hispanic blacks and non-Hispanic whites in comparison with non-Hispanic whites.

Other factors than seem to predispose to developing FM are obesity, smoking behavior and being divorced or separated (35).

Therefore, epidemiological data in relation to FM seem to point out that low-educated middle-aged women living in rural areas are more prone to be diagnosed with FM.

Diagnosis

'Fibromyalgia, like beauty, may be in the eye of the beholder (the clinician)' Frederick Wolfe (36).

There is no binding definition of FM or objective medical tests that guide the diagnostic process of this health condition. The minimum requirements to establish the diagnosis of FM have evolved since Smythe and Moldofsky (37) published for the first time in 1977 criteria based on pain and non-restorative sleep, which they considered the central symptoms of the syndrome. In relation to pain, they focused the diagnostic process on the evaluation of 14 anatomical sites, of which 12 had to show pressure sensitivity, although they did not propose a clear method of evaluating the rest of the symptoms. Therefore, the assessment of sensitive points became the gold standard of that time to diagnose FM.

These criteria were not without criticism since patients with such a high number of sensitive points are rarely found in daily clinical practice. Consequently, other researchers and clinicians proposed to reduce the number of sensitive points evaluated and that should be positive to establish the diagnosis of FM (38).

In 1981, Yunus et al. (39) studied 50 subjects diagnosed with primary FM with the aim of clinically characterizing this health condition and raised new diagnostic criteria. The results of this study took an alternative approach, more focused on the overall set and not only on applying pressure on sensitive points. Their criteria were based on references by patients of pain or stiffness of at least three months in three different body areas and the presence of at least five sensitive points. In addition, symptomatic modulation because of physical activity, atmospheric conditions, poor sleep quality, anxiety, stress, chronic headache, fatigue, swelling, paraesthesia, and irritable bowel syndrome should be taken into account. These criteria also considered heterogeneity among patients, so that those who reported less painful areas had to present a greater number of symptoms, and vice versa, to establish the diagnosis.

In 1990 the American College of Rheumatology (ACR) (6) studied the number of sensitive points needed to establish a FM diagnosis given the lack of agreement on previous criteria. There was also a clear need to unify how these points should be assessed, so that they established an assessment by applying a total force of 4kg with the pulp of thumb or with the first two or three fingers. The ACR also established a definition of FM as a "syndrome associated with generalized pain and multiple painful regions, particularly in the axial skeleton…sleep disturbances, fatigue, and stiffness are the central symptoms of fibromyalgia...other symptoms, such as anxiety, irritable bowel syndrome, modulating factors etc., are less common". Although the definition highlighted the multisymptomatic nature of FM, the 1990 ACR criteria for FM diagnosis were based exclusively in the assessment of pain (6).

Nonetheless, bearing in mind that widespread pain is highly prevalent (10-12%) in the general population (40), the above presented criteria could lead to misdiagnosis. Furthermore, these criteria did not permit the assessment of other commonly reported symptoms among people suffering from FM such as poor sleep quality, fatigue, and cognitive alterations, among others. Consequently, the ACR developed a new tool for the diagnosis of FM in 2010 which did not replace the 1990 but represented a complementary method of diagnosis (41).

These last criteria were updated in 2011 with the aim of facilitating their use in clinical and epidemiological studies without the need for an examination by a specialist doctor. The main modification was the assessment of symptomatic severity by the doctor, which was replaced by a self-reported symptomatic severity scale and that maintained a high sensitivity index (42).

Despite the great utility and high sensitivity of the 2010/2011 diagnostic criteria, they were criticized by Mader et al. (43), who stated: "It is also true that by the 2010 criteria, the responsibility to diagnose the patient shifts from the physician to a research assistant or a nurse. The authors consider CWP as a surrogate for FM, allowing an unbiased diagnosis. Why use a surrogate instead of the real thing? A

diagnosis that is based solely on the patient's description and interview, without physical examination and at least some objective or semiobjective signs, is often extremely biased. Quantity is not a substitute for quality". The later statement underscores the author's disagreement with the new criteria and emphasizing that the clinical judgment of physicians should be more relevant throughout the diagnostic process. Thus, these authors opted to return to the assessment of the sensitive points established in the 1990 criteria since, in their view, when evaluated by trained health professionals and together with the general clinical assessment, they were a more objective measure than the 2010/2011 diagnostic criteria.

In a subsequent study of the ACR, it was observed that the 2010/2011 criteria presented classification errors of patients with regional pain syndromes derived from the lack of clarity regarding the criteria of generalized pain. When these criteria were modified, the classification errors disappeared and the new diagnostic criteria were established (44). Additionally, these criteria address another important aspect in the diagnostic process of FM and that until now had caused confusion both at clinical and research levels, such as the validity of FM diagnosis even when other health conditions are present.

The American Pain Society together with the U.S. Food and Drug administration started the ACTTION-APS Pain Taxonomy (AAPT) creating an international working group of experts in FM to develop new diagnostic criteria that were recently published (45). The AAPT criteria are divided into two dimensions: Dimension 1: Core Diagnostic Criteria, Dimension 2: Common features. Dimension 1 include the assessment of multisite pain, sleep problems and fatigue, which were considered by the AAPT the core symptoms of FM. Dimension 2 include other symptoms that may support the diagnosis such as tenderness, dyscognition, musculoskeletal stiffness, and environmental sensitivity or hypervigilance.

The AAPT diagnostic criteria were not without criticism and Wolfe (46) considered that these criteria suppose a retrogression to a dichotomous view of FM when a general agreement exists that FM "quantity" is continuous. Wolfe also criticized the inclusion of pain assessment in head, chest and abdomen as this body sites were deliberately excluded in the most recent ACR criteria. Likewise, Salaffi et al. (47) found that the AAPT do not have good performance when compared with clinical judgement.

In accordance with the results of Salaffi et al. (47) the ACR 2011 criteria showed the best performance and highlighted the importance of including pain, sleep problems and fatigue as the core symptoms of the diagnostic process.

More innovative approaches for the diagnosis of FM are focused on biomarkers-based methods and biosensors. In regards to the former, it seems to provide a valid and a reliable source for differentiating patients with FM with patients with other rheumatologic diseases such as osteoarthritis, rheumatoid arthritis and systemic lupus erythematosus (48). As for biosensors, da Silva et al. (49) performed a

minireview and concluded that this analytical devices permit the analysis of different biological correlates (e.g. hormones) and, therefore, could offer a valid basis in the assistance of FM diagnosis.

Despite the easy access and use of the criteria described, they are not widely used at the clinical level and it is usual for FM to be diagnosed by exclusion. Primary health care professionals report lack of confidence and uncertainty regarding FM diagnostic criteria (50) which may explain why they do not use them in their daily base practice. This leads to a very long diagnostic process involving multiple medical visits (51). In addition, there are studies suggesting that this delay in the diagnosis negatively influences the quality of life of these patients (51,52), increases the use of health resources and, therefore, the economic costs derived from it (51,53,54).

Another important issue in diagnosing FM is the experience of patients when receiving the FM diagnosis. According to the results of a meta-ethnographic study (55), being diagnosed with FM only provide a short term relief as patients are informed that there is no curative treatment for their health condition, and that the available ones are far from effective in alleviating the symptoms. Although receiving the diagnosis of FM is initially perceived as validating their suffering, this perception transforms when they feel that health care professionals are skeptical about FM being a "real" health condition. Therefore, the challenge for health care professional when diagnosing FM is providing enough information to the patients for them to be able to attach a meaning to the "label" of FM, and facilitating them guidance on how to manage the symptoms that accompany this health condition. Otherwise, the diagnosis lacks its utility and becomes an empty and meaningless concept.

Etiology and Pathophysiology of Fibromyalgia

There is still no scientific consensus on both the etiology and the pathophysiology of FM and there are many theories that have been developed so far in this regard. However, in general terms, it is accepted that FM is a multifactorial health condition, that is, the development and maintenance of symptoms of FM are produced by the interaction of various factors at the biological, psychological and social level (56).

Genetic Factors

Familial Aggregation

The first evidence of a possible hereditary pattern of FM can be traced back to the late 80s when Pellegrino et al. (57) studied 17 families of people diagnosed with FM with 50 individuals. The results showed that 52% of the subjects had FM symptoms and 22% were asymptomatic but showed an abnormal muscle consistency, although there was no evidence of tender points. The remaining 26% had no symptoms of FM or alterations at the muscular level. The authors concluded that their results showed

evidence that FM could be an autosomal dominant hereditary condition. Following this line, Buskila et al. (58) found that of the 58 subjects analyzed, 28% met the clinical criteria for FM diagnosis and observed that family and psychological factors did not differ between descendants with and without FM. Therefore, the authors concluded that the presence of this syndrome in direct relatives of people who suffer from it could be attributed to genetic factors and not so much to psychosocial factors. Likewise, in another study (59) similar results were found as 26% of blood relatives of patients with FM could also be diagnosed with this syndrome. Finally, these findings were verified more recently by Arnold et al. (60) with a sample of 611 subjects, of whom 78 were people diagnosed with FM and the remaining 533 were first-degree relatives. The prevalence of FM among family members was 6.4% and it was shown that the family aggregation of this syndrome was independent of the aggregation of mood disorders, which is in line with the results of previous investigations (58). The authors concluded that both the FM and a low pain pressure threshold showed hereditary patterns. However, it must be noted that the inheritance mechanisms of FM are a current issue of research and, given the multifactorial nature of FM, a polygenic inheritance mode is postulated (61).

Genetic Linkage Analysis

The first study that showed a possible hereditary pattern of FM through genetic screenings was carried out by Yunus et al. (62) with a sample of 40 Caucasian families with multiple FM cases in two or more first-degree relatives, with a total of 85 subjects diagnosed and 21 unaffected relatives. The authors analyzed the possible existence of a genetic linkage by typing the human leukocyte antigens (HLA) for three different alleles (A, B and DRB1) and determining the haplotypes without knowing the diagnosis of each individual. This investigation results indicated a possible genetic link with the HLA region and heritability of this health condition. Additionally, when the family member diagnosed with FM also had depression, subgroup analyzes showed that this variable did not have a significant influence with the observed genetic results.

Candidate Genes

Besides the studies of the family aggregation of FM, and based on the results got by Lee et al. (63) in their SR with meta-analysis, there are many researches that have tested the possibility that various genetic polymorphisms in the catecholaminergic, dopaminergic and serotoninergic systems are associated with a greater susceptibility to develop FM. In this SR there were 17 candidate genes and over 35 polymorphisms that could predispose to the development of FM. Finally, data related to the genes Catechol-O-Methyl Transferase (COMT), serotonin transporter (5-HTTLPR) and serotonin 2A receptor (5-HT2A receptor) were meta-analyzed and the results showed a significant association for three

polymorphisms in the 5-HT2A receptor, which is indicative that said polymorphism may confer susceptibility to the development of FM.

A more recent review (64) notes that, although the association of the COMT gene with a greater susceptibility to FM remains a topic of scientific discussion, the Single Nucleotide Polymorphism (SNPs) rs4680 seems to be significantly associated with the development of FM in samples of Brazilian, Spanish, Turkish and Israeli people. In addition, there are indications that said polymorphism is also related to a greater severity of pain (65) and that acts moderating the relationship between catastrophizing and attention of pain as well as pain intensity (66). Although this polymorphism has not been significantly associated with FM in a Korean population sample, the polymorphisms rs4818 and rs4633 do seem to predispose to the development of this syndrome and are associated with greater pain sensitivity in said sample (67).

Focusing on the COMT gene haplotypes instead of individual SNPs, there is evidence indicating that the ACCG haplotype of the COMPT gene is associated with a greater sensitivity to the perception of painful stimuli, a greater presence of FM and higher scores in the Fibromyalgia Impact Questionnaire (FIQ) (68). Thus, although the COMT gene is one of the most studied FM susceptibility candidates, the results are inconclusive given the lack of statistical significance in the studies and meta-analyzes carried out so far.

In relation to the dopaminergic genes, only one study has been found (69) in which a repeating polymorphism of exon III of the dopamine (DA) receptor D4 is associated with personality traits in patients with FM. Taking into account the important role of DA in the descending modulation of pain (70), Park and Lee (64) concluded that more studies analyzing polymorphisms in this gene are necessary.

Genome-Wide Association Studies

The Genome-Wide Association Studies (GWAS) is a technique that allows to identify genetic variations related to diseases and is especially useful when it is intended to analyze the heritability and/or the genetic architecture of specific health conditions in observational studies (71). However, one of the most important disadvantages is that usually large sample sizes are needed when the incidence of the pathology, as in the case of FM, is low (72). In relation to FM, Feng et al. (73) performed a complete sequencing of the exome in a sample of 19 patients and, after filtering more than 80,000 SNPs found per patient, the results showed two nonsense mutations related to high plasma levels of inflammatory substances such as Monocyte Chemoattractant Protein 1 (MCP-1), Interferon γ-induced Protein 10 (IP-10) and Interleukin 12 (IL-12). These results suggest that alterations in the production of certain inflammatory substances may be linked to the development of FM. In another research (74) the genotype was determined and GWAS was performed in 116 families with multiple cases of FM. The authors found a possible genetic link in the

region of chromosome 17p11.2-q11.2, which coincidentally co-exists with the coordinates of the map for the vanilloid 2 potential transient gene and the serotonin transporter gene, both possibly related to FM (75–77).

DoCampo et al. (78) in a more recent study carried out in Spain with an initial sample of 313 patients affected with FM with low comorbidity and 220 controls, GWAS and array Comparative Genomic Hybridization (aCGH) experiments were performed. A significant association between SNPs and FM could not be demonstrated. However, the authors selected the 21 SNPs that showed more association and were replicated in a sample of 952 patients and 644 controls, observing that a polymorphism of the MYT1L gene, which encodes transcription factors that contribute to the development of the CNS in mammals and convert fibroblasts into neural cells, could be linked to FM with low comorbidities. Similarly, analyzes by aCGH showed that alterations in the NRXN3 gene, which encodes proteins at the CNS level that function as receptors and cell adhesion molecules, were also associated with FM with low comorbidities.

Based on the data presented, it could be considered that FM has a high component of family aggregation and that there are indications that genetic alterations act as predisposing factors that, combined with environmental stressors, could precipitate the development of FM (79).

Gene expression studies

Gene expression analysis "is the study of gene products by imaging, amplification, probe hybridization or sequencing-based detection methods" (80) providing a measure of mRNA concentration at a specific point in time. A recent study (81) performed in 54 women with FM demonstrate that three interrelated pathways involved in cellular growth and proliferation appear to be more active in patients with FM compared to matched controls. In this analysis, CENPK expression substantially differed between women with FM and healthy controls. CENPK is one of the complex protein subunits of CENP-H-I, which assist with the formation of kinetochore, the effective synthesis of centromere protein A (CENPA), and chromosomal segregation. Abnormal chromosome segregation can derive in genomic instability that has been demonstrated to be associated with multiple health conditions such as cancer, Alzheimer disease, arthritis, and systemic lupus erythematosus (81–83).

In response to environmental factors and in disease, MicroRNAs or miRNAs act as important modulators of gene expression in tissue-specific physiologic pathways (84–86). In this sense, alterations in miRNAs in the context of chronic health conditions may provide important information on complex gene expression network deregulations. Regarding this approach, Genome-wide expression profiling of miRNAs was assessed in Peripheral Blood Mononuclear Cells (PBMCs) in a pilot study performed by Cerdá-Olmedo

and colleagues (87). The results evidenced a marked downregulation of hsa-miR223-3p, hsa-miR451a, hsa-miR338-3p, hsa-miR143-3p, hsa-miR145-5p and hsa-miR-21-5p in the FM group compared to controls. In this context the authors proposed a signature of six strikingly downregulated miRNAs to be used as biomarkers of FM. However, validation in larger study groups must be required before the results can be transferred to the clinic.

Epigenetic Factors

The literal meaning of epigenetics is "in addition to changes in genetic sequence" and it refers to "any process that alters gene activity without changing the DNA sequence, and leads to modifications that can be transmitted to daughter cells" (88). These modifications can derive directly or be modified by the environment (89) and, although some of them may have negative effects on health status and lead to maladaptive behavioral changes, the epigenetic alterations must be understood as crucial and natural modifications that contribute to many essential physiological functions (88,89); usually through processes that can turn on and off some genes as well as modify their level of genetic expression (90). There are different types of epigenetic processes but the most studied at present is methylation (88).

Regarding FM, Menzies et al. (91) studied methylation patterns and the frequency of spontaneously occurring micronuclei (MN) in a sample of 10 patients with FM compared to 8 controls for methylation and 42 controls for MN. It was observed that 91% of the differentially methylated sites were related to genes with functions in the development of the CNS, neuronal differentiation, organic and skeletal development, and chromatin compaction. In addition, these differences in methylation patterns were due to increases in the sample values of patients with FM. A more current pilot study (92) with a sample of 24 people with FM and 24 healthy controls the authors observed a pattern of hypomethylation in genes with relevant functions related to DNA repair and/or elimination of free radicals and also in genes that modulate the physiological responses to stress.

Brain-Derived Neurotrophic Factor (BDNF) seems to have an important role in modulating nociceptive signals and hyperalgesic states, which is why it was postulated to being involved in the pathophysiology of FM (93). A recently published study (94) measured serum levels of BDNF and DNA methylation in a sample of 28 with Chronic Fatigue Syndrome/FM and 26 healthy controls. The results demonstrated that, in comparison with the control group, people with FM a BDNF DNA hypomethylation in promoter exon IX that predicted an increase in serum levels of BDNF. Likewise, higher levels of BDNF were shown to predict widespread hyperalgesia, among other symptoms.

Given that chronic widespread pain is the cardinal symptom of FM, it is considered of interest to present the results of studies that investigate the possible implication of epigenetic factors in their development

and/or maintenance. In this regard, a study carried out by Burri et al. (95) with a discovery sample of 281 homozygous twins and a replication sample of 756 women and 729 twin men with no family ties, found that both samples presented discordant CWP reports. In the analyzes between twins, 20 differentially methylated major positions were found, including one mapped to monoamine oxidase B, a gene that had already been investigated and associated with post-surgical and neuropathic pain (96,97). In the sample of twins without family ties, differentially methylated positions were found in a region of the REST gene, which has also recently been linked to the development and maintenance of neuropathic pain (98).

In summary, epigenetic studies in patients with FM are scarce, but they are considered of special interest for their potential in the search for biomarkers that serve, not only for the characterization of the syndrome but also for the development of possible treatment strategies.

Physical and Psychological Trauma

The Royal Academy of the Spanish Language (99) defines psychological trauma as an "Emotional shock that produces lasting damage in the unconscious" and as an "Emotion or negative impression, strong and lasting" and, as for the trauma of physical origin, affirms that it is of a "lasting injury produced by a mechanical agent, usually external".

Probably the physical and psychological trauma are the most controversial factors at the scientific level and have been the subject of complex discussions between a group of renowned researchers and FM experts which led to accusations among them of being more concerned with serving political interests than to the people themselves affected by this health condition (43). This confrontation clearly derived from the different perspectives among them regarding trauma as an etiological factor of FM during the celebration of the "Vancouver Fibromyalgia Consensus Conference" in 1994. After the conference, a consensus report was published (100) in which the obtained results after the respective votes in relation to aspects of FM and disability were detailed, noting that "there is insufficient data at this time to establish a causal relationship between FM and trauma". This report was followed by a publication led by Yunus (101) in which the authors stated that “our viewpoint in this paper states that both research data and clinical experience should be used to meaningfully address different aspects of FMS covered in the consensus report”. A few years later, Pellegrino (102), also showing his disagreement with the consensus report said “in the ensuing years, however, several studies have linked trauma and FM in a cause/effect relationship. If a vote were held today, I am certain that it would be different”. Finally, Wolfe, lead author of the consensus report, along with other colleagues recently published a review (103) in which they concluded that the majority of studies that relate FM with previous traumatic episodes are case or case

series reports and observational studies of very low to moderate methodological quality, which makes it difficult to confirm a true causal relationship.

Hypothalamic–pituitary–adrenal axis dysregulation

Although available scientific evidence about physical or psychological trauma as predisposing factors of FM is controversial, and that only 5 to 10% of people who has previously exposed to stressors are diagnosed with this syndrome (104), there are authors that argued that early life or adult stress could derive in alterations in the Hypothalamic-pituitary-adrenal axis (HPA) leading to a heightened severity of the symptoms in people with chronic pain conditions (105).

As depicted in Figure 2, under normal circumstances the hypothalamus releases corticotropin-releasing factor (CRF) when experiencing acute stress, leading to the activation of the pituitary gland with the consequent release of adrenocorticotrophic hormone (ACTH) which, in turn, will stimulate the adrenal cortex to release glucocorticoids. The release of CRF can also activate Mast cells, which release cytokines and growth factors that can activate peripheral nociceptors (105).

The stabilization of the HPA system is produced by a negative feedback loop in which cortisol (the main glucocorticoid involved in the stress response in humans) exerts a negative feedback to the hypothalamus and the pituitary gland and the release of CRF and ACTH is ceased, returning the systemic homeostasis. Other brain structures like the hippocampus and the amygdala are key in resetting the HPA axis after the cessation of the acute stressor by modulating the inhibition or activation of the HPA system, respectively (105).

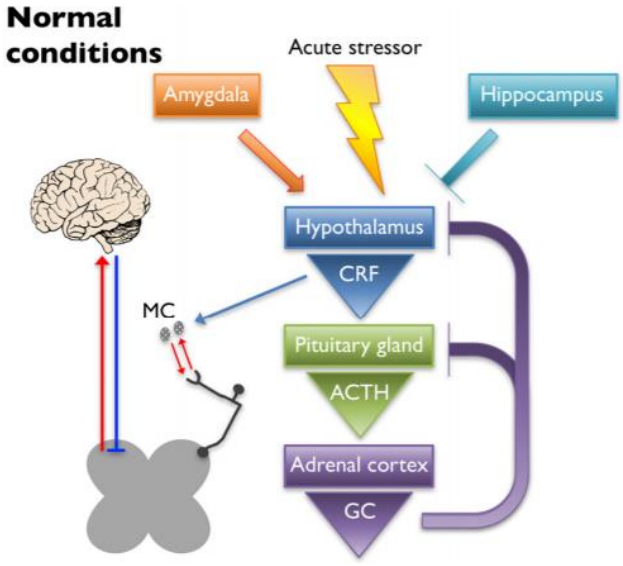

Figure 2. Response to the Hypothalamic-pituitary-adrenal axis to acute stressor in normal conditions. From Eller-Smith et al. (105).

As represented in Figure 3, when a person is exposed to a chronic or an early life stressor, the limbic system structures involved in the regulation of the HPA activity are altered. It has been observed that there is an augmentation of CRF release driven by the excitatory effects of the amygdala on the hypothalamus. Moreover, the inhibitory function of the hippocampus is impaired because of a decreased expression of brain-derived neurotrophic factor (BDNF) and glucocorticoid receptors (GR) as a consequence of chronic or early life stress. These alterations derive in an increased activity of the hypothalamus leading, in turn, to an increase in the release of CRF and a more prolonged and intense release of ACTH by the pituitary gland. Consequently, the adrenal cortex will increase the production of GC. Furthermore, as the modulating functions of the limbic system structures and the HPA system are impaired, this altered release of GC will be maintained even after cessation of the stressor (105).

As for the impact of this impaired stress response system on pain, Mast cells are the key elements that mediate this relationship. An increase in the release of CRF leads to a massive activation of Mast cells which ultimately derive in a process known as hyperalgesic priming by which a damaging event produces changes in the peripheral afferents that result in an exaggerated and prolonged hyperalgesic response to minimal or non-harmful subsequent stimulation. Likewise, it has been also observed that a greater activation of Mast cells derives in alterations at the Central Nervous System level leading to a process called wind up which alters pain processing (105).

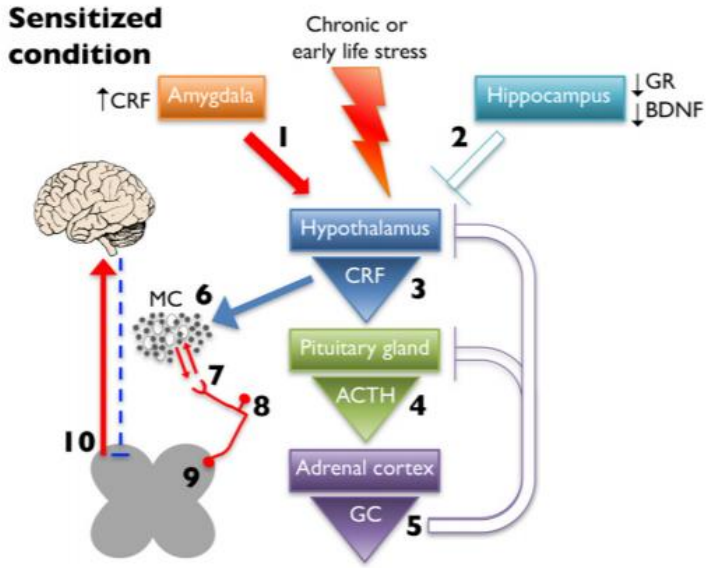

Figure 3. HPA axis and pain processing alterations derived from chronic of early life stress. From Eller-Smith et al. (105).

As for FM, there is a lack of studies describing accurately the alterations of the HPA axis in these patients. While there are evidences that people diagnosed with FM show a hypoactivation of the HPA axis there are also studies suggesting the opposite, that the HPA axis becomes hyperactive in FM (106).

Furthermore, other studies suggest that the dysfunction of the HPA may play a role only in a subset of people with chronic pain, as it has only been demonstrated in a very limited percentage of people diagnosed with chronic overlapping pain conditions (104). Therefore, further research is needed to explain what is the actual role of the HPA axis in FM.

Pain processing alterations

Pain is normal

If for a moment we consider a hypothetical reality in which we cannot feel pain, in a first impression it can be attractive given the unpleasantness of pain experience. However, we can consider ourselves fortunate to have a highly efficient system that protects us against situations that may even threaten our survival. In fact, it has been demonstrated that insensitivity to pain leads to a high incidence of injuries and disability (107). Therefore, as Butler and Moseley claimed (108) "pain is normal" and we must understand it as a strategy of our brain to protect ourselves and as a mechanism that favors healing in case of injury.

The International Association for the Study of Pain (IASP) recently announced a revised definition of pain (109) and stated that pain is "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". In accordance with the IASP definition, pain is not only the result of multiple complex physiological processes but it is also a subjective experience in which psychological and social factors are intimately involved. Therefore, the IASP understands pain as a biopsychosocial phenomenon and moves away from the Cartesian physiological theory of pain that, although it was a highly relevant scientific advance, led to a simplistic conception of pain experience.

The IASP, in the additional notes to the definition of pain, states that (110): "This definition avoids tying pain to the stimulus. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause". Consequently, a nociceptive stimulus per se does not necessarily leads to the perception of pain and is not always the origin of the experience of pain. Accordingly, in this doctoral thesis it is understood that, although pain is a potential consequence of the transmission of nociceptive information, nociception cannot be conceived as the unique cause of pain or understood as synonymous with pain.

Despite the fact that pain serves an essential protective function, it can become a pathological process in itself when its experience cannot be associated with a current or potential injury, having a great impact on the quality of life of people who suffer from it (111), as is the case of FM. In the following sections the

neurophysiology of pain and the central and peripheral mechanisms that have been demonstrated to be involved in the development and/or maintenance of chronic widespread pain in FM are summarized.

The neurophysiology of pain

Understanding why nociception is not a synonymous with pain is key to consequently understand the neurophysiology of pain. While nociception must be understood as a physiological response against an actual or potential tissue damage that is aimed at transmitting the noxious stimulus to the Central Nervous System , pain is always a response of the brain to an actual or potential tissue damage based on cognition, emotion and behavior (112).

Under normal physiological conditions, a peripheral noxious stimulus causes the activation of peripheral nociceptors, the receptors that relay nociceptive information and that are localized in multiple body areas as the skin, viscera, muscles and joints. Nociceptors conduct impulses through thinly myelinated A-δ fibers and unmyelinated high threshold C-fibers which convert chemical, thermal or mechanical stimuli into electrical stimuli firing action potentials. This electrical stimulus (action potential) is conducted from the periphery to the dorsal horn of the spinal cord. Once the action potential reaches the spinal cord, the presynaptic neurons release glutamate, substance P and calcitonin gen-related peptide (CGRP) which act as pronociceptive neurotransmitters and bind to AMPA, NK-1 and CGRP receptors, respectively. Consequently, secondary neurons are activated sending the information to higher centers such as the thalamus, the periaqueductal gray matter (PAG) and the nucleus raphe magnus (NRM) through the lateral spinothalamic and the medial spinoreticular tracts. From the thalamus the nociceptive information travels to the primary and secondary somatosensory cortices via tertiary neurons where the sensory quality of pain is processed, and to other limbic regions such as the insula and the anterior cingulate cortex (ACC) which are involved in the emotional and affective pain components. The ascending nociceptive pathways and the brain areas involved in pain processing are depicted in Figure 4 and Figure 5, respectively.

Melzack and Wall (113) published the gate control in the mid-60s explaining how nociceptive signals can be modulated when reach the spinal cord and that nociceptive signals are not integrated in a lineal manner. Consequent investigations demonstrated that nociceptive signals can be modulated at any level of the Central Nervous System and that this modulation can be facilitatory or inhibitory (114). Likewise, pain signals can be modulated at both the ascending and the descending pathways and the main substances involved in the modulation are opioids, dopamine, norepinephrine, serotonin, cholecystokinin, GABA, and galanin (70).

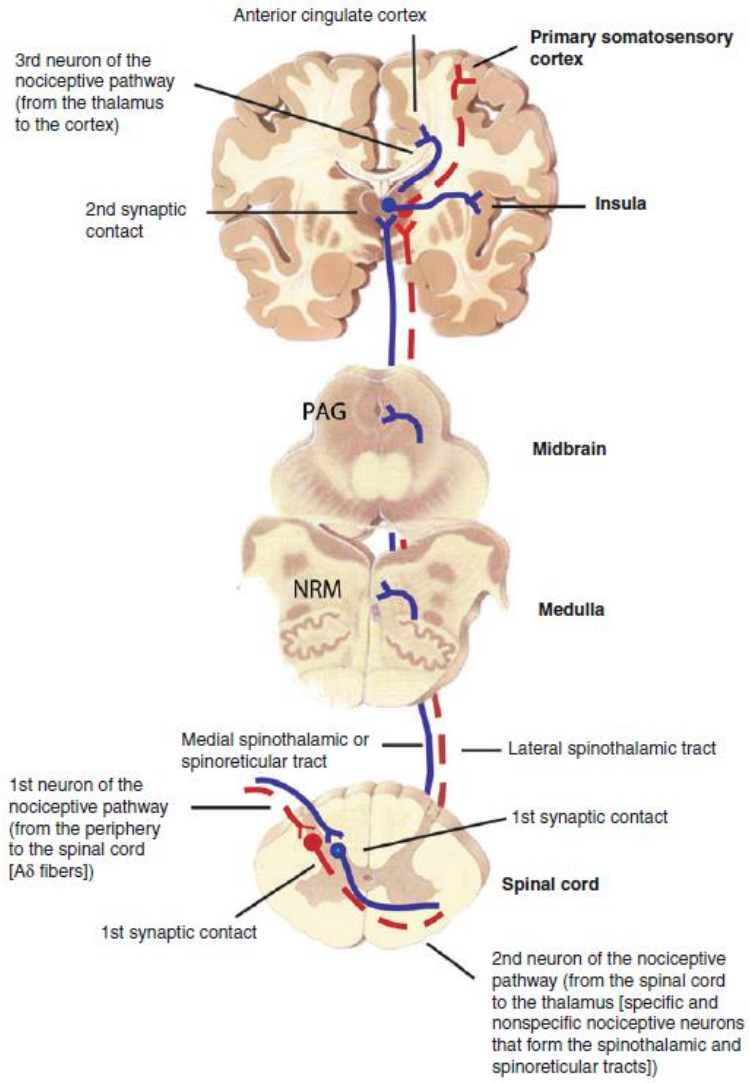

Figure 4. Ascending nociceptive pathways. From Marchand et al. (114).

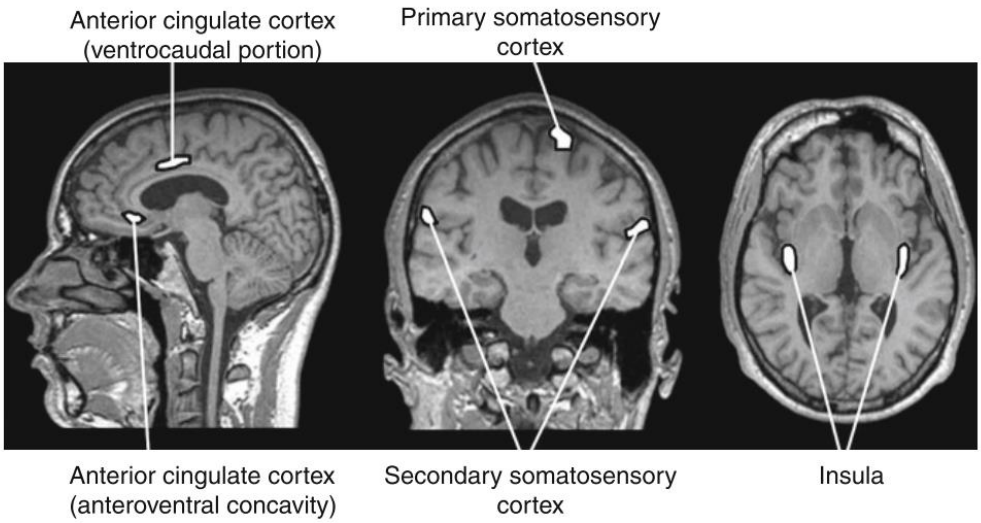

Figure 5. Brain areas involved in the processing of pain. From Marchand et al. (114).

Central and peripheral mechanisms of pain in people diagnosed with FM

FM is classified as a central sensitivity syndrome as there are evidences that a process known as central sensitization (CS) is involved in the development and maintenance of chronic widespread pain, the cardinal symptom of this health condition (115).

Nijs et al. (116) defined CS as ‘‘an augmentation of responsiveness of central pain-signaling neurons to input from low-threshold mechanoreceptors”. Traditionally, CS has been hypothesized to derive from continued nociceptive inputs. However, it has been demonstrated that this phenomenon can also occur without evidences of peripheral injuries (104).

CS occurs at spinal and supraspinal pain processing networks and it involves an array of changes at presynaptic and postsynaptic levels. The neurobiological mechanisms responsible for CS has been recently described in a review by Harte, Harris and Clauw (104). In the review, the authors summarized the available scientific evidence demonstrating an altered pain processing in the Central Nervous System using neuroimaging techniques and quantitative sensory testing. The studies compiled in the review demonstrated alterations in the gray matter of structures that are intimately involved in the processing of pain as the anterior cingulate cortex (ACC), the somatosensory cortex, the PAG and the insula. The main neurochemical alterations described were an increase in the levels of glutamate (the principal excitatory neurotransmitter) and in the levels of γ-aminobutyric acid (GABA) in the insula. Also, alterations in the connectivity between pronociceptive brain regions were observed and the connectivity between antinociceptive areas was decreased.

Activation of the N-methyl-D-aspartate (NMDA) glutamate receptor is postulated as a key mechanisms contributing to the development of neuroplastic changes contributing to and maintaining CS. In CS glutamate binds not only to AMPA receptors, but also to NMDA receptors which are blocked by magnesium in physiological conditions. The removal of magnesium activates NMDA receptors allowing the influx of calcium, not only depolarizing postsynaptic neurons, but also generating a series of intracellular changes which ultimately amplify the nociceptive signal and, therefore, the Central Nervous System becomes sensitized (117).

There are strong evidences that CS plays an important role in the development and maintenance of chronic widespread pain in FM (118–121). Furthermore, CS may be intimately related with other extramusculoskeletal symptoms of FM such as fatigue, non-restorative sleep, and paresthesia and swollen feelings. The directionality of the relationship between non-restorative sleep and CS is yet to be elucidated, although it seems that this relationship may be bidirectional since poor sleep quality can exacerbate CS and CS may cause sleep problems (122).

Peripheral mechanisms must be also considered in understanding the pain processing abnormalities in patients with FM. In recent years, small fiber neuropathy has become one of the main focus at the research level given the postulated implications of this phenomenon in the pathophysiology of FM. Small fiber neuropathy is defined as a type of peripheral neuropathy that causes damage in A-δ and C-fibers causing morphological abnormalities or that can even derive in a loss of said fibers. People with small fiber neuropathy usually present symptoms of allodynia, shooting and burning pain, and hyperesthesia (123).

A recently published systematic review and meta-analysis including 8 studies with a total sample of 222 patients with FM (124) showed that small fiber neuropathy is highly prevalent among people suffering from FM with an estimated prevalence of 49% (the heterogeneity was moderate I^2=68%). Although it has been demonstrated that small fiber neuropathy is common among people diagnosed with FM, a general skepticisms regarding the implications of this alterations in the pathophysiology of this health condition remains. It has been hypothesized that an autoimmune dysfunction may be one of the causes of small fiber neuropathy in FM (125). However, the underlying mechanisms by which small fiber neuropathy is contributing to pain in FM are yet to be described.

Objective and Subjective sleep abnormalities

Sleep phenomenology and architecture

Sleep is a complex behavior that, together with wakefulness, make up the so-called sleep-wake cycle determined by its circadian rhythmicity and which results from the conjugated activity of encephalic regions at brainstem, diencephalic and cortical levels (126).

Sleep is characterized by a decreased motor and perceptual activity, and by a diminished response to the environment. It is typically accompanied by a stereotypical posture and, unlike other states of altered consciousness, it is a self-regulating and rapidly reversible process (126–128). There are two well-defined types of sleep, “non-rapid eye movement” sleep (NREM) and “rapid eye movement” (REM) or paradoxical sleep (126).

NREM sleep is characterized by a decrease in the general physiological activity that is manifested by a reduction in various parameters such as blood pressure, heart and respiratory rate, body temperature, and basal metabolic rate. It is also accompanied by a marked decrease in muscle tone and slow and mostly unconjugated eye movements (129). NREM sleep is conventionally divided into four phases (127–129):

In the first phase (N1), although the conscious perception of the environment begins to decrease, there is a great susceptibility to awakening to any stimulus, which is why this phase is described as “light sleep”. The α waves registered during calm wakefulness are replaced by slower oscillations that predominate in a 4-7 Hz interval characteristic of the θ rhythm and that reflect greater synchrony of brain activity.

During phase 2 (N2) perception of the environment disappears completely, increasing the activation threshold and therefore requiring a more intense stimulus to wake up. As a result of the synchronization of neuronal groups at the thalamic level, bursts of fast waves with an activity of 11-16 Hz and a duration of approximately 1.5 seconds, known as sleep spindles, are occasionally registered in the electroencephalogram. Sleep spindles are usually preceded by a waveform known as K complex, which consists of a sharply negative high-voltage peak, immediately followed by a slower positive deflection. During N2, eye movements slow down further and at the muscular level, periods of spontaneous activity are combined with periods of relaxation.

Phases 3 and 4 (N3-4), together called slow wave sleep or delta sleep, are characterized by the presence of δ brain waves between 1,2-2 Hz. During these phases, considered the deepest of NREM sleep, the physiological variables reach their lowest values, there are hardly any eye movements and the muscle tone is minimal.

With REM sleep, the brain waves are fast and desynchronized, similar to the α rhythm registered during calm wakefulness (129). Such brain activity is considered being associated with dreaming, as around 80% of individuals who wake up during REM sleep report a vivid memory of the dream. Unlike in NREM sleep, in this phase the physiological variables become unstable, breathing becomes faster, irregular and shallow, and an increase and variability in heart rate and blood pressure are also observed. Abundant and phasic rapid eye movements appear and the voluntary musculature is temporarily paralyzed, although interrupted by small random fasciculations (128). The brainwaves registered during NREM and REM sleep through PSG are depicted in Figure 6.

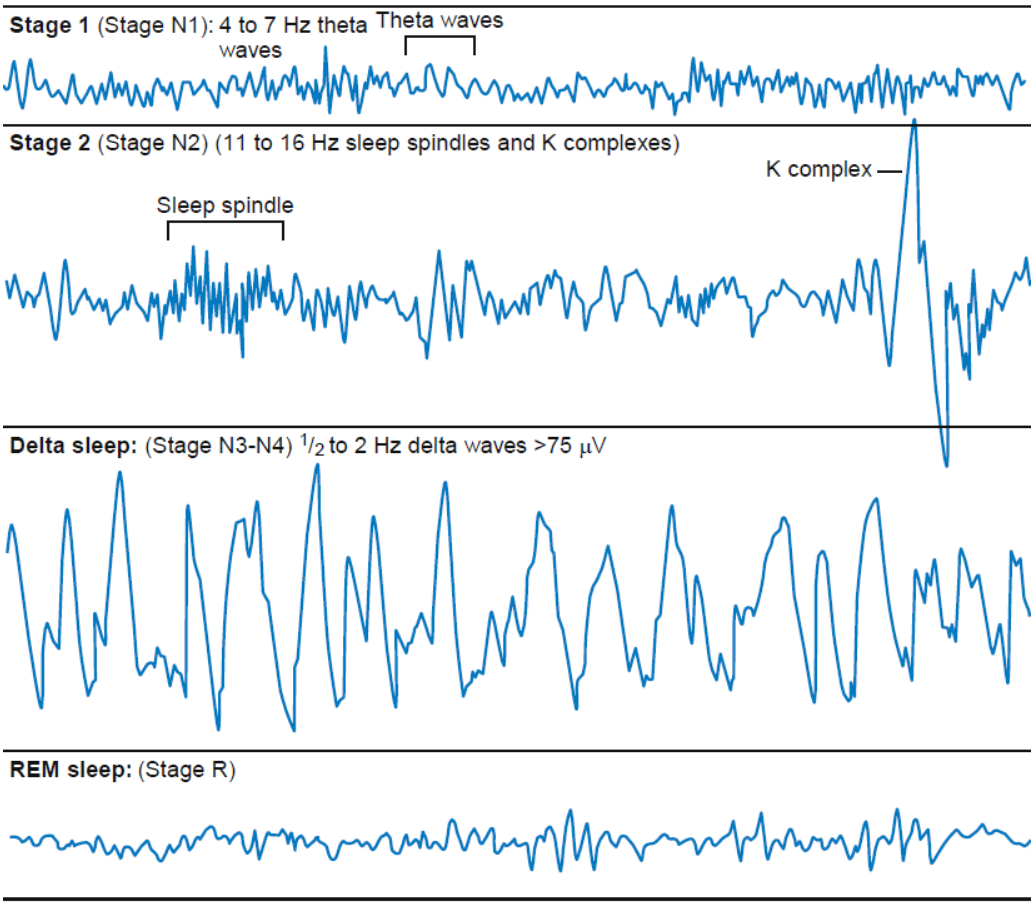

Figure 6. Brain waves registered with PSG during NREM sleep stages (N1-N4) and REM sleep. Adapted from Arrigoni and Fuller (127).

In normal sleep, a pattern of alternation between NREM and REM sleep, defined as "sleep architecture", is observed. Normally sleep begins with N1 NREM and deepens as N2 and N3-4 appear, followed by a first brief episode of REM sleep. Thereafter, the NREM and REM phases will alternate in a predictable pattern of cycles that will last between 90 and 120 minutes each and will repeat between 3 and 7 times throughout the night (129).

NREM sleep generally accounts for 75-80% of total sleep time. If we consider each phase of NREM sleep we find that N1 lasts only a few minutes and represents 2-5% of the total sleep time, N2 lasts between 10 and 20 minutes and normally constitutes between 45 and 55% of the total time of sleep. N2 progresses to N3, which lasts a few minutes, followed by N4, which lasts 40 minutes, constituting 5-8% and 10-15% of the total sleep time, respectively. REM sleep accounts for 20-25% of the total sleep time and its duration is increased as alternating cycles occur (129). The sleep architecture is represented in Figure 7.

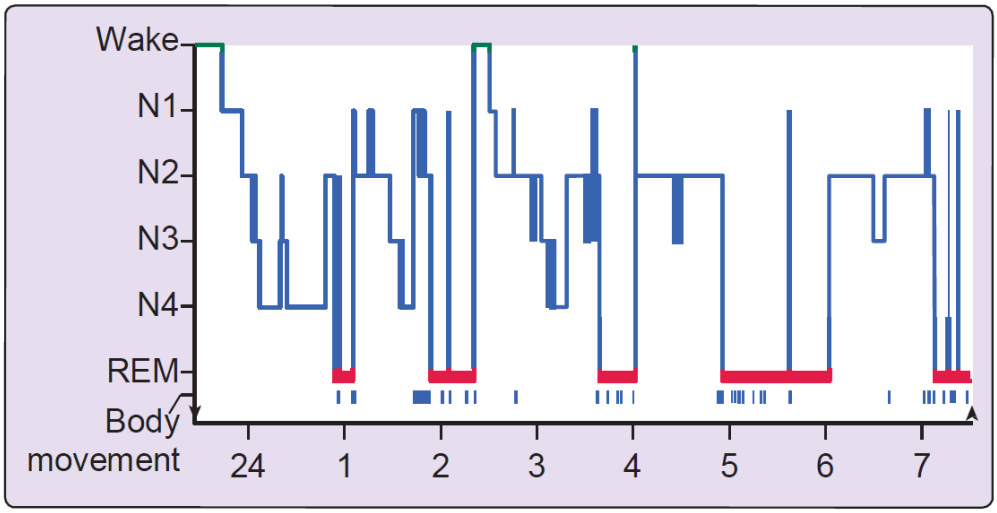

Figure 7. Hypnogram representing the sleep architecture. Adapted from Carskadon and Dement (128).

Poor sleep quality and Fibromyalgia

Along with chronic widespread musculoskeletal pain and fatigue, poor sleep quality is considered a central symptom of FM (45,130), with an estimated prevalence of 65–99%; only 11.2% of people with FM do not show sleep problems (8,11). Poor sleep quality is also one of the principal causes behind exacerbation of FM symptoms (11,131,132). Evidence demonstrates that poor sleep quality aggravates pain (131,133), fatigue and cognitive problems (131) and has a negative impact on quality of life and social functionality in people with FM (134). Likewise, people diagnosed with FM who suffer from comorbid insomnia show an augmented risk of future use of anti-epileptic drugs, antidepressants, opioids and muscle relaxants, compared with their non-insomniac counterparts (132).

Despite the wide range of research focused on describing sleep disturbances in patients with FM, there is no single consistent pattern pathognomonic of this syndrome. In the mid-70s, Moldofsky et al. (135) were the first researchers to perform polysomnographic records in patients with FM and described a characteristic pattern of α-wave intrusions during NREM sleep which they called α-δ sleep. The authors speculated that some symptoms of FM were consequently produced by this pattern and proposed that FM should be considered as a "non-repairing sleep syndrome". However, it is currently a controversial issue since there is scientific evidence showing that the α-δ rhythm is also recorded in subjects with other health conditions and even in healthy individuals (136,137). In contrast, other authors concluded that the frequency of the α-δ rhythm is greater in subjects with FM and in people with sleep fragmentation in comparison with healthy controls (138,139). Roizenblatt et al. (140) stated that the α-δ rhythm is associated with an increase in the number of painful body areas as well as with the duration and intensity

of pain. In addition, α waves intrusion during NREM sleep has been associated with decreased levels of growth hormone (GH), which is usually released during N3-N4 phases and that one of its principal functions is related to physiological healing mechanisms in the musculoskeletal system (141). The later could at least partially explain why patients with FM experience more intense pain after doing some types of physical exercise. In normal conditions GH is released in response to physical exercise and it has been observed that people diagnosed with FM show abnormal GH levels after doing physical exercise (141). In fact, it has been shown that a therapy based on GH replacement improved pain intensity in people diagnosed with FM (142).

Despite this lack of agreement regarding the α-δ sleep, there seems to be consensus regarding other important changes in the sleep continuity and sleep architecture in FM. In comparison with healthy controls, people with FM show significantly lower sleep efficiency and sleep quality, shorter sleep duration, and longer wake time after sleep onset and more percentage of light sleep stages when assessed with polysomnography (10,137). Previous studies also described a reduction of N2 and N4 NREM sleep, and a substantial decrease of REM sleep time (143–147) and N2 sleep spindles (148), and longer sleep onset and REM onset latencies (145,149).

In 1989, Buysse et al. (150) stated that because of the complexity of the sleep quality as a phenomenon and that the meaning of sleep quality is subjective and may differ between individuals, objective measures should not be the gold standard to define sleep quality in clinical samples. Therefore, subjective assessments are essential in order to understand how people with health conditions that are associated with sleep disturbances experience sleep. In this regard, patient-reported outcomes measures offer a more patient-centered assessment and provide important information that help health care professionals and researchers to understand more comprehensively the patients' sleep experience.

Subjective assessments of sleep quality using the Pittsburgh Sleep Quality Index (PSQI) showed that the prevalence of sleep disturbances in people diagnosed with FM revolves around 92.9% and that some sociodemographic characteristics are related with poorer sleep quality. In general, women with FM suffer more sleep problems than men diagnosed with this health condition (11), although in another study (151) also using the PSQI it was found that women have lower sleep onset latencies than men. Andrade et al. (11) showed that patients with FM that had a job sleep worse that those who are unemployed. In addition, people diagnosed with FM that practice more physical activity had a better sleep quality than those who are more sedentary.

A meta-analysis of case control studies including seven studies that assessed sleep quality with the PSQI (10) showed that patients with FM present higher total scores than healthy controls which demonstrate a

poorer sleep quality in people with FM. Other common sleep problems in patients with FM were poor sleep efficiency, increased sleep onset latency and decreased total sleep time. Other authors (152) found that people diagnosed with FM report experiencing poor quality of sleep, greater difficulty falling asleep, frequent awakenings during the night, and waking up very early with difficulty getting back to sleep again. In addition, they refer to excessive daytime sleepiness and fatigue (153).

Another interesting approach to explore how people diagnosed with FM experience poor sleep quality is the qualitative. In this regard, two of the studies (study II and study III) that composed this doctoral thesis aimed at synthesizing the available qualitative studies describing poor sleep quality experiences in the context of FM (study II) and to explore how women diagnosed with FM experience and manage poor sleep quality using personal semi-structured interviews (study III).

As previously described, some sleep alterations could be involved in worsening the experience of pain in people diagnosed with FM. However, poor sleep quality also impacts negatively on other symptoms such as memory and concentration problems, mood disorders, and anxiety (11) highlighting the importance of sleep in the pathophysiology of this chronic health condition.

Neurobiological and psychosocial factors mediating the relationship between sleep disturbances and pain

Although there is evidence that sleep and pain are closely related, the mechanisms underlying this relationship have not been yet fully elucidated and, therefore, can only be partially explained. In this regard, the present section describes the different structures at the Central Nervous System that seem to be involved in the sleep-pain relationship and the potential neurochemical underlying mechanisms.

Reward System

The reward system, also known as the Mesolimbic Reward Pathway or the Mesocorticolimbic Reward Pathway, refers to a group of nucleus and neural structures that have historically been associated with the modulation of cognitive and behavioral factors related with hedonic or pleasant feelings (154).

Specifically, this section focuses on specific structures, such as the Ventral Tegmental Area (VTA), the Nucleus Accumbens (NAc) and the Prefrontal Cortex (PC), which appear to be mostly involved in the relationship between sleep and pain.

At mesencephalic level, more specifically in the midline of the midbrain floor, we can find the Ventral Tegmental Area (VTA) (154) which is comprised by groups of dopaminergic (55-65%), GABAergic (30%) and glutamatergic (5%) neurons that play a major role in modulating reward and motivation (155).

Interestingly, between 5 to 15% of dopaminergic neurons respond to aversive stimuli, or to both rewarding and aversive stimuli, releasing DA; meaning that the so called reward system could also modulate behavioral factors associated with negative or aversive feelings, such as those evoked by the experience of pain (156). In fact, a research conducted by Brischoux et al. (157) showed that dopaminergic neurons in the ventral area of the VTA are activated by noxious stimuli. Some research groups (156,158–160), have observed that the dopaminergic reward system could be involved in the affective responses to chronic pain, the perception of nociceptive stimuli, and in the efficacy of pharmacological treatments aimed at pain management. In addition, alterations in the connections between the VTA and other structures, such as the striatum and the substantia nigra, result in an increase in the intensity of pain before nociceptive stimuli and in the development of maladaptive behaviors related to pain (158,161).

The NAc is part of the basal ganglia and is widely connected with brain structures that are part of the limbic system. For this reason, the NAc is considered providing an interface between the motor system and the limbic system, so that it is closely related to the mediation of motivational processes. Under normal conditions, the NAc generates a reward response to pain relief. The latter implies that the NAc is involved in the motivational salience of pain avoidance, that is, when a person experiences pain, the NAc will motivate a certain behavior so that the person seeks relief from it (162).

In recent years, it has been observed that VTA and NAc, the two main structures of the dopaminergic mesolimbic system, are intimately involved in the regulation of the sleep-wake cycle (163). In 2017, Oishi & Lazarus (164) published a review in which the authors detailed how these structures promote and/or maintain wakefulness and/or sleep states. Specifically, the functions of VTA in the maintenance of wakefulness have been widely discussed at the scientific level, since the first electrophysiological studies in this regard did not show conclusive results. However, the development of more innovative techniques, such as optogenetics through the use of light-activated ion channels (this technique is used to produce an acute activation of the stimulated brain area), have shown that the activation of dopaminergic neurons in the VTA allow the consolidation of wakefulness and that, in fact, the inhibition of said neurons in animal experimentation decreases the waking time by approximately two hours (164,165).

In the VTA we can also find neurons that express glutamic acid decarboxylase 67 (Gad67), an enzyme that is responsible for catalyzing the decarboxylation of glutamate to GABA. Chowdhury et al. (166) observed that the VTA_{Gad67+} neurons could be involved in the regulation of NREM sleep via inhibition of the Lateral Hypothalamus (LH). The authors activated these neurons using chemogenetic techniques (this technique is used to cause a long-lasting activation of the stimulated area) and inhibited them using optogenetic techniques. The results show that the activation of VTA_{Gad67+} neurons promoted NREM slow wave sleep while activating them derived in brain arousal. The proposed mechanisms by which VTA_{Gad67+}

regulate NREM sleep is the releasing of the neurotransmitter GABA so as to inhibit orexinergic neurons in the LH.

Perogamvros et al. (163) reviewed different investigations in which a peak of VTA activity in the transition from NREM to REM sleep was discovered. Although the functions of this peak of activity are not known, a possible involvement of VTA in the long-term memory processing along with the hippocampus is postulated.

The role of NAc in the regulation of sleep-wake cycles has been more widely studied and, according to available scientific evidence, it seems that this brain structure is key in regulating various neurobiological processes that promote and maintain both wakefulness and sleep (165,167-171). Eban-Rothschild et al. (165) carried out a study and observed that the connections between the VTA and the NAc can mediate the effects of the ATV on waking states since the optogenetic stimulation of these connections favors the waking state and significantly reduces the NREM and REM sleep time.

Apparently, the functions of the NAc related to the maintenance of wakefulness depend on the neurotransmitter DA since stimulation by agonist components of the dopaminergic receptors D1 and D3 in the NAc promotes motor activity and wakefulness (167). Likewise, optogenetic stimulation of D1r neurons (neurons with D1 DA receptors) in the NAc induces immediate awakenings in animals that are in the NREM sleep (168), which reinforces previous observations and confirms the involvement of NAc in the promotion of wakefulness. In this same investigation (168) it was shown that optogenetic stimulation of the D1r neuron fiber terminals of the NAc at the mesencephalic level and the HL increased the wake time considerably and decreased the time of the NREM and REM sleep. Thus, this research suggests that the effects of NAc on the promotion and maintenance of wakefulness are mediated by its connections with these structures, which are part of the neural circuits that control wakefulness.

Regarding the functions of NAc in the promotion or maintenance of sleep, it has been observed that this brain structure also contains adenosine A2a receptors, which are excitators of neural activity (adenosine is a key mediator in homeostatic sleep regulation, that is, the accumulation of adenosine during the waking period increases sleep pressure). In 1994, Barraco et al. (169) studied the function of A2a receptors in the NAc by using agonists of A2a receptors and showed a significant decrease in locomotor activity, so it was concluded that endogenous adenosine concentrations were a key factor in modulating the stimulatory effects of DA in the reward system. The results from another research (170) supported the findings of Barraco et al. (169) as the chemogenetic activation of the A2a receptors of the NAc neurons significantly decreased locomotor activity during the next 5 hours after the stimulation of said receptors were performed. In addition, electroencephalographic and electromyographic measurements revealed that the

chemogenetic activation of these receptors resulted in a significant increase in NREM slow waves sleep. Regarding the optogenetic activation of adenosine A2a receptors in the NAc, the results showed the induction of the NREM slow wave sleep phase, as well as an increase in the number of periods of said phase.

Qiu et al. (171) developed a study in which they differentiated the functions of the NAc cortex and core areas. The authors selectively injured one or another area of the NAc and examined the effects on wakefulness and sleep cycles in rats. The lesion of the NAc core produced an increase in the waking state that was accompanied by a considerable decrease in the NREM and REM sleep. In addition, injury to the NAc core resulted in an increase in sleep-wake transition states, although the time spent on wakefulness was not significantly longer than in the control group. The lesions of the NAc cortex did not cause significant changes in REM sleep, but significantly increased the waking time of the experimental group compared to the control group. Likewise, the total NREM sleep time was reduced and sleep patterns were altered, generating sleep fragmentation and causing an increase in the number of NREM sleep episodes. Finally, it was also observed that after a period of sleep deprivation, the lesion of the NAc cortex and core areas limited the increase in NREM sleep that occurs in normal situations after sleep deprivation.

The results of a study (170) showed that these effects may be mediated by neurons with A2a receptors in the NAc core since the photostimulation of these neurons with chemogenetic and optogenetic techniques increased sleep and the time of NREM slow wave sleep, respectively. In addition, it was observed that these neurons could be key to the induction of slow wave sleep since their inhibition by chemogenetic techniques reduced by 80% the total amount of time and the number of episodes of slow wave sleep. A generalized hypothesis is that A2aR neurons release the neurotransmitter GABA when activated, so that the effects of NAc on promoting slow wave sleep could be mediated by the inhibition of structures innervated by the NAc.

In summary, the available scientific evidence seems to point out that NAc is an essential nucleus in the regulation of wakeful periods by DA receptors and sleep periods through adenosine A2a receptors in the NAc core neurons. It seems that the NAc cortex and core may have differentiated functions for the promotion and maintenance of the different phases of sleep.

As for CP, despite its extensive connections with brain structures that promote wakefulness, its role in the regulation of sleep-wake cycles is still poorly understood. (172). During wakefulness, one of the functions of the CP is the so-called executive function that relates to the skills of decision making, self-observation, planning and prioritization (173). CP activity is mainly related to the waking state, while this cortical

structure undergoes a relative deactivation during sleep states, both in NREM and REM sleep phases (174).

In the same way that the implications of the reward system in the regulation of sleep-wake cycles are not fully understood, the evidence that explains how these structures can mediate the sleep-pain relationship are rather scarce. However, what has been demonstrated is that the sleep-pain interaction has a great impact on the biological, psychological and social spheres (175) (Figure 8).

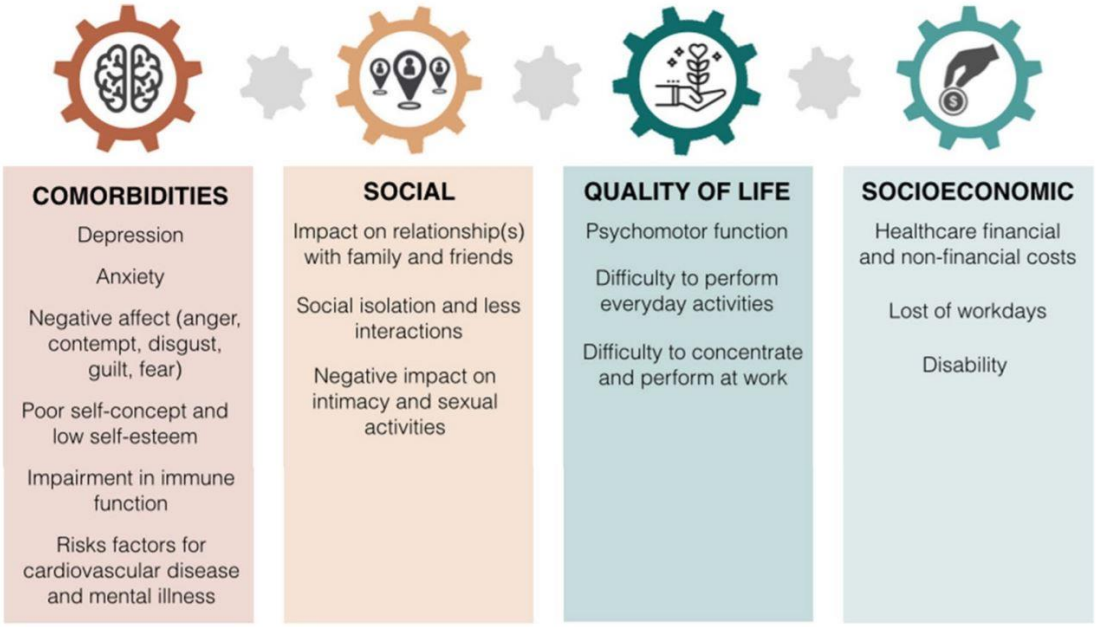

Figure 8. Biopsychosocial impact of the sleep pain relationship. From Herrero-Babiloni et al. (175).

Despite the lack of studies describing the mechanisms that underlie the sleep-pain relationship, in the last years, scientific publications have been increasing.

In 2016, Finan and Remeniuk (176) established an implication of the reward system in the sleep-pain relationship by reviewing a series of studies that investigated the effects of sleep deprivation on dopaminergic levels and the expression of their receptors. As the authors presented, sleep deprivation can alter the dopaminergic neural connections causing a downregulation of the D2 and D3 DA receptors. In the context of chronic pain, this downward regulation can have important implications in the response to the experience of pain since it has been observed that the activation of dopaminergic neurons in the face of noxious stimuli motivates behaviors driven by a reward (with pain, its relief) (156). Thus, a deregulation of this system caused by sleep deprivation can lead to behavioral alterations that prevent an adequate response to pain (176).

In animal experimentation it has been observed that REM sleep deprivation causes a pronociceptive effect mediated by the NAc, whose functioning is dependent on the balance between DA and adenosine levels. Thus, after a 24-hour period of REM sleep deprivation there was a long-term pronociceptive effect (48 hours), reducing that effect with sleep recovery, although no complete regression was observed. In addition, the authors observed that the pronociceptive effect mediated by the NAc could be prevented by injuring said nucleus, by administering an adenosine A2a receptor antagonist or a DA D2 receptor agonist, which shows that the NAc is involved in the sleep-pain relationship directly (177).

As for CP, there are currently no studies that analyze how sleep deprivation can affect its functions in processing and responding to nociceptive stimuli. What has been observed is that sleep deprivation affects the connections between the cerebral cortex and other brain areas, such as the amygdala, which is involved in cognitive-affective responses to pain. In this way, sleep deprivation causes a loss of functionality in the connections between the prefrontal cortex and the amygdala, which can lead to an exaggerated response of the amygdala to negative emotional stimuli due to an alteration of the prefrontal control (178). However, the impact of these alterations in the processing and response to nociceptive stimuli has not been studied yet.

Opioid Signaling

The endogenous opioid system has been extensively studied and is involved in the mechanisms of the descending modulation of pain since its receptors are distributed virtually throughout the nervous system (179). However, despite the important role of the opioid system in the experience of pain and that its receptors are also widely located in brain areas that regulate sleep-wake cycles (180), the amount of research studying the implication of such a system in the sleep-pain relationship are rather scarce.

In a review carried out by Finan, Goodin & Smith in 2013 (180), the results showed that sleep deprivation alters the functioning of the mu and gamma opioid receptors in the reward system, downregulates opioid receptors and derives in a reduction of opioid substances levels in the nervous system. In addition, sleep deprivation could attenuate the analgesic efficacy of opioid receptor agonists, especially those of mu receptors.

Therefore, despite the lack of evidence that points directly to the opioid system as a key mediator in the sleep-pain relationship, sleep deprivation could alter the mechanisms of pain inhibition of both endogenous and exogenous opioids.

The periaqueductal grey matter (PAG) is involved in the descending modulation of pain and this function is dependent on opioids (181). Interestingly, in an animal experimental study conducted by Sardi et al.

(181), it was observed that chronic sleep deprivation produces a pronociceptive effect that appears to be mediated by the PAG. In that study, rats were deprived of sleep a total of six hours a day for 12 or 26 days. The results showed that at 12 days there was a significant increase in the neural activity of the PAG that was significantly correlated with the induction of a pronociceptive effect which progressively increased as the days in which the animal was subjected to sleep deprivation progressed.

Other neurobiological correlates

Other neurobiological correlates that appear to be involved in the sleep-pain relationship are proinflammatory states, Vitamin D and the stress system.

In relation to pro-inflammatory states, a meta-analysis of cohort studies and experimental studies of sleep deprivation (182) got diverse results depending on the type of sleep analysis used in the different studies. In relation to cohort studies, the evaluation of sleep problems through questionnaires was significantly correlated with high levels of IL-6 and C-reactive protein, while the reporting of sleep problems symptoms by the subjects was only correlated with high levels of IL-6. However, by analyzing all the data together, sleep problems were significantly correlated with high levels of both IL-6 and C-reactive protein. Regarding the duration of sleep, and taking as normal values for adults between 7 and 8 hours of sleep a day, it was observed that both a duration of sleep below and above these values was significantly correlated with elevated levels of IL-6. In addition, subjects with a longer duration of sleep showed an increase in levels of C-reactive protein. The results of experimental sleep deprivation studies showed no significant correlation for any of the systemic inflammation markers evaluated.

In 2013, de Goeij et al. (183) induced a systematic inflammation by intravenous administration of an endotoxin in 27 healthy participants that resulted in an increase in baseline levels of proinflammatory substances such as Tumor Necrosis Factor alpha, IL-6, IL-10 and IL-1RA. To test whether a systemic pro-inflammatory state could lead to a decrease in the pain threshold, subjects were subjected to a cold pressure test (CPT) as a noxious stimulus. The results revealed that subjects with high levels of systemic proinflammatory substances showed a significant decrease in the pain threshold, and there were even subjects who could not complete the CPT. Therefore, it is possible that the pro-inflammatory state derived from sleep deprivation mediates the sleep-pain relationship, although more research is necessary.

In 2017, Leite de Oliveira et al. (184) published a review in which they presented the role of vitamin D in the sleep-pain relationship. Interestingly, it seems that vitamin D is involved in both the regulation of wake-sleep cycles and in the processes of pain regulation, in addition to acting as an anti-inflammatory. Thus, it has been observed that low levels of calcifediol, a prohormone that converts to calcitriol (the active form of vitamin D), are associated with a short duration of sleep and can affect the sleep onset latency and

promote a decrease of REM sleep. Similarly, women with serum levels of calcifediol below 20ng/mL are more likely to develop pain. The authors concluded with a hypothesis raising the possibility of including vitamin D supplementation in people suffering from chronic pain and sleep problems as a way to complement current treatments.

Another neurobiological correlate that seems to mediate the sleep-pain relationship is the alteration in the functioning of the Hypothalamic-Pituitary-Adrenal (HPA) axis due to poor sleep quality. In this regard, Goodin et al. (185) investigated if poor sleep quality could induce a hyperalgesic state in a sample of 40 healthy participants. Sleep quality was assessed with the Pittsburgh Sleep Quality Index and the response to noxious stimuli was evaluated by performing a CPT. Likewise, the cortisol levels and pain intensity were examined pre and post intervention. Participants with poor sleep quality showed increases in cortisol levels and pain intensity after the CPT. Therefore, the HPA contribute to the hyperalgesic states after periods of poor sleep quality.

Cognitive factors

As the results of a review (180) showed, it is very possible that the cognitive factors associated with pain are key in the sleep-pain relationship. In 2012, Buenaver et al. (186) investigated whether pain catastrophizing was linked to a greater severity of pain and if this relationship could be mediated by sleep problems in a sample of 214 participants with temporomandibular myofascial disorder. The results showed that pain catastrophizing was directly and indirectly related to a greater severity of pain. Apparently, sleep problems can mediate the indirect relationship between pain catastrophizing and pain, although the mechanisms of this association have not yet been elucidated. Smith et al. (187) postulated that this relationship could derive from the development of ruminative and catastrophic thoughts related to pain just at bedtime. In their research, they found that people with chronic pain think more often about their pain in the previous moments of going to sleep and that, in fact, a higher incidence of such thoughts can affect the onset and maintenance of sleep.

In a longitudinal study (188) with a sample of 1860 participants with depressive or anxiety disorder, a 6-year follow-up was carried out to assess whether these disorders could be correlated with the onset of long-term musculoskeletal pain. In addition, insomnia was evaluated and participants' sleep duration was recorded at the start of the study. As can be seen in Figure 9, the results showed that, although there is a significant direct relationship of insomnia and a short duration of sleep (<6 hours) with the development of chronic pain, depressive states can mediate the relationship between insomnia and the onset of chronic pain. Therefore, it seems that pain catastrophizing and depressive states could be involved in the sleep-pain relationship.

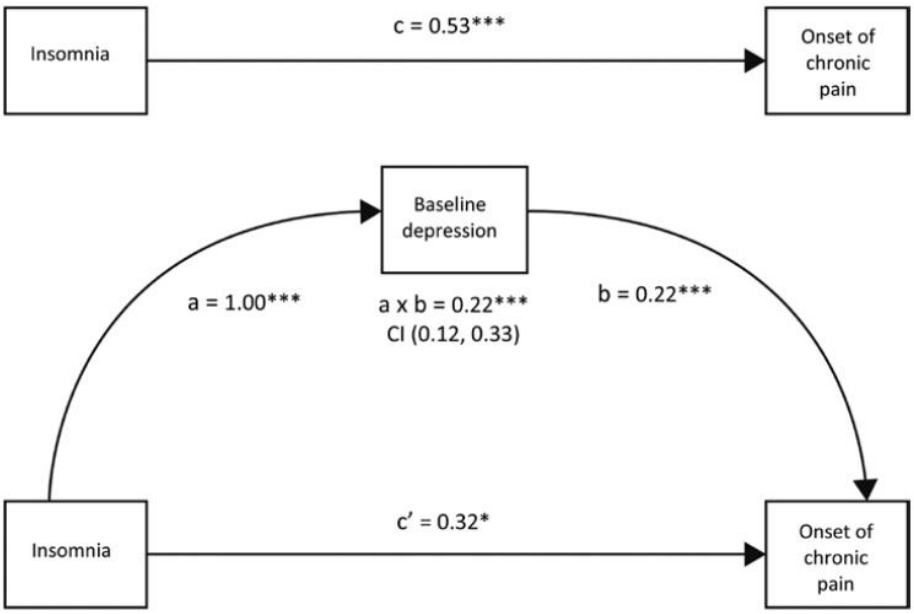

Figure 9. Insomnia correlates significantly with the onset of chronic pain. Depressive states can mediate the sleep-pain relationship. From Generaal et al. (188).

Treatment of FM

Given the complexity and the lack of knowledge regarding the etiology of FM, there are no curative treatments and the ones available are focused on symptoms alleviation. The current treatments of FM include both pharmacological and non-pharmacological approaches, and the multidisciplinary treatment is the most recommended (189).

Pharmacological Treatments

Pregabalin, duloxetine and milnacipran are the three medications approved by the Food and Drug Administration for the management of FM (190). Bennet et al. (191) performed an internet survey and observed that most people diagnosed with FM used drugs that are not approved by the FDA, being the most commonly used acetaminophen (94%), ibuprofen (87%), naproxen (66%), cyclobenzaprine (64%), amitriptyline (55%), and aspirin (53%). The participants perceived that the most effective medications are hydrocodone (75%), alprazolam (70%), oxycodone (67%), diazepam (65%), and zolpidem (64%). In 2016, Liu et al. (192) showed that around 70% of people diagnosed with FM are not prescribed pharmacological treatments in accordance with the ACR recommendations and that the adherence rates to pharmacological agents is far from optimal. The most common causes for pharmacological treatments withdrawal are side effects and a perceived lack of effectiveness.

In 2017, Kia and Choy (193) reviewed and compared the recommendations of the available international clinical practice guidelines for the management of FM with a special focus on pharmacological approaches. In this regard, the authors found several discordances between the European League Against Rheumatism (EULAR) 2016 guidelines (189), the 2012 Canadian guidelines (CPG) (194), and the Association of the Scientific Medical Societies in Germany (AWMF) 2012 guidelines (195). The only drugs recommended by all three guidelines are duloxetine for patients with FM with comorbid depression, and amitriptyline; although the AWMF recommend 10-50mg/day, the EULAR only low doses and the CPG recommended all categories of tricyclic antidepressants. Pregabalin and gabapentin are only recommended for research purposes by the EULAR while the AWMF recommended the prescription of Pregabalin (150-450mg/day) only when it is not possible prescribing amitriptyline as the first line option, while the CPG recommend the use of anticonvulsants in general. The Selective Serotonin Reuptake Inhibitors such as fluoxetine and paroxetine are recommended by the AWMF and the CPG whilst the EULAR does not recommend their prescription. The opioid drug tramadol is recommended by the EULAR and the CPG whilst the AWMF does not make any recommendations about it. Regarding Non-Steroidal Anti-Inflammatory drugs (NSIADs) and acetaminophen are not recommended by the EULAR and the AWMF. However, the CPG recommend the prescription of this medications at low doses and during short periods of time in people that have FM and other comorbid conditions as osteoarthritis. The authors concluded that this lack agreement between the above-mentioned guidelines derives from methodological differences in the development of the respective guidelines and from the lack of randomized controlled trials with good methodological quality, which ultimately prevents doing strong recommendations for any pharmacological treatment.

Concerning poor sleep quality, it has been demonstrated that some pharmacological treatments usually prescribed or self-administered in patients with FM impact negatively on sleep. Regarding NSIADs, Tang, Goodchild and Webster (196) stated that this drug may disrupt sleep by suppressing deep sleep (N3 and N4) and REM sleep and increase awakening. However, Woo and Ratnayake (197) recently suggested that the available scientific evidence is inconclusive and more studies investigating the actual effects of NSIADs on sleep are needed. As for opioids, it has been observed that a single oral dose reduces slow wave sleep and long-term opioids consumption reduces not only slow wave sleep but also REM sleep. Anticonvulsants such as clonazepam are shown to increase the total sleep time but also to have detrimental effects on slow wave sleep and REM sleep. Finally, antidepressants as duloxetine and amitriptyline are found to significantly suppress REM sleep (197).

Physical Exercise

The term physical exercise must not be confused with the term physical activity. In accordance with the WHO (198) physical activity refers to “any bodily movement produced by skeletal muscles that require energy expenditure” while exercise is understood as a “subcategory of physical activity that is planned, structured, repetitive, and aims to improve or maintain one or more components of physical fitness”.

In regards to FM, a recently published umbrella review (199) including 37 systematic reviews, examined the effects of physical exercise in people diagnosed with FM. The authors found that the most investigated type of physical exercise was the aerobic, with a total of 21 reviews and 161 studies. The results revealed that aerobic exercise was well tolerated among participants as adverse events were rarely reported. Aerobic exercise may have beneficial effects on pain intensity, fatigue, stiffness, physical function, and quality of life. However, the long term effects on pain and physical function were not substantial. Moderate to high intensity aerobic exercise improved heart rate variability and reduced autonomic dysfunction.

Strength training was investigated in 14 on the included reviews showing beneficial effects on tenderness, pain, fatigue, and muscle strength when participant followed a 21-week strength training program. It seems that strength training is more effective than an aerobic exercise in the improvement of tender points.

Resistance training showed high rates of adherence and contribute to improvements on both physical and psychological symptoms such as pain, tenderness, fatigue, functional capacity, anxiety, and depression.

As for the effects of aquatic exercises were only analyzed in three systematic reviews and, although the results suggested beneficial effects on tenderness, stiffness, sleep, quality of life, and other physical parameters, the results presented high heterogeneity and imprecision which led the authors to conclude that these results should be considered with caution. In comparison with terrestrial exercises and passive control groups, aquatic exercises may have more benefits on FM symptoms.

In relation to movement therapies such as yoga, qigong, Pilates or tai chi, it seems that may be beneficial for pain intensity, sleep, fatigue, depression and quality of life.

Cognitive-Behavioral Therapy

Cognitive-Behavioral Therapy (CBT) is a problem-oriented psychotherapeutic approach that combines both cognitive and behavioral-based treatments. The main objective of CBT is to change cognitive and behavioral patterns that may interfere with life and cause mental distress (200).

In people diagnosed with FM, a systematic review of randomized controlled trials (201) investigated the efficacy of different CBT approaches such as operant therapy, traditional CBT, self-management education programs and acceptance-based CBT, in comparison with passive and active control groups at a short and long term. The author also compared the efficacy of CBT with pharmacological treatments of FM approved by the FDA (pregabalin, duloxetine). The results showed that CBT approaches were superior to control groups based on waiting list, attention control, conventional treatments and other non-pharmacological treatments on pain relief, quality of life, negative mood and disability in a short term follow up and on pain relief, negative mood and disability in a long-term follow up. As for pharmacological treatments, CBT approaches were only superior for pain coping.

Cognitive Behavioral Therapy for insomnia (CBT-i) is a non-pharmacological approach that aims to change the cognitive and behavioral processes linked to the perpetuation of insomnia, and promote healthy sleep habits that favor the improvement of sleep patterns (196). Depending on the individual requirement, the main components of CBT-i programs may include sleep education, sleep hygiene training, stimulus control, sleep restriction and sleep compression, relaxation training, and different cognitive approaches such as cognitive therapy, cognitive refocusing, cognitive restructuring or problem solving-therapy, among others (202,203).

In adults with primary insomnia, CBT-i is an effective treatment for short and long-term sleep outcomes with no associated adverse events (204). In patients with chronic pain CBT-i has shown promising benefits on sleep outcomes such as sleep latency, number of awakenings, sleep efficiency, wake after sleep onset, and long term effects on total sleep time (205). Moreover, CBT-i may improve functional aspects of pain although the effects on pain severity (205,206) and mood states (205) are less clear. CBT-i seems to be effective in improving fatigue in patients with stable heart failure (207), breast cancer survivors (208) and multiple sclerosis (209). It is argued that the effects of CBT-i on fatigue may be partially mediated by changes in dysfunctional beliefs and attitudes about sleep (207).

Studies investigating the effects of CBT-i on other aspects of pain as pain catastrophizing are scarce. In patients with knee osteoarthritis, one study compared the efficacy of CBT-i with an active placebo based on behavioral desensitization (210). The results showed that participants in both groups significantly reduced diurnal and nocturnal catastrophic thoughts about pain and these changes were maintained at 6 months' follow-up.

Besides, CBT-i is also beneficial for people suffering from low and high depressive symptoms by improving self-esteem and reducing the severity of depressive symptoms and suicidal ideation thoughts (211). In breast cancer survivors, CBT-i improved mood and global and cognitive dimensions of quality of life (208).

In regards to FM, there are five studies (212–216) investigating the effects of CBT-i on objective and subjective sleep measures, and on other physical and psychosocial symptoms of FM. The results of the studies suggest that CBT-i may not be superior to Sleep Hygiene (SH) for improving sleep onset latency, total sleep time, and sleep efficiency when assessed using polysomnography or actigraphy. In fact, there are data evidencing that SH may be more effective than CBT-i for improving time in bed, decreasing wake after sleep onset and increasing REM percentage when measured with polysomnography. However, CBT-i is more beneficial than SH in decreasing the percentage of N1, increasing the percentage of N4, decreasing REM onset latency, and improving sleep quality and insomnia severity in accordance to objective and subjective assessments. In relation to other symptoms, CBT-i is not better than SH to alleviate pain intensity. However, CBT-i showed more positive effects than SH on anxiety, depression, daily functioning, and mood states. Therefore, although it seems than CBT-i could provide significant clinical benefits on sleep and other symptoms of FM, there is a lack of literature comparing this approach with other pharmacological or non-pharmacological treatments.

Therapeutic Patient Education

TPE is defined by the World Health Organization (217) as a strategy "to train patients in the skills of self-managing or adapting treatment to their particular chronic disease and in coping processes and skills. It should also contribute to reducing the cost of long-term care to patients and to society. It is essential to the efficient self-management and to the quality of care of all long-term diseases or conditions." Patient education programs are both cost-effective (218) and beneficial for patients with chronic health conditions in that they reduce patients' distress associated with their symptoms and improve their awareness of their health condition (219). Similarly, improving self-management skills has long-term effects on quality of life and depression in people diagnosed with chronic disorders (220). In fact, Vargas-Schaffer and Cogan (111) stated that therapeutic patient education is essential to pain management programs as it increases patients' knowledge and enables them to modify maladaptive attitudes and behaviors.

In the Internet era, most people look for information on health-related issues online (221). An online survey that investigated information-seeking behaviors in people diagnosed with FM showed that the Internet was the most used resource and two of the most frequently searched topics were how to understand the meaning of FM and how to manage the symptoms (222). A review of websites for people diagnosed with FM (223) classified only 32% as having very good quality according to DISCERN criteria. With respect to the type of information conveyed, 72% of the reviewed websites provided information on treatment options and only 40% provided resources on coping strategies. Additionally, 86% of the websites used difficult to

understand medical and technical language and were therefore not accessible to people with low literacy levels.

Promoting and designing evidence-based websites as a therapeutic tool has potential usefulness. For patients with chronic health conditions having symptoms that are difficult to cope with, websites may help change the cognitive and behavioral factors associated with poor symptom management strategies, improving patients' health status and quality of life.

CONCEPTUAL FRAMEWORK

A Conceptual Model for Symptom Management

According to the University of California San Francisco (UCSF) School of Nursing Symptom Management Group (224) *"A symptom is defined as a subjective experience reflecting changes in the biopsychosocial functioning, sensations, or cognition of an individual"* and *"is often what brings the patient into the health care system, particularly after self-care management strategies have failed"*. Based on this assumption, it is essential for healthcare professionals to have access to effective tools that provide guidance for the symptom assessment and management process in their daily clinical practice.

The UCSF Symptom Management Model

The UCSF Symptom Management Model is a deductive, middle range theory, which originated in the mid-90s when Larson et al. (225) identified the need for models providing a comprehensive and multidimensional approach for the assessment of patients' symptom/s experience. Most of the research in the field of symptom management was focused on strategies aimed at the improvement of a single feature of the symptom management, which did not provide enough guidance for health providers to implement integral symptom management strategies. Therefore, the Symptom Management Model was also aimed to provide direction to the development of proper and specific symptom management strategies based on the needs of the patients (225).

The first version of the UCSF Symptom Management Model derived from the research and clinical practice experience of the UCSF School of Nursing Symptom Management Faculty Group. After years of testing and collegial discussions, a revised version of the Symptom Management Model (see Figure 10) was published in 2001. The last update of the model was in 2008 and was renamed as the Symptom Management Theory (SMT) (224).

The Symptom Management Theory

The SMT was developed on the basis of the following six basic principles (224,226):

- The patients' perception of the symptom/s is the gold standard for the symptom/s assessment.
- The application of this model extends beyond the treatment of a symptom, i.e. it can be used as a prevention model if it is detected that an individual is at risk of developing a certain symptom/s.
- In subjects who do not have the ability to express themselves verbally, it is imperative that a family member or a caregiver accurately detail the experience of the symptom to develop effective symptom management strategies.
- It is essential to manage all troublesome symptoms.

- Symptom management strategies can be applied to the patient and to a group of patients with similar characteristics, patients' relatives or work environment.
- The process of symptomatic management should be understood as a dynamic process that can be modified depending on the needs of each subject and the influence of the three domains of the model that are the Person, Environment and Health & Illness.

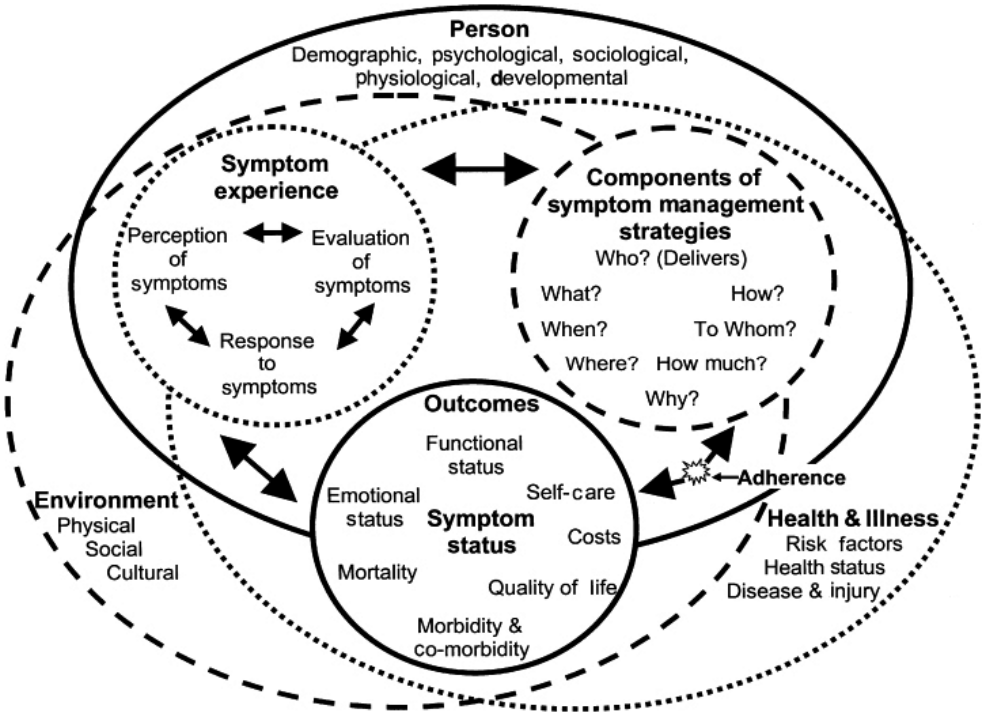

Figure 10. Symptom Management Theory. From Dodd et al. (Reproduced with permission from Wiley) (226).

Domains and Dimensions of the Theory

As depicted in figure 10, the UCSF SMT was built around three crucial dimensions that constitute the conceptual basis of the model: 1) Symptom Experience, 2) Symptom Management Strategies, and 3) Outcomes. According to the SMT, these three dimensions are interconnected and all of them must be considered for developing an effective symptom management intervention. The three dimensions are nested within the three essential domains of health care professionals practice, which are: 1) Person, 2) Environment, and 3) Health & Illness (225–227).

Additionally, the authors highlight that those symptom management interventions with low rates of adherence cannot be considered successful as it could interfere with the got outcomes. Therefore, in the revised version of the model, the adherence component was added as a potential disruptor between the Symptom Management Strategies and the Outcomes dimensions. Therefore, ensuring and assessing the patients' adherence is mandatory when testing symptom management strategies based on the SMT

model. Adherence depends on both the characteristics of the patient and the healthcare provider and system (225–227).

Description of the Person, Environment and Health & Illness domains (225–227)

Person

The person domain refers to how the demographic, biological, psychological and social variables, understood as intrinsic variables of each patient, influence the symptom experience not only in terms of perception but also in terms of symptom evaluation and response.

Environment

The environment domain aims to contextualize the symptom experience around physical, social and cultural variables that may contribute to the variance in the perception, evaluation and response to a symptom. The physical variable refers to the place where the person is experiencing the symptom and it is considered important as the symptom would not be experienced the same at home compared to in a working or hospital environment. Likewise, the symptom experience may be influenced by the individual' social support network and may be determined by cultural aspects such as religion, ethnicity or race.

Health & Illness

Finally, the health or illness state is distinctive for each individual and is directly influenced by three main variables of the health & illness domain that are the risk factors, the general health status and the disease or injury characteristics.

In short, these three domains are key elements that shape the symptom experience and management strategies as well as the outcomes in a different manner in each patient. Therefore, they must be carefully analyzed so as to develop comprehensive and effective strategies directed to the symptom management.

The above described domains directly influence those that are considered the three dimensions of the model: 1) symptom experience, 2) management strategies and 3) outcomes.

3.1.3.2. Symptom Experience, Symptom Management Strategies and Outcomes dimensions

Symptom Experience

Symptom experience is determined by three major factors that occur simultaneously when an individual has an unusual feeling: symptom perception, evaluation and response. The perception is related with the patients' awareness of a symptom/s manifestation (i.e. symptom identification). The evaluation is understood as the meaning that a person attributes to the experienced symptom/s in terms of effects,

severity, temporality, cause and treatability. The symptom response is associated with the person's reactions at physiological, psychological and social level (224–226).

This chain of events, derived from the symptomatic experience, does not necessarily have to follow a predictable pattern of behavior. The perception, evaluation and response to a symptom depend on the characteristics of each person, the physical, social and cultural environment in which they find themselves, as well as their own health and illness status. Likewise, it is important to highlight that these three processes show a bidirectional relationship as all of them can influence or be influenced by the others (224,226).

Symptom Management Strategies

Developing symptom management strategies is not only about preventing, diminishing or delaying the occurrence of negative outcomes, but it is also about controlling and influencing the whole symptom experience. Prior to the development of symptom management strategies, the symptom/s experience from the patient's perspective should have been comprehensively evaluated (224–226).

Clinicians and researchers that base their intervention on the present model should clearly specify the professional/s who deliver the treatment (WHO), the nature of the intervention (WHAT) and the justification of its use (WHY) as well as to describe the WHEN (e.g. timing of day, frequency), WHERE (e.g. location of delivery), HOW (e.g. in person, online, group) and HOW MUCH (dose) (226).

Outcomes

This dimension results from the interaction of the other two, that is, both the symptom experience and the strategies developed for its approach will influence the effectiveness of the intervention. Likewise, treatment adherence is an important factor to bear in mind when evaluating the results of the intervention. The proposed outcomes in the model to be evaluated include functional and emotional status, self-management, quality of life, mortality, morbidity and comorbidity and social and economic costs (226).

The Symptom Management Theory as a Conceptual Framework

The UCSF SMT has been widely used at the research level, both to explore the symptomatic experience of people with different health conditions and for the development of symptomatic management interventions (227). However, to the knowledge of the author, there are no studies using this model as the basis for symptom experience assessment and/or symptom management strategies development in people diagnosed with FM.

As previously stated, FM is a complex chronic health condition for which curative treatments are currently nonexistent. Therefore, the main approach is focused on developing symptom management strategies that help alleviate the severity of symptoms such as pain, poor sleep quality, fatigue and mood disturbances. Because of the later, a symptom-focused conceptual framework could contribute to the development of research projects that help to understand how people diagnosed with FM experience the symptoms that characterize this health condition, and also to evaluate the effectiveness of symptom management strategies from a biopsychosocial perspective.

In this research document, the SMT was taken as a biopsychosocial conceptual framework with the ultimate aim of conceptualizing poor sleep quality in the context of FM including patients' experience and a proposal of a poor sleep quality management strategy based on a therapeutic education intervention approach.

As depicted in Figure 11, each of the four studies that are part of the present doctoral thesis are related with one or more dimensions of the SMT and are developed taking into account the dimensions that compose said theory, providing a biopsychosocial approach to understand the phenomenon of poor sleep quality in the context of FM.

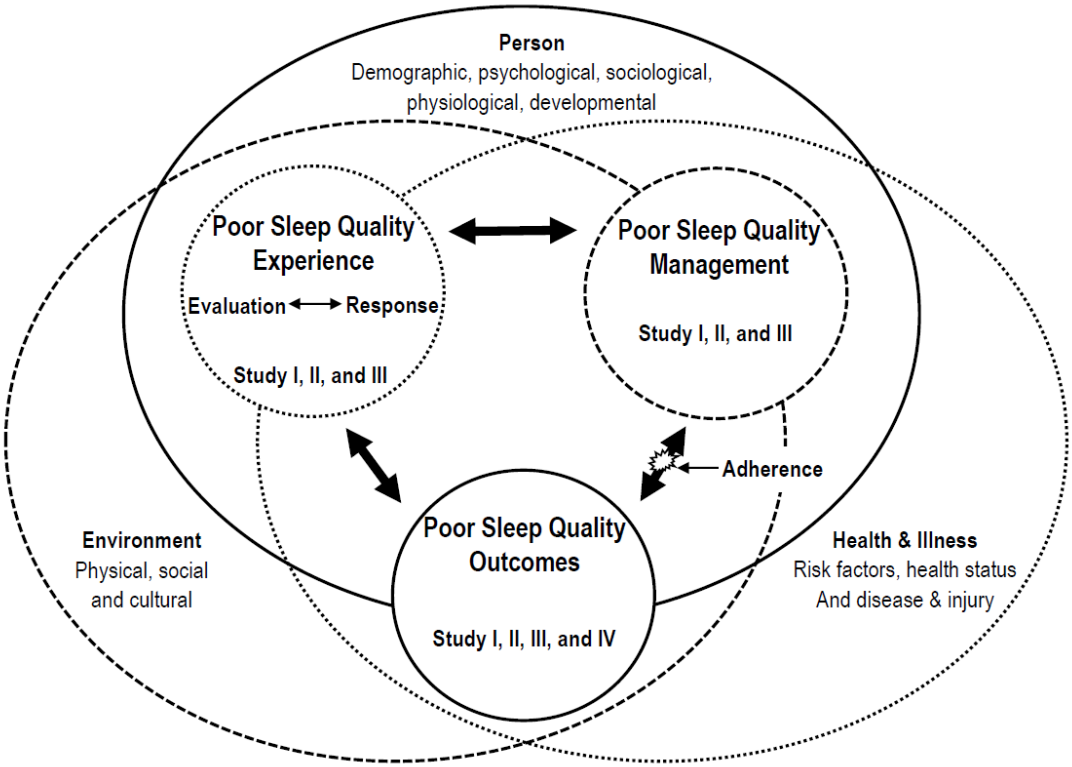

Figure 11. Integration of the studies presented in this Doctoral Thesis on the Symptom Management Theory domains. Adapted from Dodd et al. (226).

OBJECTIVES

General and Specific Objectives

The general objective of this Doctoral Thesis was to conceptualize poor sleep quality in FM taking the Symptom Management Theory as a biopsychosocial conceptual framework.

The specific objectives were:

To develop a protocol for a Web-Based Therapeutic Education Intervention about sleep and pain for women diagnosed with Fibromyalgia.

To identify and synthesize the available qualitative literature on the experience of poor sleep quality in Fibromyalgia.

To explore how Spanish adult women diagnosed with Fibromyalgia experience and manage poor sleep quality.

To describe and analyze the psychometric properties of the validated Self-Reported Outcome Measures for assessing sleep quality in Fibromyalgia.

METHODOLOGY

The articles included in this Doctoral Thesis were developed using different methodological approaches in order to respond to each of the established objectives, combining both qualitative and quantitative methods. The methodology implemented in study I provided guidance for the development of the studies II, III and IV.

Study I. Sequential exploratory mixed-methods research protocol

Study II. Qualitative Metasynthesis

Study III. Qualitative Inquiry

Study IV. COSMIN Systematic Review

STUDY I. A Sequential Exploratory Mixed-Methods Research Protocol

Promoting and designing evidence-based websites as a therapeutic tool has potential usefulness. For people with chronic health conditions having symptoms that are difficult to cope with, websites may help change the cognitive and behavioral factors associated with poor symptom management strategies, improving people's health status and quality of life.

This project proposes to adopt a sequential exploratory mixed methods research design. The researchers will begin by exploring and analyzing qualitative data and will use the results to develop a web-based TPE intervention. The effects of the intervention will be analyzed in the quantitative phase of the study (228). This research design is useful when the aim is to develop new instruments due to unavailability or inadequacy of alternatives (229).

A three-phase procedure will be used:

1. Qualitative phase: Qualitative data will be collected and analyzed.
2. Connection phase: Based on the results of the qualitative phase, the content of the web-based TPE intervention will be developed.
3. Quantitative phase: The web-based TPE intervention will be tested in a sample of the target population and quantitative data will be collected and analyzed.

Using mixed methods in this study is justified by the need to link both qualitative and quantitative methods to develop new symptom management strategies in FM.

Qualitative phase

The qualitative study proposed in the present project is defined as generic, as it does not explicitly follow or accept the philosophical assumptions of other defined qualitative methodologies (230).

Connection phase

The connection phase is of special importance in the development of projects with an exploratory sequential mixed methodology: in this phase, the integration of the qualitative and quantitative phases is clear. In the proposed project, the data obtained during the qualitative phase are essential to develop the content of the TPE intervention, the effects of which will be evaluated in the quantitative phase by means of a randomized control trial.

Once the qualitative data are analyzed, the authors will develop the content and materials (videos, dossiers) of the TPE intervention that will be made available on the website for the study participants allocated to the experimental group.

Using the data from the qualitative phase will ensure that the materials are developed based on the needs of patients with FM. The best and most current scientific evidence will be consulted so as to provide the participants a high-quality website with appropriate information about pain and sleep in the context of FM. This project is an innovative approach in this field of research because it aims to respond to the actual needs of patients with FM based on their own experience.

With the help of an information technology technician, the authors will design, create and maintain the website. The website will be accessible with a user number and password provided to participants once they are allocated to the treatment condition.

Quantitative phase

The proposed quantitative study will be a parallel, double-blinded, randomized controlled trial conducted in a secondary care setting in the city of Lleida, Spain.

Hypothesis

In a sample of Spanish women diagnosed with FM in a secondary care setting, a web-based TPE intervention for pain and poor sleep quality will show more significant clinical effects than a web-based education intervention based on the Catalonian clinical practice guideline for FM treatment in managing pain, poor sleep quality, pain catastrophizing, chronic pain self-efficacy expectations, dysfunctional beliefs and attitudes in relation to sleep and state of health and quality of life associated with FM.

Intervention plan

Participants assigned to the experimental group will complete a web-based TPE intervention for pain and poor sleep quality. The intervention will be password protected and only participants assigned to the experimental group will have access to the educational materials.

Based on the Internet-Based Arthritis Self-Management Program developed by Lorig et al. (231), the TPE intervention will last six weeks, to increase participants' knowledge of pain and sleep in the context of FM and empowering them to develop effective pain and sleep quality management strategies. All participants will have free access to the website from any device with Internet access and may consult it as many times as they wish during the intervention.

When participants access the website for the first time, they will fill out a sociodemographic data sheet and questionnaires that will provide the baseline characteristics of the sample. Fulfillment of this step will be mandatory to access the educational materials. Second, participants will watch a video where the authors explain the objective, characteristics and functions of the web platform.

Knowledge of health and disease is predominantly based on the biomedical model and people diagnosed with FM face constant rejection and stigmatization at both the clinical and social levels (232). This can have a great influence on symptom perception, mediated by a phenomenon known as symptom magnification. Symptom magnification triggers a conscious or unconscious exaggeration of the symptom's severity with the sole purpose of increasing the patient's believability and the credibility of their health status (233). Therefore, symptom perception may be influenced by how society in general and health professionals in particular, assess and treat such patients. Thus, the third step for participants of the experimental group after accessing the website will be to watch a video designed by the authors where FM and its associated symptoms are validated. According to Marsha Linehan (234), validation is "a process in which a listener communicates that a person's thoughts and feelings are understandable and legitimate." The aim of the validation video will be to send the message that FM is a legitimate health condition and so are its associated symptoms.

Weeks 1 and 2 of the intervention will focus on cognitive factors (evaluation) and weeks 3 and 4 will focus on behavioral factors (response) associated with pain and poor sleep quality. Based on the research of Valenzuela et al (235), gamification techniques will be implemented to individualize the intervention and respond to the different educational needs of each participant. After watching the validation video, participants will begin the intervention for the cognitive factors. Participants will select which symptom (pain or poor sleep quality) they prefer to learn about first. Following this, a list of different statements from the qualitative phase of the project will be presented and participants will click the one that best represents their thoughts about the symptom they selected. They will then be referred to a specific video and written material aimed to respond to this statement. The same procedure will be implemented during weeks 3 and 4 for the intervention focused on the behavioral factors.

During weeks 5 and 6, participants will continue to have access to all the educational materials, but the intervention will focus on different activities to challenge participants to implement daily management strategies for pain and poor sleep quality based on what they learned during the previous four weeks. They will also have access to a personal diary, which (if they consent) can be used to express and share their experiences with other participants implementing daily management strategies. Gamification techniques will also be used during weeks 5 and 6 to motivate participants and consolidate their knowledge acquired during the previous four weeks.

Participants assigned to the control group will also have access to the web-based platform and the first mandatory step on access will be to complete the sociodemographic data sheet and questionnaires. Instead of following the TPE intervention, control group participants will watch a video and have access to written materials based on the clinical practice guideline to treat FM, "Guide of Fibromyalgia," developed

by the Department of Health of the Generalitat de Catalunya and the Servei Català de Salut (236). Participants will also have access to the web platform to complete the questionnaires established for evaluation at different time points.

Sample/participants

Qualitative phase

Inclusion criteria for participants in the qualitative phase are 1) a diagnosis of FM based on the 2016 criteria of the American College of Rheumatology (44); 2) adult women between 18 and 65 years of age; and 3) ability to understand and speak Spanish and/or Catalan. All participants will be required to accept and sign an informed consent form.

Sampling, sample size and method of approach

A theoretical sample will be recruited using the snowball technique. In the first step, participants will be recruited from the community through the Fibromyalgia Association in Lleida. Inclusion of participants will stop when new ideas or data about the research topic stop appearing—that is, when the information is saturated (237).

Quantitative phase

Inclusion criteria for participants in the quantitative phase are 1) a diagnosis of FM based on the 2016 criteria of the American College of Rheumatology (44); 2) adult women between 18 and 65 years of age; 3) ability to understand and speak Spanish and/or Catalan; and 4) access to a fixed computer, laptop, or tablet with Internet access. Participants will be excluded if they are or have previously received similar interventions. All participants will be required to sign an informed consent form.

Recruitment and sampling method

Patients will be recruited from a list of women diagnosed with FM provided by the rheumatology service board of the “Hospital Universitari Santa Maria” of the city of Lleida. A systematized and randomized sampling method will be used to ensure that all women in the list have the same chance to participate in the study. The principal investigator will call the women on the list and meet with those showing interest in participating to assess their compliance with the inclusion criteria and provide them with the information sheet and informed consent form.

Sample size calculation

Sample size was calculated based on the minimum clinically significant difference in pain intensity according to VAS measurements (0-100). The literature indicates that a change of 15 points is the minimum required to indicate a clinically significant difference in people with chronic pain (238), with a common standard deviation of 12.63 points (239). Additionally, the sample size for the proposed study was calculated with the aim of comparing two independent groups.

According to the Granmo sample size calculation program (version 7.12) (240), accepting an alpha risk of 0.05 and a beta risk of 0.05 in a two-sided test, 24 subjects are required in each of the two groups to recognize a difference greater of 15 or more points as statistically significant, with the common standard deviation of 12.63. A dropout rate of 20% is anticipated.

Randomization: Type and sequence generation

A simple randomization method will be used. Participants will be allocated to each group using a 1:1 ratio to ensure the same number of subjects in the experimental and control groups. The randomization list will be generated using STATS® software by statistics specialist not affiliated with the study.

Allocation concealment mechanism and implementation

To avoid introducing a selection bias, allocation will be hidden from the researchers responsible for patient recruitment (241). During the investigation, because pertinent evaluations will be made via the website, none of the researchers will be responsible for assessing participants.

To ensure allocation concealment, centralized randomization will be conducted via the Internet. Once the principal researcher ensures compliance with the inclusion criteria and the participant reads, accepts and signs the informed consent form, the participant's number will be requested online. This number will not be related to the intervention groups in any way and therefore, neither the researcher nor the participant will be able to anticipate their assignment. The participant will enter the number when first accessing the website and will receive on-screen instructions according to her group assignment.

Blinding

A double-blind study is proposed, where neither the participants nor the researchers will know which group each subject has been assigned to. Evaluations will be conducted through the website.

Data collection and analysis

Qualitative phase

According to the guidelines provided by Fontana and Frey (242), qualitative data will be collected through in-depth individual interviews. Semi-structured interviews will be conducted as they allow exploration of the topic in greater detail and in-depth understanding of the participants' answers (243).

Interviews will be conducted individually by two of the study's researchers in Spanish or Catalan, depending on the interviewee's native language. Participants will choose where the interviews take place to ensure they are in a comfortable environment.

All interviews will be recorded digitally, transcribed verbatim and subsequently imported into the NVivo 12 qualitative analysis software for thematic analysis. Emerging codes will be assigned to fragments of the interviews with the same meaning and categories will be formed by grouping the different codes that emerge (244). Interview transcripts and field notes capturing participants' non-verbal responses will also be included in the data analysis through an iterative process. Resulting codes and themes will be discussed and agreed by all research members, allowing a triangulation of researchers and ensuring analytic rigor. Additionally, the interviewees will verify the results to ensure that the analysis reflects their understanding and experience of pain and sleep in the context of FM.

Quantitative phase

Study variables will be evaluated based on questionnaires completed by the participants of both intervention groups through the website. The questionnaires will be presented immediately before and after the intervention and at three and six months after the intervention.

At each of the four data collection time points, participants in both treatment conditions will receive an email and a WhatsApp message as a reminder that the questionnaires are available on the website. If they fail to complete the questionnaires after these reminders, they will be contacted by telephone.

Each participant's completed questionnaires will be automatically sent to a database that only the statistician can access. After each assessment point, data will be exported to the Statistical Package for Social Sciences (SPSS) software.

Primary outcome

Pain intensity. Pain intensity will be measured using the Visual Analogue Scale (VAS), which was developed in the later 1970's and is considered the most sensitive test for pain intensity (245–248). This user-friendly tool consists of a numerically graduated line from 0 to 100, with 0 representing "no pain" and 100 representing "unbearable pain."

Secondary outcomes

Sleep quality. Sleep quality will be measured using the Pittsburgh Sleep Quality Index (PSQI), designed by Buysse et al. (150). This self-administered questionnaire evaluates the quality of and alterations in sleep over a one-month interval. A total of 19 individual items, scored from 0 ("no difficulty") - 3 ("severe difficulty"), are used to assess seven sleep components: 1) subjective quality of sleep; 2) sleep latency; 3) sleep duration; 4) efficiency of usual sleep; 5) sleep disturbances; 6) use of medication for sleep; and 7) daily functionality. Overall scores range from 0-21 points, with 0 indicating no difficulty and 21 indicating severe difficulties in all areas. The Spanish version of the Pittsburgh Sleep Quality Index has been validated in a sample of people diagnosed with FM with a Cronbach's alpha coefficient of 0.81 and a Spearman's correlation coefficient of 0.077 ($p < 0.001$) for total score, demonstrating good internal consistency and acceptable test-retest reliability (249).

Pain catastrophizing. Pain catastrophizing will be measured using the Pain Catastrophizing Scale (PCS), a self-administered questionnaire developed by Sullivan, Bishop and Pivik (250) to measure the impact of catastrophic thoughts on the subject's experience of pain. The scale includes a total of 13 items assessing the three dimensions of pain catastrophizing: 1) rumination; 2) magnification; and 3) helplessness. The score of each of the 13 items can range from 0-4 which leads to a total score from 0-52. The PCS allows to assess which of the dimensions are more affected by summing the score for the following items: 1) rumination: 8, 9, 10, 11; 2) magnification: 6, 7, 13; and 3) helplessness: 1, 2, 3, 4, 5, 12. Higher scores represent higher catastrophizing thoughts related to pain.

The Spanish version of the instrument has been validated in people diagnosed with FM with a sample of 230 participants (251). The scale presented the same factorial structure with three dimensions and showed adequate psychometric properties, with a Cronbach's alpha coefficient of 0.79 and an intra-class ratio of 0.84.

Chronic pain self-efficacy. Chronic pain self-efficacy will be measured using the Chronic Pain Self-Efficacy Scale (CPSS). Based on Bandura's (252) assertion that personal expectations regarding self-efficacy influence coping behaviors Anderson et al. (253) developed the scale to measure self-efficacy beliefs in people suffering from chronic pain. The instrument is based on the Arthritis Self-Efficacy Scale. The total score can range from 0-60 and is calculated by the sum of the items. Higher scores are indicative of higher self-efficacy in the management of chronic pain. The Spanish version (254) of the scale has been validated in a sample of 113 patients referred to an outpatient pain unit of the Hospital General y Universitario de Alicante, with a Cronbach's alpha of 0.91 for total score.

Dysfunctional beliefs and attitudes about sleep. Dysfunctional beliefs and attitudes about sleep will be measured using the Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS). The original full

version of the scale was created by Morin (255) to evaluate dysfunctional thoughts that cause and/or maintain insomnia. It includes 30 items grouped into five theoretical dimensions: 1) consequences of insomnia on state of mind, greeting, or daily activity; 2) concerns about loss of control and prediction of sleep; 3) unrealistic expectations about the need for sleep; 4) causal attributions of insomnia; and 5) beliefs about habits or behaviors that favor sleep.

Health status and quality of life associated with FM. Health status and quality of life will be measured using the Revised Fibromyalgia Impact Questionnaire (FIQ-R), developed by Bennet et al. (256) and validated in Spanish by Salgueiro et al. (257). This FIQ-R is the most current version of the Fibromyalgia Impact Questionnaire, which was created and validated in 1991 by Burckhardt, Clark and Bennet (258). *Additional data.* Data will also be collected on number of visits to and time spent on the website by participants in both groups and the number of visits to each video.

Statistical analysis

For univariate analysis, the variables will be described through measures of central tendency and position, such as mean, median and mode; dispersion measures including interquartile range, standard deviation and variance will also be calculated. Graphs and tables will be prepared to facilitate interpretation of the data.

For bivariate analysis, chi-square tests, Pearson's correlation coefficient and Student's *t*-tests will be used to identify relationships between the dependent and independent variables. The efficacy of the intervention will be assessed using Student's *t*-test. Analysis to determine statistical significance will assume a confidence interval of 95% and an alpha value of 5% (0.05).

Clinically significant improvements in pain intensity, pain catastrophizing and health status and quality of life related to FM will be identified according to the following values. For pain intensity (VAS), a score reduction between 10% and 20% represents a minimum level of clinical improvement; a reduction between 30-50% represents moderate clinical improvement; and a reduction of 50% or represents substantial clinical improvement change (238). For pain catastrophizing (PCS), a reduction between 15-30% indicates a minimum level of clinical improvement; a reduction between 30-50% indicates moderate clinical improvement; and a reduction of 50% or more indicates substantial clinical improvement (259). For health status and quality of life related to FM (FIQ-R), a change of 45.5% or 27.04 points in overall score indicates a minimum level of clinical improvement (260). For measurement tools without established values indicating minimal clinical improvement, the standard median deviation will be calculated.

Ethical considerations

A favorable report of the proposed project was obtained from the "Hospital Universitari Arnau de Vilanova" Ethics Committee (Code CEIC-1999). All participants will be provided with a written informed consent document accompanied by a full explanation of the investigation, the authors' use of the data and the laws protecting the participants' rights.

Validity and reliability/Rigor

The description of the project's mixed methodology was developed based on the recommendations of the Good Reporting of a Mixed Methods Study (GRAMMS) statement (261). The Consolidated Criteria for Reporting Qualitative Research (COREQ) (262) were also considered to report the qualitative methodology and the Consolidated Standards of Reporting Trials (CONSORT 2010) guidelines (263) to report the quantitative methodology.

STUDY II. Qualitative Metasynthesis

In health conditions as FM in which poor sleep quality shows a strong tendency to chronification (264), exploring the cognitive and behavioral factors that act as perpetuators of such symptom could be essential to develop effective management strategies. Besides, understanding how people diagnosed with FM experience and manage poor sleep quality could help health providers to contextualize and conceptualize the content of the sleep educational programs to this health condition.

Qualitative research provides an opportunity to engage the participation of people diagnosed with FM in the development of future treatment approaches, especially those based on educational interventions aimed at changing cognitive and behavioral factors associated with the symptoms experience.

Qualitative studies are rarely aimed at having a direct impact on healthcare practice or policymaking. However, conducting systematized reviews of qualitative studies could be a valuable method in facilitating the transferability of qualitative data to improve healthcare attention (265).

Although the vast majority of meta-syntheses of qualitative studies are published in the fields of nursing and sociology, there is a clear trend towards the publication of metasynthesis in all disciplines of health science (266).

Therefore, the authors considered it appropriate to carry out a metasynthesis aimed at summarizing the available qualitative research exploring the experience and management of poor sleep quality in people diagnosed with FM. Carrying out this meta-synthesis could improve the understanding of the phenomenon of poor sleep quality in the context of FM and provide valuable information for the development of treatment strategies.

The metasynthesis was reported according to the 'Enhancing Transparency in Reporting the Synthesis of Qualitative Research' statement recommendations (267).

Aim

We aimed to develop a metasynthesis of qualitative studies to evaluate how people diagnosed with FM experience and manage poor sleep quality.

Methodological approach

In accordance with Sandelowski and Barroso (268), we integrated the findings of original qualitative research reports through a metasynthesis approach, including both a metasummary and a metasynthesis of the findings. A qualitative metasynthesis must ensure an interpretative integration of the findings in a way that "the integrations are more than the sum of parts in that they offer novel interpretation of findings

that are the result of interpretive transformations" (268). The six steps of a qualitative metasynthesis established by Sandelowski and Barroso (268) were followed: 1) Formulating the review question, 2) Conducting a systematic literature search, 3) Screening and selecting appropriate research articles, 4) Analyzing and synthesizing qualitative findings, 5) Maintaining quality control, and 6) Presenting findings.

Research Question

There is a necessity for increasing the understanding of the phenomenon of poor sleep quality in the context of FM. Therefore, this metasynthesis was developed to answer the research question "How people diagnosed with fibromyalgia experience and manage poor sleep quality?".

Approach to searching

We implemented a pre-planned approach to develop a comprehensive search strategy to gather available qualitative reports about the experience and management of poor sleep quality in people diagnosed with FM.

Inclusion criteria

For the inclusion in this metasynthesis the qualitative reports were required to fulfill the subsequent criteria: 1) Qualitative or mixed methods research in which a qualitative phase was carried out including adult people diagnosed with FM, 2) Studies totally o partially exploring the experience and/or management related to poor sleep quality in adult people diagnosed with FM 3) Studies published in English or Spanish since 1990.

Data sources

Systematized searches were performed on the computerized databases PubMed, Scopus, ISI WebofScience, and Cinahl Plus. The reference lists of the included studies were scanned to identify additional studies.

The last update of the search was carried out on January 3, 2020.

Electronic Search strategy

The "Peer Review of Electronic Search Strategies" guideline recommendations were followed to develop the search strategy (269). We combined MeSH (and their equivalent in other databases) and free-text terms such as 'Fibromyalgia', 'Sleep', 'Sleep quality', 'Qualitative research'. The complete search strategy for PubMed can be consulted in Table 1.

Table 1: Search strategies Study II
Database: PubMed
(“Fibromyalgia”[Mesh] OR Fibromyalgia*[Tiab] OR “Muscular Rheumatism”[Tiab] OR “Fibrositis”[Tiab] OR “Secondary Fibromyalgia”[Tiab] OR “Primary Fibromyalgia”[Tiab]) AND (“Sleep”[Mesh] OR “Sleep”[Tiab] OR "Sleep Hygiene"[Mesh] OR "Sleep Hygiene"[Tiab] OR Good Sleep Habit*[Tiab] OR "Sleep Initiation and Maintenance Disorders"[Mesh] OR "Sleep Initiation and Maintenance Disorders"[Tiab] OR Insomnia*[Tiab] OR “Sleep Initiation Dysfunction”[Tiab] OR “Sleep Dysfunction*”[Tiab] OR “Sleeplessness”[Tiab] OR “Sleep Quality”[Tiab]) AND ("Interviews as Topic"[Mesh] OR “Focus Groups”[Mesh] OR “Narration”[Mesh] OR "Qualitative Research"[Mesh] OR "Personal Narratives as Topic”[Mesh] OR ((“semi-structured”[Tiab] OR semistructured[Tiab] OR unstructured[Tiab] OR informal[Tiab] OR “in-depth”[Tiab] OR “in depth”[Tiab] OR indepth[Tiab] OR “face-to-face”[Tiab] OR structured[Tiab] OR guide[Tiab] OR guides[Tiab] OR guided[Tiab]) AND (interview*[Tiab] OR discussion*[Tiab] OR questionnaire*[Tiab])) OR “focus group”[Tiab] OR “focus groups”[Tiab] OR qualitative[Tiab] OR ethnograph*[Tiab] OR fieldwork[Tiab] OR “field work”[Tiab] OR “key informant”[Tiab] OR “critical social research”[Tiab] OR “Ethical Inquiry”[Tiab] OR Delphi[Tiab] OR “Grounded Theory”[Tiab] OR “Life History”[Tiab] OR “Action Research”[Tiab] OR “Action-Research”[Tiab] OR “mixed model*”[Tiab] OR “mixed design*”[Tiab] OR “mixed method*”[Tiab] OR “multiple method*”[Tiab] OR multimethod*[Tiab] OR
Database: Scopus
TITLE-ABS-KEY((Fibromyalgia* OR "Fibromyalgia Syndrome" OR "Muscular Rheumatism" OR Fibrositis OR "Secondary Fibromyalgia" OR “Primary Fibromyalgia") AND ("Sleep" OR "Sleep Hygiene" OR "Good Sleep Habit" OR “Sleep Initiation and Maintenance Disorders" OR Insomnia* OR "Sleep Initiation Dysfunction" OR “Sleep Dysfunction*” OR Sleeplessness OR "Sleep Quality") AND ("Interviews as Topic" OR "Focus Groups" OR Narration OR "Qualitative Research" OR "Personal Narratives as Topic") OR (Semi-structured OR semistructured OR unstructured OR informal OR "in-depth" OR “in depth” OR indepth OR "face-to-face" OR structured OR guide OR guides OR guided AND interview* OR discussion* OR questionnaire*) OR (“Focus group*” OR qualitative OR ethnograph OR fieldwork OR "field work" OR "key informant" OR "critical social research" OR "ethical inquiry" OR Delphi OR "Grounded Theory" OR "Life History" OR "Action Research” OR "Action-Research" OR “mixed model*” OR "mixed design" OR "mixed method*" OR "multiple method*" OR multimethod* OR metasynthesis OR meta-synthesis OR "meta-synthesis")

Table 1: Search Strategies Study II (cont.)
Database: Cinahl Plus
((MH "Fibromyalgia") OR (MH "Fibromyalgia syndrome") OR “Secondary Fibromyalgia” OR “Primary Fibromyalgia” OR (MM "Fibromyalgia") OR Fibromyalgia* OR "Muscular Rheumatism" OR Fibrositi*) AND ((MH "Sleep") OR (MH "Sleep Initiation and Maintenance Disorders") OR “Good Sleep Habits” OR “Insomnia” OR “Sleep Initiation Dysfunction” OR “Sleep Dysfunction” OR “Sleep Quality” OR “Sleeplessness”) AND ((MH “Interviews as Topic”) OR (MM “Interviews as Topic”) OR (MH “Focus Groups”) OR (MM “Focus Groups”) OR (MH “Narration”) OR (MM “Narration”) OR (MH “Qualitative Research”) OR (MM “Qualitative Research”) OR (MH “Personas Narratives as Topic”) OR (MM “Personas Narratives as Topic”) OR *structured OR “Informal” OR in*depth OR “face-to-face” OR guide* AND Interview* OR Discussion* OR Questionnaire* OR “Focus Groups” OR “Qualitative” OR Ethnograph* OR Fieldwork OR “Field Work” OR “Key Informant” OR “Critical Social Research” OR “Ethical Inquiry” OR Delphi OR “Grounded Theory” OR “Life History” OR Action*research OR “Mixed Model” OR Mixed Design* OR Multiple Method* OR Multimethod*)
Database: ISI Web of Knowledge
TS=((Fibromyalgia OR “Fibromyalgia Syndrome” OR “Primary Fibromyalgia” OR “Secondary Fibromyalgia” OR Fibrositi* OR “Muscular Rheumatism”) AND (Sleep OR "Sleep Hygiene" OR “Good Sleep Habit*” OR "Sleep Initiation and Maintenance Disorders” OR Insomnia* OR “Sleep Initiation Dysfunction” OR “Sleep Dysfunction*” OR “Sleeplessness” OR “Sleep Quality”) AND ("Narration" OR (("semi-structured" OR semistructured OR unstructured OR informal OR "in-depth" OR "in depth" OR indepth OR "face-to-face" OR structured OR guide OR guides OR guided) NEAR/2 (interview* OR discussion* OR questionnaire*)) OR "focus group*" OR qualitative OR ethnograph* OR fieldwork OR "field work" OR "key informant" OR "critical social research" OR "Ethical Inquiry" OR Delphi OR "Grounded Theory" OR "Life History" OR "Action Research" OR "Action-Research" OR "mixed model*" OR "mixed design*" OR "mixed method*" OR "multiple method*" OR multimethod* OR triangulat* OR metasynthesis OR meta-synthesis OR "meta synthesis")) AND PY=(1990-2018)

Screening methods of the studies and appraisal of the methodological quality

The studies screening process and the appraisal of the methodological quality were carried out through a peer-review process in which two authors (CCS and GMA) screened the title and abstract of the retrieved reports in the first phase and the full-text in the second phase. After the selection process of the studies, the authors appraised the methodological quality of the included reports using the Critical Appraisal Skills Program (CASP) qualitative checklist (270). The whole process was supervised by a third author to solve discrepancies.

Analyzing and synthesizing qualitative findings

Under Sandelowski and Barroso (268), the synthesizing process was implemented considering two approaches: the qualitative metasummary defined as "a quantitatively oriented aggregation of qualitative findings" and the qualitative metasynthesis that is "an interpretive integration of qualitative findings that are themselves interpretive syntheses of data".

For the qualitative metasummary, we reported the characteristics of the included studies, the frequency of appearance of each of the target findings, the inter-study frequency effect sizes (i.e., representation of subthemes in individual studies), and the intra-study intensity effect sizes (i.e., individual studies' contribution to sub-themes).

To metasynthesize the findings, the quotations of adult people diagnosed with FM were established as the target finding and were imported, structured, and analyzed using the qualitative analysis software Nvivo12 Plus.

In this metasynthesis we took the Symptom Management Theory (SMT) (224) as a biopsychosocial conceptual framework. The SMT is a deductive, middle-range theory developed by Larson et al. (225) providing a new model for nurses to assess the patients' symptom experience in a comprehensive and multidimensional manner. Besides, the SMT is also aimed at providing a framework for the development of symptom management strategies and to evaluate their outcomes in the biological, psychological, and social spheres of the patient.

As previously stated, FM is a complex chronic health condition for which curative treatments are currently nonexistent. Therefore, the main approach is focused on developing symptom management strategies that help alleviate the severity of symptoms such as pain, poor sleep quality, fatigue, and mood disturbances. Because of the latter, a symptom-focused conceptual framework could help to understand how people diagnosed with FM experience the symptoms that characterize this health condition.

STUDY III. Qualitative Inquiry

Although sleep problems commonly emerged as a concern of people diagnosed with FM (271–273), qualitative studies specifically focused on the patient's sleep experiences FM are scarce (274). These studies showed that poor sleep quality is often considered as the worst symptom of FM by people diagnosed with it, and that the most common sleep disturbances associated with FM are those related with the maintenance of sleep which is also associated with the development of frustration and the feeling of being continuously sleep deprived (274–277).

As to date no curative treatments are available, efforts of health providers should be focused on providing treatment approaches that facilitate the development of effective self-management strategies to their FM patients (12). Treatments and recommendations should be patient-centered, adapted to the specific needs of patients with FM. Therefore, understanding how people with FM experience poor sleep quality could help to improve the attention provided by health professionals.

The aim of this study was to explore the experience and manage strategies for poor sleep quality in adult women diagnosed with FM.

Design

A qualitative study belonging to a wider research project (278).

Participants

The participants were 21 adult women diagnosed with FM by rheumatologists. A theoretical sample was previously defined to reach heterogeneity among participants, taking into account the inclusion criteria: different age, educational level, employment status, civil status, and their participation or not in FM Associations. Participants were recruited from a FM association and from a Primary Health Care Center of a city of Lleida (Catalonia, Spain). Two gatekeepers from both institutions directly invited women to participate and facilitated a list of women interested in participating in the study. The first author contacted the women by phone and, after explaining the objective and procedures of the study, they stablished an appointment at the University or at a medical consultation of the Primary Health Care Centre.

Data collection

Data was collected using in-depth semi-structured personal interviews, following an interview guide of open questions about the experience and management of poor sleep quality. The interview guide was developed based on two of the domains of the SMT "Symptom Experience" and "Symptom Management Strategies" (Table 2).

Table 2. Interview Guide

1. What does it mean for you to sleep well or have a good sleep quality?
2. Could you tell me what a night of yours is like from the moment you go to bed to the moment you get up?
3. When you don't sleep well one night, what do you usually think?
4. What do you think can happen to you in the future if you continue to sleep poorly?
5. What worries you most about your sleep?
6. What have health professionals explained to you about sleep in the context of fibromyalgia?
7. What do you think is the origin or the cause of your poor sleep quality?
8. What advice have health professionals given you to help you sleep better?
9. What do you do when you lie down and can't sleep?
10. What do you do when you wake up in the middle of the night and find it hard to go back to sleep?
11. What do you do when you wake up too early?
12. The day after a bad night's sleep, what do you usually do to deal with the consequences?
13. Why do you think you continue to have sleep problems despite the advice of healthcare professionals and having developed your own management strategies?
14. If you had a chance to talk to the world's greatest sleep expert, what would you ask him/her?

Ethical Considerations

The present study followed the principles of the Declaration of Helsinki and Belmont Report. Approval was obtained from the ethics committee of the 'Hospital Universitari Arnau de Vilanova' (Code CEIC-1999). Prior to data collection, participants were provided with oral and written information about the project and they had the opportunity to ask any doubts or questions regarding the project. They voluntarily participated after signing written informed consent.

Data analysis

All interviews were digitally recorded and transcribed verbatim. Both interview transcripts and field notes capturing participants' non-verbal responses were imported into the NVivo 12 qualitative analysis software to help organize the information.

A thematic qualitative analysis was conducted guided by the SMT developed by Humphreys et al. (224). In accordance with the SMT, the results were organized around two pre-established themes

corresponding to the domains of 'Symptom Experience' and 'Symptom Management Strategies', and the sub-themes were established according to the factors nested within each of the domains.

Two authors assigned emerging open codes to sentences of the transcriptions, summarizing their meaning, and created groups of codes according to their similar meaning. After putting in common their analysis, they classified those groups of codes under the pre-established subthemes (279).

Rigour

The results were discussed and agreed by all research members, allowing a triangulation of researchers and ensuring analytic rigour.

STUDY IV. COSMIN Systematic Review

The assessment of sleep quality in people diagnosed with FM could guarantee comprehensive assistance in patients with FM and can provide important information on the effectiveness of prescribed treatments, both pharmacological and non-pharmacological (280). In the field of research, the assessment of sleep quality may be of especial interest when evaluating the effectiveness of new treatments, and also to improve the knowledge on how this symptom can influence the general health status of people who suffer from FM (11).

Therefore, the main objective of this systematic review was to identify and describe the available PROMs of sleep quality in adults diagnosed with FM and their psychometric properties. In addition, adaptations and translations of these tools to other languages were also presented.

This review was carried out following the "COnsensus-based Standards for the selection of health Measurement Instruments" (COSMIN) (281) and the "Preferred Reporting Items for Systematic reviews and Meta-Analyses" (PRISMA) (282) guidelines.

The review protocol was registered with PROSPERO (Record ID = CRD42018114218).

Criteria for Considering Studies for this Review

Type of Studies

Validation or cross-cultural adaptation studies published in English or Spanish (the research team did not speak fluently other languages) with no restriction regarding the year of publication.

Additionally, the development studies for each of the included PROMs were searched so as to analyze the content validity for those PROMs originally developed in the context of FM. In the case of the PROMs that were developed for other target populations, the report was also searched and the results presented.

Type of Participants

Validation or cross-cultural adaptation studies involving adult participants (18 years or older) diagnosed with FM.

Type of Outcome Measures

Studies that met the above inclusion criteria were included regardless of whether they did not report all the psychometric properties stablished in the COSMIN guidelines (281): Content validity, structural

validity, internal consistency, cross-cultural validity, reliability, measurement error, criterion validity, hypotheses testing for construct validity, and responsiveness.

Search Strategy

An electronic systematized search in the electronic databases PubMed, Scopus, Cinahl Plus, PsycINFO, and ISI Web of Science was carried out.

The search strategy was developed by two authors based on the COSMIN "search filters for finding studies on measurement properties" provided as an additional tool in the COSMIN website (https://www.cosmin.nl/tools/pubmed-search-filters/). The Peer Review of Electronic Search Strategies guidelines [14] recommendations were also implemented for the development of the search strategy in the selected databases. The following MeSH terms were used for the development of the search strategy: "Fibromyalgia", "Sleep", "Surveys and Questionnaires", "Psychometrics", and "Validation Studies as Topic". Entry Terms and Free Text Terms derived from or related with each selected MeSH Term were also included in the search strategy. The last search was run on March the 6th, 2020. The search strategies used in the databases can be consulted in Table 3.

Searching other sources

A manual search of studies was carried out based on the bibliographic references of the included articles.

Selection of studies

The selection of studies process was developed with the online software "COVIDENCE". The identified studies were first stored and checked for duplicates. After duplicates were removed and, based on the inclusion criteria, two authors carried out first the title and abstract screening, and subsequently the full-text screening of the studies through a peer review process. In case of discrepancy in any of the two phases of the selection of the studies, a third author discussed the suitability of the studies to be included.

Data collection and data items

The data collection process was carried out by two authors independently, and, a third author reviewed the extraction so as to ensure accuracy of the data.

For each of the included PROMs the following data items were extracted in accordance with the COSMIN recommendations (281): Characteristics of the included PROMs, characteristics of the included study populations, results of studies on measurement properties.

Table 3. Search strategies Study IV

Database: PubMed

("Sleep"[Mesh] OR "Sleep Hygiene"[Mesh] OR "Sleep"[tiab] OR "DIMS"[TIAB]) AND ("Fibromyalgia"[Mesh] OR Fibromyalgia*[TIAB] OR "Muscular Rheumatism"[TIAB] OR Fibrositi*[TIAB]) AND (instrumentation[sh] OR methods[sh] OR "Validation Studies"[pt] OR "Comparative Study"[pt] OR "psychometrics"[MeSH] OR psychometr*[tiab] OR clinimetr*[tw] OR clinometr*[tw] OR "outcome assessment (health care)"[MeSH] OR "outcome assessment"[tiab] OR "outcome measure*"[tw] OR "observer variation"[MeSH] OR "observer variation"[tiab] OR "Health Status Indicators"[Mesh] OR "reproducibility of results"[MeSH] OR reproducib*[tiab] OR "discriminant analysis"[MeSH] OR reliab*[tiab] OR unreliab*[tiab] OR valid*[tiab] OR "coecient of variation"[tiab] OR coecient[tiab] OR homogeneity[tiab] OR homogeneous[tiab] OR "internal consistency"[tiab] OR (cronbach*[tiab] AND (alpha[tiab] OR alphas[tiab])) OR (item[tiab] AND (correlation*[tiab] OR selection*[tiab] OR reduction*[tiab])) OR agreement[tw] OR precision[tw] OR imprecision[tw] OR "precise values"[tw] OR test-retest[tiab] OR (test[tiab] AND retest[tiab]) OR (reliab*[tiab] AND (test[tiab] OR retest[tiab])) OR stability[tiab] OR interrater[tiab] OR inter-rater[tiab] OR intrarater[tiab] OR intra-rater[tiab] OR intertester[tiab] OR inter-tester[tiab] OR intratester[tiab] OR intra-tester[tiab] OR interobserver[tiab] OR inter-observer[tiab] OR intraobserver[tiab] OR intra-observer[tiab] OR intertechnician[tiab] OR inter-technician[tiab] OR intratechnician[tiab] OR intra-technician[tiab] OR interexaminer[tiab] OR inter-examiner[tiab] OR intraexaminer[tiab] OR intra-examiner[tiab] OR interassay[tiab] OR inter-assay[tiab] OR intraassay[tiab] OR intra-assay[tiab] OR interindividual[tiab] OR inter-individual[tiab] OR intraindividual[tiab] OR intra-individual[tiab] OR interparticipant[tiab] OR inter-participant[tiab] OR intraparticipant[tiab] OR intra-participant[tiab]OR kappa[tiab] ORkappa's[tiab]ORkappas[tiab]Orr epeatab*[tw] OR ((replicab*[tw] OR repeated[tw]) AND (measure[tw] OR measures[tw] OR findings[tw] OR result[tw] OR results[tw] OR test[tw] OR tests[tw])) OR generaliza*[tiab] OR generalisa*[tiab] OR concordance[tiab] OR (intraclass[tiab] AND correlation*[tiab]) OR discriminative[tiab] OR "known group"[tiab] OR "factor analysis"[tiab] OR "factor analyses"[tiab] OR "factor structure"[tiab] OR "factor structures"[tiab] OR dimension*[tiab] OR subscale*[tiab] OR (multitrait[tiab]ANDscaling[tiab]AND(analysis[tiab] OR analyses[tiab])) OR "item discriminant"[tiab] OR "interscale correlation*"[tiab] OR error[tiab] OR errors[tiab] OR "individual variability"[tiab] OR "interval variability"[tiab] OR "rate variability"[tiab] OR (variability[tiab] AND (analysis[tiab] OR values[tiab])) OR (uncertainty[tiab] AND (measurement[tiab] OR measuring[tiab])) OR "standard error of measurement"[tiab] OR sensitiv*[tiab] OR responsive*[tiab] OR (limit[tiab] AND detection[tiab]) OR "minimal detectable concentration"[tiab] OR interpretab*[tiab] OR ((minimal[tiab] OR minimally[tiab] OR clinical[tiab] OR clinically[tiab]) AND (important[tiab] OR significant[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR (small*[tiab] AND (real[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR "meaningful change"[tiab] OR "ceiling effect"[tiab] OR "floor effect"[tiab] OR "Item response model"[tiab] OR IRT[tiab] OR Rasch[tiab] OR "Differential item functioning"[tiab] OR DIF[tiab] OR "computer adaptive testing"[tiab] OR "item bank"[tiab] OR "cross-cultural equivalence"[tiab]) NOT ('delphi-technique'[ti] OR cross-sectional[ti] OR "addresses"[Publication Type] OR "biography"[Publication Type] OR "case reports"[Publication Type] OR "comment"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "festschrift"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "popular works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "practice guideline"[Publication Type]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]).

Table 3: Search strategies Study IV (cont.)
Database: Cinahl Plus
(MH "Sleep Hygiene") OR (MH "Sleep") OR TI Sleep OR AB sleep AND (MH "Fibromyalgia") OR TI (Fibromyalgia* OR "Muscular Rheumatism" OR Fibrositi*) OR AB (Fibromyalgia* OR "Muscular Rheumatism" OR Fibrositi*) AND (MH "Psychometrics") or (TI psychometr* or AB psychometr*) or (TI clinimetr* or AB clinimetr*) or (TI clinometr* OR AB clinometr*) or (MH "Outcome Assessment") or (TI outcome assessment or AB outcome assessment) or (TI outcome measure* or AB outcome measure*) or (MH "Health Status Indicators") or (MH "Reproducibility of Results") or (MH "Discriminant Analysis") or ((TI reproducib* or AB reproducib*) or (TI reliab* or AB reliab*) or (TI unreliab* or AB unreliab*)) or ((TI valid* or AB valid*) or (TI coefficient or AB coefficient) or (TI homogeneity or AB homogeneity)) or (TI homogeneous or AB homogeneous) or (TI "coefficient of variation" or AB "coefficient of variation") or (TI "internal consistency" or AB "internal consistency") or (MH "Internal Consistency+") or (MH "Reliability+") or (MH "Measurement Error+") or (MH "Content Validity+") or "hypothesis testing" or "structural validity" or "cross-cultural validity" or (MH "Criterion-Related Validity+") or "responsiveness" or "interpretability" or (TI reliab* or AB reliab*) and ((TI test or AB test) OR (TI retest or AB retest)) or (TI stability or AB stability) or (TI interrater or AB interrater) or (TI inter-rater or AB inter-rater) or (TI intrarater or AB intrarater) or (TI intra-rater or AB intrarater) or (TI intertester or AB intertester) or (TI inter-tester or AB inter-tester) or (TI intratester or AB intratester) or (TI intra-tester or AB intra-tester) or (TI interobserver or AB interobserver) or (TI inter-observer or AB inter-observer) or (TI intraobserver or AB intraobserver) or (TI intra-observer or AB intra-observer) or (TI intertechnician or AB intertechnician) or (TI inter-technician or AB inter-technician) or (TI intratechnician or AB intratechnician) or (TI intra-technician or AB intra-technician) or (TI interexaminer or AB interexaminer) or (TI inter-examiner or AB inter-examiner) or (TI intraexaminer or AB intraexaminer) OR (TI intra-examiner or AB intra-examiner) or (TI intra-examiner or AB intraexaminer) or (TI interassay or AB interassay) or (TI inter-assay or AB inter-assay) or (TI intraassay or AB intraassay) or (TI intra-assay or AB intra-assay) or (TI interindividual or AB interindividual) or (TI inter-individual or AB inter-individual) OR (TI intraindividual or AB intraindividual) or (TI intra-individual or AB intra-individual) or (TI interparticipant or AB interparticipant) or (TI inter-participant or AB inter-participant) or (TI intraparticipant or AB intraparticipant) or (TI intra-participant or AB intra-participant) or (TI kappa or AB kappa) or (TI kappa's or AB kappa's) or (TI kappas or AB kappas) or (TI repeatab* or AB repeatab*) or (TI responsive* or AB responsive*) or (TI interpretab* or AB interpretab*)

Table 3: Search strategies Study IV (cont.)
Database: Scopus
TITLE-ABS-KEY (("Sleep" OR "DIMS") AND (fibromyalgia* OR "Muscular Rheumatism" OR fibrositi*) AND (psychometr* OR clinimetr* OR clinometr* OR "outcome assessment" OR "outcome measure*" OR "observer variation" OR reproducib* OR reliab* OR unreliab* OR valid* OR "coefficient of variation" OR coefficient OR homogeneity OR homogeneous OR "internal consistency" OR (cronbach* AND (alpha OR alphas)) OR (item AND (correlation* OR selection* OR reduction*)) OR agreement OR precision OR imprecision OR "precise values" OR test-retest OR (test AND retest) OR (reliab* AND (test OR retest)) OR stability OR interrater OR inter-rater OR intrarater OR intra-rater OR intertester OR inter-tester OR intratester OR intra-tester OR interobserver OR inter-observer OR intraobserver OR intra-observer OR intertechnician OR inter-technician OR intratechnician OR intra-technician OR interexaminer OR inter-examiner OR intraexaminer OR intra-examiner OR interassay OR inter-assay OR intraassay OR intra-assay OR interindividual OR inter-individual OR intraindividual OR intra-individual OR interparticipant OR inter-participant OR intraparticipant OR intra-participant OR kappa OR kappa's OR kappas OR repeatab* OR ((replicab* OR repeated) AND (measure OR measures OR findings OR result OR results OR test OR tests)) OR generaliza* OR generalisa* OR concordance OR (intraclass AND correlation*) OR discriminative OR "known group" OR "factor analysis" OR "factor analyses" OR "factor structure" OR "factor structures" OR dimension* OR subscale* OR (multitrait AND scaling AND (analysis OR analyses)) OR "item discriminant" OR "interscale correlation*" OR error OR errors OR "individual variability" OR "interval variability" OR "rate variability" OR (variability AND (analysis OR values)) OR (uncertainty AND (measurement OR measuring)) OR "standard error of measurement" OR sensitiv* OR responsive* OR (limit AND detection) OR "minimal detectable concentration" OR interpretab* OR ((minimal OR minimally OR clinical OR clinically) AND (important OR significant OR detectable) AND (change OR difference)) OR (small* AND (real OR detectable) AND (change OR difference)) OR "meaningful change" OR "ceiling effect" OR "floor effect" OR "Item response model" OR irt OR rasch OR "Differential item functioning" OR dif OR "computer adaptive testing" OR "item bank" OR "cross-cultural equivalence"))

Table 3: Search strategies Study IV (cont.)
Database: PsycInfo (ProQuest)
((MAINSUBJECT.EXACT("Sleep") OR MAINSUBJECT.EXACT("Insomnia") OR MAINSUBJECT.EXACT("Sleep Wake Disorders") OR MAINSUBJECT.EXACT.EXPLODE("Sleep")) OR tiab(sleep OR dims)) AND (MAINSUBJECT.EXACT("Fibromyalgia") OR tiab(fibromyalgia* OR fibrositi* OR "muscular rheumatism*")) AND (cl("Psychometrics & Statistics & Methodology" OR "Research Methods & Experimental Design") OR (psychometr* OR clinimetr* OR clinometr* OR "outcome assessment" OR "outcome measure*" OR "observer variation" OR reproducib* OR reliab* OR unreliab* OR valid* OR coefficient OR homogeneity OR homogeneous OR "internal consistency" OR agreement OR precision OR imprecision OR "precise values" OR test-retest OR reliab* OR stability OR interrater OR inter-rater OR intrarater OR intra-rater OR intertester OR inter-tester OR intratester OR intra-tester OR interobserver OR inter-observer OR intraobserver OR intra-observer OR intertechnician OR inter-technician OR intratechnician OR intra-technician OR interexaminer OR inter-examiner OR intraexaminer OR intra-examiner OR interassay OR inter-assay OR intraassay OR intra-assay OR interindividual OR inter-individual OR intraindividual OR intra-individual OR interparticipant OR inter-participant OR intraparticipant OR intra-participant OR kappa* OR repeatab* OR generaliza* OR generalisa* OR concordance OR discriminative OR "known group" OR "factor analys*" OR dimension* OR subscale* OR "item discriminant" OR "interscale correlation*" OR error* OR "individual variability" OR "standard error of measurement" OR sensitiv* OR responsive* OR "meaningful change" OR "Item response model" OR IRT OR Rasch OR "Differential item functioning" OR DIF OR "computer adaptive testing" "item bank" OR "Cross-cultural equivalence" OR "Ceiling effect" OR "floor effect") OR ("cronbach* alpha*" OR "replicab* test*" OR "repeated measure" OR "repeated measurement" OR "repeated measurements" OR "repeated measures" OR "repeated finding" OR "repeated result*" OR "repeated testing" OR "repeated tests" OR "item correlation*" OR "item selection" OR "item reduction*" OR "Test retest" OR "intraclass correlation" OR "multitrait scaling analys*" OR "uncertainty measur*" OR "variability analys*" OR "variability value*" OR "minimal* important change" OR "minimal* important difference" OR "minimal* significant change" OR "minimal* significant difference" OR "minimal* significant change" OR "minimal* significant difference" OR "minimal* detectable change" OR "minimal* detectable difference" OR "clinical* important change" OR "clinical* important difference" OR "clinical* significant change" OR "clinical* significant difference" OR "clinical* detectable change" OR "clinical detectable difference" OR "small* real change" OR "small* real difference" OR "small* detectable change" OR "small* detectable difference") OR SU.EXACT.EXPLODE("Error Analysis") OR SU.EXACT.EXPLODE("Measurement") OR SU.EXACT.EXPLODE("Factor Analysis") OR SU.EXACT.EXPLODE("Statistical Reliability") OR SU.EXACT.EXPLODE("Factor Structure") OR SU.EXACT.EXPLODE("Testing Methods") OR SU.EXACT.EXPLODE("Consistency (Measurement)") OR SU.EXACT.EXPLODE("Test Construction") OR SU.EXACT.EXPLODE("Interrater Reliability") OR SU.EXACT.EXPLODE("Error of Measurement") OR SU.EXACT.EXPLODE("Statistical Validity") OR SU.EXACT.EXPLODE("Prediction") OR SU.EXACT.EXPLODE("Content Analysis") OR SU.EXACT.EXPLODE("Prediction Errors") OR SU.EXACT.EXPLODE("Computerized Assessment"))

Table 3: Search strategies Study IV (cont.)

Database: ISI Web of Science

TS=(("Sleep" OR "DIMS") AND (fibromyalgia* OR "Muscular Rheumatism" OR fibrositi*) AND (psychometr* OR clinimetr* OR clinometr* OR "outcome assessment" OR "outcome measure*" OR "observer variation" OR reproducib* OR reliab* OR unreliab* OR valid* OR "coefficient of variation" OR coefficient OR homogeneity OR homogeneous OR "internal consistency" OR (cronbach* AND (alpha OR alphas)) OR (item AND (correlation* OR selection* OR reduction*)) OR agreement OR precision OR imprecision OR "precise values" OR test-retest OR (test AND retest) OR (reliab* AND (test OR retest)) OR stability OR interrater OR inter-rater OR intrarater OR intra-rater OR intertester OR inter-tester OR intratester OR intra-tester OR interobserver OR inter-observer OR intraobserver OR intra-observer OR intertechnician OR inter-technician OR intratechnician OR intra-technician OR interexaminer OR inter-examiner OR intraexaminer OR intra-examiner OR interassay OR inter-assay OR intraassay OR intra-assay OR interindividual OR inter-individual OR intraindividual OR intra-individual OR interparticipant OR inter-participant OR intraparticipant OR intra-participant OR kappa OR kappa's OR kappas OR repeatab* OR ((replicab* OR repeated) AND (measure OR measures OR findings OR result OR results OR test OR tests)) OR generaliza* OR generalisa* OR concordance OR (intraclass AND correlation*) OR discriminative OR "known group" OR "factor analysis" OR "factor analyses" OR "factor structure" OR "factor structures" OR dimension* OR subscale* OR (multitrait AND scaling AND (analysis OR analyses)) OR "item discriminant" OR "interscale correlation*" OR error OR errors OR "individual variability" OR "interval variability" OR "rate variability" OR (variability AND (analysis OR values)) OR (uncertainty AND (measurement OR measuring)) OR "standard error of measurement" OR sensitiv* OR responsive* OR (limit AND detection) OR "minimal detectable concentration" OR interpretab* OR ((minimal OR minimally OR clinical OR clinically) AND (important OR significant OR detectable) AND (change OR difference)) OR (small* AND (real OR detectable) AND (change OR difference)) OR "meaningful change" OR "ceiling effect" OR "floor effect" OR "Item response model" OR irt OR rasch OR "Differential item functioning" OR dif OR "computer adaptive testing" OR "item bank" OR "cross-cultural equivalence")) OR TI=(("Sleep" OR "DIMS") AND (fibromyalgia* OR "Muscular Rheumatism" OR fibrositi*) AND (psychometr* OR clinimetr* OR clinometr* OR "outcome assessment" OR "outcome measure*" OR "observer variation" OR reproducib* OR reliab* OR unreliab* OR valid* OR "coefficient of variation" OR coefficient OR homogeneity OR homogeneous OR "internal consistency" OR (cronbach* AND (alpha OR alphas)) OR (item AND (correlation* OR selection* OR reduction*)) OR agreement OR precision OR imprecision OR "precise values" OR test-retest OR (test AND retest) OR (reliab* AND (test OR retest)) OR stability OR interrater OR inter-rater OR intrarater OR intra-rater OR intertester OR inter-tester OR intratester OR intra-tester OR interobserver OR inter-observer OR intraobserver OR intra-observer OR intertechnician OR inter-technician OR intratechnician OR intra-technician OR interexaminer OR inter-examiner OR intraexaminer OR intra-examiner OR interassay OR inter-assay OR intraassay OR intra-assay OR interindividual OR inter-individual OR intraindividual OR intra-individual OR interparticipant OR inter-participant OR intraparticipant OR intra-participant OR kappa OR kappa's OR kappas OR repeatab* OR ((replicab* OR repeated) AND (measure OR measures OR findings OR result OR results OR test OR tests)) OR generaliza* OR generalisa* OR concordance OR (intraclass AND correlation*) OR discriminative OR "known group" OR "factor analysis" OR "factor analyses" OR "factor structure" OR "factor structures" OR dimension* OR subscale* OR (multitrait AND scaling AND (analysis OR analyses)) OR "item discriminant" OR "interscale correlation*" OR error OR errors OR "individual variability" OR "interval variability" OR "rate variability" OR (variability AND (analysis OR values)) OR (uncertainty AND (measurement OR measuring)) OR "standard error of measurement" OR sensitiv* OR responsive* OR (limit AND detection) OR "minimal detectable concentration" OR interpretab* OR ((minimal OR minimally OR clinical OR clinically) AND (important OR significant OR detectable) AND (change OR difference)) OR (small* AND (real OR detectable) AND (change OR difference)) OR "meaningful change" OR "ceiling effect" OR "floor effect" OR "Item response model" OR irt OR rasch OR "Differential item functioning" OR dif OR "computer adaptive testing" OR "item bank" OR "cross-cultural equivalence"))

Risk of Bias and quality of the results assessment

Two authors rated independently the RoB of each of the included studies and the quality of the results following the COSMIN RoB checklist (283). A third author intervened in case of discrepancy. The COSMIN RoB is comprised by ten checklists evaluating the following methodological aspects: 1) PROM development, 2) Content validity, 3) Structural validity, 4) Internal consistency, 5) Cross-cultural validity/Measurement invariance, 6) Reliability, 7) Measurement error, 8) Criterion validity, 9) Hypotheses testing for construct validity, and 10) Responsiveness. Each of the checklists includes different items that can be rated as "very good", "adequate", "doubtful", "inadequate", and "not applicable". An excel document is provided at the COSMIN website to facilitate the RoB assessment (https://www.cosmin.nl/tools/guideline-conducting-systematic-review-outcome-measures/?portfolioCats=19)

The quality of the results was evaluated after the data extraction regarding the measurement properties of each of the included PROM in accordance with the COSMIN pre-stablished criteria (281,284) (more details in Table 4).

Data analysis and Synthesis of results

A narrative synthesis of the results was carried out.

Table 4. Criteria for evaluation of the quality of results

Measurement property	**Rating**	**Criteria**
Structural validity	+	CTT CFA: CFI or TLI or comparable measure > 0.95 OR RMSEA < 0.06 OR SRMR < 0.08a IRT/Rasch No violation of unidimensionality[b]: CFI or TLI or comparable measure > 0.95 OR RMSEA < 0.06 OR SRMR < 0.08 AND no violation of local independence: residual correlations among the items after controlling for the dominant factor < 0.20 OR Q3's < 0.37 AND no violation of monotonicity: adequate looking graphs OR item scalability > 0.30 AND adequate model fit IRT: $\chi 2 > 0.001$

		Rasch: infit and outfit mean squares ≥ 0.5 and ≤ 1.5 OR Z-standardized values > − 2 and < 2
	?	CTT: not all information for '+' reported IRT/Rasch: model fit not reported
	-	Criteria for '+' not met
Internal consistency	+	At least low evidence[c] for sufficient structural validity[d] AND Cronbach's alpha(s) ≥ 0.70 for each unidimensional scale or subscale[e]
	?	Criteria for "At least low evidence[c] for sufficient structural validity[d]" not met
	-	At least low evidence[c] for sufficient structural validity[d] AND Cronbach's alpha(s) < 0.70 for each unidimensional scale or subscale[e]
Reliability	+	ICC or weighted Kappa ≥ 0.70
	?	ICC or weighted Kappa not reported
	-	ICC or weighted Kappa < 0.70
Measurement error	+	SDC or LoA < MIC[d]
	?	MIC not defined
	-	SDC or LoA > MIC[d]
Hypotheses testing for construct validity	+	The result is in accordance with the hypothesis[f]
	?	No hypothesis defined (by the review team)
	-	The result is not in accordance with the hypothesis[f]
Cross-cultural validity/measurement invariance	+	No important differences found between group factors (such as age, gender, language) in multiple group factor analysis OR no important DIF for group factors (McFadden's R2 < 0.02)
	?	No multiple group factor analysis OR DIF analysis performed
	-	Important differences between group factors OR DIF was found
Criterion validity	+	Correlation with gold standard ≥ 0.70 OR AUC ≥ 0.70
	?	Not all information for '+' reported
	-	Correlation with gold standard < 0.70 OR AUC < 0.70
Responsiveness	+	The result is in accordance with the hypothesis[f] OR AUC ≥ 0.70
	?	No hypothesis defined (by the review team)
	-	The result is not in accordance with the hypothesis[f] OR AUC < 0.70

 AUC area under the curve, *CFA* confirmatory factor analysis, *CFI* comparative fit index, *CTT* classical test theory, *DIF* differential item functioning, *ICC* intraclass correlation coefficient, *IRT* item response theory, *LoA* limits of agreement, *MIC* minimal important change, *RMSEA* root mean square error of approximation, *SEM* standard error of measurement, *SDC* smallest detectable change, *SRMR* standardized root mean residuals, *TLI* Tucker–Lewis index, + sufficient, − insufficient, ? indeterminate

[a]To rate the quality of the summary score, the factor structures should be equal across studies. [b]Unidimensionality refers to a factor analysis per subscale, while structural validity refers to a factor analysis of a (multidimensional) patient-reported outcome measure. [c]As defined by grading the evidence according to the GRADE approach. [d]This evidence may come from different studies. [e]The criteria "Cronbach alpha < 0.95" was deleted, as this is relevant in the development phase of a PROM and not when evaluating an existing PROM. [f]The results of all studies should be taken together, and it should then be decided if 75% of the results are in accordance with the hypotheses

RESULTS

STUDY II. Poor Sleep Quality Experience and Self-Management Strategies in Fibromyalgia: A Qualitative Metasynthesis

The search in the different databases produced a total of 541 results. After the removal of 112 duplicates, 429 reports were screened against title and abstract and 404 were excluded. Finally, 25 reports were assessed for full-text eligibility. Of those, 14 compiled with the inclusion criteria and were included in the analysis. Additionally, 3 reports were retrieved from the reference lists of the included studies. Therefore, 17 studies were finally included in the present metasynthesis. The results from the processes of identification, screening, eligibility, and inclusion of studies are presented in Figure 12 in accordance with the Prisma statement (282).

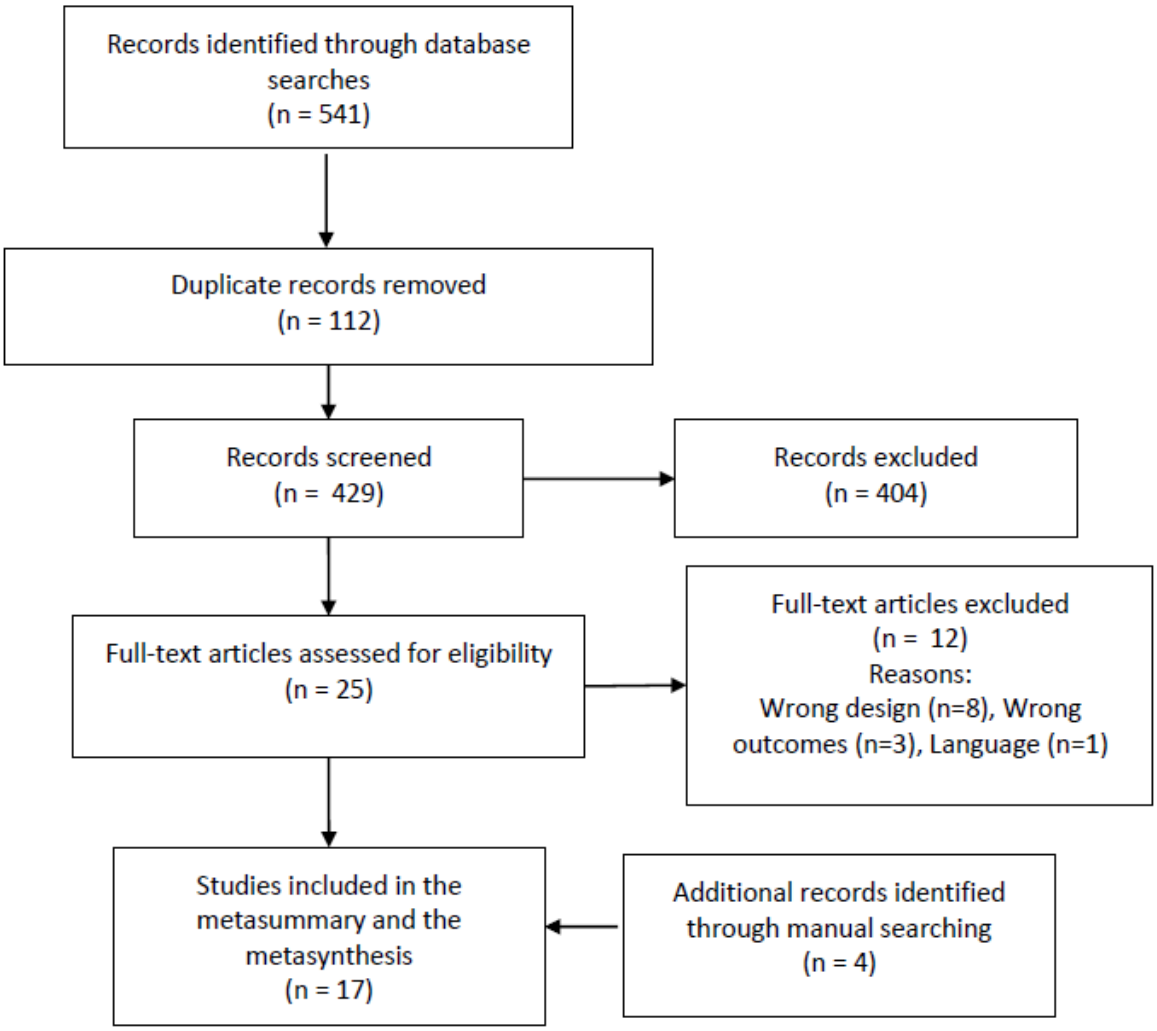

Figure 12. Flow diagram for the identification, screening, eligibility and inclusion of studies

Metasummary

The characteristics of the included reports and the methodological quality and the intra-study intensity effect sizes, and inter-study frequency effect sizes of subthemes are presented in Table 5 and Table 6, respectively.

Table 5. Characteristics of the included reports

Authors and year of publication	**Country**	**Sample Characteristics**	**Method of approach**	***CASP Checklist n. of items fulfilled/n. of items***
Ramlee et al. (2018)	England	n=6 (3♀/3♂) Mean age = 49 years	Personal Semi-structured Interviews	*10/10*
Russell et al. (2018)	North Ireland	n=14 (12♀/2♂)	Focus groups	*10/10*
Vincent et al. (2016)	USA	n=44 (34♀/10♂) Mean age: 45 years	Open-ended Interview administered electronically	*10/10*
Kleinman et al. (2014)		n=34 (30♀/4♂) Mean age = 47.8 years	Focus groups	*9/10*
Traska et al. (2011)	USA	n=8♀ Mean age = 61 years	Interview group	*9/10*
Sallinen et al. (2011)	Finland	n=20♀ Mean age = 54 years	Narrative Interview	*9/10*
Humphrey et al. (2010)	USA Germany France	n=40 Mean age = 48.7 years	Open-ended Interviews	*10/10*
Theadom et al. (2010)	England	n=16 (14♀/2♂) Mean age (50.95 years)	Semi-structured Interviews	*9/10*

Martin et al. (2009)	USA	n=20 (16♀/4♂) Mean age = 50.3 years	Personal Structured Interviews	*9/10*
Lempp et al. (2009)	England	n=12 (11♀/1♂) Mean age = 49 years	Personal Semi-structured Interviews	*9/10*
Arnold et al. (2008)	USA	n=48♀ Mean age = 51 years	Focus groups	*9/10*
Crooks et al. (2007)	Canada	n=55♀	Personal Semi-Structured Interviews	*9/10*
Cunningham et al. (2006)	Canada	n=8 (7♀/1♂) Age range 30-70	Personal In-depth Interviews	*9/10*
Söderberg et al. (2002)	Sweden	n=25♀ Mean age = 46.8 years	Personal Narrative Interviews	*9/10*
Cudney et al. (2002)	USA	n=10♀	Unstructured, online Support Group	*9/10*
Sturge-Jacobs et al. (2002)	Canada	n=9♀ Age range 20-57 years	Personal Unstructured Interviews	*10/10*
Raymond and Brown (2000)	Canada	n=7 (6♀/1♂)	Personal in-depth Semi-Structured Interviews	*9/10*

Table 6. Intrastudy intensity effect sizes and interstudy frequency effect sizes of subthemes

overarching Theme	**Experience of poor sleep quality in FM**		**Poor sleep quality management strategies in FM**			**Intrastudy intensity effect sizes**
Sub-Themes	Evaluation of poor sleep quality	Response to poor sleep quality	Strategies to fall asleep	Nocturnal strategies	Diurnal strategies	**Individual studies' contribution to sub-themes**
Ramlee et al. (2018)	●					**0.7%**
Russell et al. (2018)		●				**0.1%**
Vincent et al. (2016)	●					**0.1%**
Kleinman et al. (2014)	●	●				**10.5%**
Traska et al. (2012)					●	**0.1%**
Sallinen et al. (2011)	●		●			**0.2%**
Humphrey et al. (2010)	●					**0.3%**
Theadom et al. (2010)	●	●	●	●	●	**29%**
Martin et al. (2009)	●					**0.1%**

Lempp et al. (2009)	●		●			0.2%
Arnold et al. (2008)			●		●	0.2%
Crooks et al. (2007)	●				●	0.2%
Cunningham et al. (2006)	●				●	0.3%
Söderberg et al. (2002)	●				●	0.3%
Sturge-Jacobs et al. (2002)	●	●	●			0.3%
Cudney et al. (2002)	●	●	●		●	16.3%
Raymond and Brown (2000)			●			0.1%
Interstudy frequency effect sizes						
Representation of sub-themes in individual studies	76%	29%	41%	0.6%	41%	

Metasynthesis

The experience of poor sleep quality as a symptom of FM is presented into two pre-established overarching themes responding to the components of "symptom experience" and "symptom management strategies" domains of the Symptom Management Theory. Therefore, the results were organized into the following overarching themes: 1) Experience of poor sleep quality in FM and 2) Poor sleep quality management strategies in FM (complete list of themes, subthemes, codes, and quotations can be consulted at Table 7).

Table 7. Overarching themes, subthemes and Quotations

OVERARCHING THEMES	**Subthemes-** Codes	**QUOTATIONS**
EXPERIENCE OF POOR SLEEP QUALITY	**Evaluation of poor sleep quality**	
	Poor sleep quality is a severe symptom of FM	*"It is very frustrating. I think the problem with sleeping is sometimes the worst of this."* *"I can sleep I can go to off sleep but if I don't take anything, I do lie awake, just lie awake or I get woken up this constant being woken up is the worse thing"* *"Sleep, or lack of it, is the worst thing about this condition for me […] It's just another way my body has betrayed me."* *"Sleep is such a gift—I never take it for granted."* *"I fell asleep fine, for an hour. Then I couldn't get back to sleep for I don't know how long."* *"I don't feel like I can sleep. This is aging me; I can feel it. Sometimes I just hate life."* *"I go to bed about 10, I'm always tired and I invariably 90% of the time go straight to sleep and I will wake 1–2 hours later feeling as if it is time to get up"* *"Maybe five, yeah, four or five hours, and there's many times I wake up at 3:00, 4:00. And that's not enough…"* *"I just know I wake up, and I-and I'm like, oh, toss and turn. And then I only sleep on my shoulder for maybe like 30 minutes."* *"I can, initially, go to sleep, but it's staying asleep that's very hard. And then, I got to sleep tired and I wake up exhausted, and it's frustrating."*

	"I've become really restless throughout the night. I have trouble falling asleep. And then, I'm kind of in that dozed, as you described, state. You're never fully asleep. You're never fully awake. And I can toss and turn and just shift and move." *"You toss and turn, you can't keep still, I'm not being funny but my legs have spasms, they just jump around like someone's putting an electric shock through you every 5 seconds, your limbs jump and twitch"* *"A typical night if you can describe the sleep as typical, is I go to bed around 10, 10:30, I fall asleep straight away (clicks fingers) drop of a hat, head on the pillow and I'm away, I'll sleep for 2 or 3 hours, then I'm up for between 2 or 3 hours, then I'll sleep for 2 hours and then I'm up"* *"I am so tired most of the time, that I feel that I could nap at any time. However, I don't sleep for long and I am awake again."* *"I said I used to sleep really well. I could sleep all the way through, like before I was diagnosed with fibromyalgia or, you know, even having all the symptoms. I could sleep through the storm. Now anything will wake me up"* *"And then you're staying in bed. I pretty much stay in bed all day"*
Perceived effects of poor sleep quality in other symptoms of FM	*"I think that the pain is one thing that wears you out probably the biggest thing. I know it is a good part of the reason I don't sleep well"* *"I sometimes get so tired that I can't go to sleep. I ache everywhere, and my muscles do a little dance number"* *"I have worked about 47 hours this week, and I have been in so much pain from stress and overwork that I couldn't sleep all week"* *"I don't hardly ever sleep with my husband anymore, because I disturb his sleep so much of the time with my tossing and turning, trying to get comfortable, getting in and out of bed, because I can't get comfortable"*

"If I sleep really well at night, I'm in much worse shape in the morning as far as pain goes. If I'm up and down all night long, I'm not in as much pain because I've been moving. But then I'm a lot more tired, so I'm not going to be doing all that much"

"Pain leads to a bad night, and a bad night leads to pain the next day"

"I've quite often woke up feeling more tired than when I went to bed"

"There is no typical day, I wake up and it depends on what kind of sleep I've had, how broken and how bad a night I've had"

"In some ways it's more difficult because I'm so tired I don't have the energy to cope with things, so I think they get me down a bit more"

"'Lack of sleep affects your pain and er, and if you're in a lot of pain and you roll over, the pain will wake you up"

"And you can't get comfortable, you know…. you can never get comfortable; your neck is never in the right position…"

"Even if I do get a good night's sleep, let's assume like six hours, a good night's sleep, and I wake up at 6 in the morning, I can't function to do anything until 12:00 noon. I can't do the dishes, I can't do anything, it's like you're just-you're lethargic, you know"

"If I don't get enough sleep that will cause a flare-up, but it also causes me to not be able to sleep at the same time."

"I could sleep 20 hours and still be tired. That is terrible."

"But when you sleep, it doesn't resolve it. You still wake up tired"

"The fatigue, it's number one, because I can deal with the pain, at least up to a certain point, but the fatigue there's nothing you can do besides sleep. There is no way to help that. There's no pill you can take, there's no medicine."

I will be thinking and, and trying to explain stuff to you, but my mind will just go completely blank. That gets worse on certain days, obviously with less sleep, but on other days I can sort of string together"

"Having a bit more energy, say, after a good night's sleep, I've got a bit more energy to be able to go a whole day and to do things; after a bad night's sleep fatigue will hit me at say half 3 in

	the afternoon eventually, plug's pulled and I fall asleep standing up more or less" *"Sometimes when I've had a bad night my appetite goes as well. I have to eat something to take my medication, but I will force myself to eat a bit of toast or something, you know, just so I've got something in my tummy to take the tablets"* *"After a bad night's sleep, my muscles and my joints can be really quite painful and tight cause I haven't rested them properly"* *"It's not just the pain and the fatigue, . . . it's the nonrestorative sleep . . . it's a vicious circle because if you don't get enough sleep you feel pain more acutely . . . you're more tired and unable to sleep well"* *"I conserve energy whenever possible. Problems can arise, though, no matter how well you plan; the pain, fatigue, or irritable bowel syndrome episodes prevent you from doing anything. Sometimes all three attack at once, when you might have been fairly okay an hour ago. Even if you try to get a good sleep, that doesn't mean you can have any energy on waking, and just because you baby yourself . . . doesn't mean you won't hurt. Coping is minute-to-minute every single day"* *"Sleeplessness nights ... can you see the black circles under my eyes, because I wake up at 2 o'clock in the morning, then I wake up and feel right awake...and the next day I feel tired, I just want to sleep on but I have to get up and go to work ... I am extremely physically* *tired ... I am so tired I just can't function as a normal person"* *"Yes, you never feel as you have slept enough. Sometimes I sleep very well¼ but you are never thoroughly rested when you wake up in the morning"*
Beliefs about the temporality and cause of poor sleep quality	*"I don't know what other reason there could be, other than the fact that I'm less active now than I used to be you know, but you know it seems to have come on roughly about the same time"*

	"[After a night shift] I slept maybe an hour or hour and a half a day … you know how it is when you don't sleep practically at all for weeks and months … In fact, I was practically sleepless for years …"
Meaning of good sleep quality	*"It's that sensation of really I have switched off, I am not aware of anything. That you know, those three hours where maybe the following day my husband said to me, "Oh did you hear the thunderstorm last night?" "No," because it happened on those three hours and I didn't hear anything. I didn't hear the thunderstorm, I didn't notice the light, nothing, and that is for me a proper sleep. When I'm aware of everything else I'm not, and I get up noticing that I have not slept properly"* *"I know when I've had a good night's sleep because I would wake in the morning feeling refreshed"*
Response to poor sleep quality	
Feeling frustrated and like a failure	*"I hate this illness! I hate not being able to stand the sun, the heat, feeling tired all the time, not being able to sleep. The list goes on of things I hate about this illness"* *"It is very frustrating. I think the problem with sleeping is sometimes the worst of this"* *"The not sleeping and then not being able to function the next day when you need to perform at work . . . when you're being paid and you're meant to work and you can't function, it's horrible, it's really horrible because you feel like a failure"* *"All I know is, is that I never used to need a lot of sleep, never, and I now really resent that fact that I need so much, I'm not saying my life is so exciting but when it's, just now I think oh, I have to plan it round, oh can I have a lay in this weekend, can I do this, can I do that, I find that very hard to cope with"* *"I can, initially, go to sleep, but it's staying asleep that's very hard. And then, I got to sleep tired and I wake up exhausted, and it's frustrating"*

		"I don't feel like I can sleep. This is aging me; I can feel it. Sometimes I just hate life." *Night was described by some as a "lonely" time, and again the impact of not being able to sleep on day to day functioning was described as "an absolute nightmare"*
	Fear of going to bed	*"Sleep, or lack of it, is the worst thing about this condition for me. I have christened my bedroom "the torture chamber"* *"If there's something on my mind, that makes me a bit worried about sleeping, I don't know what it is but I sort of need to try and get to the bottom of it, but I sort of have this fear of going to bed"* *"We're wanting to start a family, so that's kind of an issue regarding sleep, actually; yes, that's a massive issue, because we've been wanting to start a family for ages, we're not even doing that because I don't think I could have that sort of sleep deprivation"* *"If there's something on my mind, that makes me a bit worried about sleeping, I don't know what it is but I sort of need to try and get to the bottom of it, but I sort of have this fear of going to bed"* *"If you're worried about one of the children or there's something particular you're worried about..., you tend to sort of go over that in your mind"* *"You almost know, that's psychological again, you almost know you've had a fairly bad period you're not going to sleep well either or is it a fact?"*
POOR SLEEP QUALITY MANAGEMENT STRATEGIES IN FM	**Management strategies to favor sleep**	
	Medication: from dependency to rejection	*"I ache almost continually, that is why I take three aspirin every night before I go to bed. When I try to skip it, I end up getting up in an hour or two and taking them anyway."*

	"Well, I cannot sleep at all if I don't have [medication], so. . .there is no sleeping without it. . . And getting up in the morning was just brutal. It's brutal. I have to drag my sorry butt out of bed every morning and go to work, and it's hard" *"I can sleep I can go to off sleep but if I don't take anything, I do lie awake, just lie awake or I get woken up this constant being woken up is the worse thing"* *"I suppose it helps a little bit but I wouldn't say it makes a tremendous difference you know, I suppose I'd rather take it than take nothing, any help is better than no help, but I still find myself waking up quite frequently every night"* *Using sleeping pills was usually not seen as an option because of side-effects, such as "foggy mornings"* *"I am on Amytriptiline to help with my sleep and other tablets... I only take them when it is right for my body. I don't like to be taken as a guinea pig. I don't trust staff to deal with me in that way. I am the only person who knows what it feels like to be ill, and what is good for my body, I don't like other people to tell me and to control me"*
Self-management: behavioral adaptations	*"I tend not to watch TV too late unless there's something really good on but I try and make an effort, like I used to really like watching DVDs late at night and now I don't do that as much or I'll listen to the radio, it's a bit more chilled really, yeah drink herb tea just sort of wind down"* *"All I know is, is that I never used to need a lot of sleep, never, and I now really resent that fact that I need so much, I'm not saying my life is so exciting but when it's, just now I think oh, I have to plan it round, oh can I have a lay in this weekend, can I do this, can I do that, I find that very hard to cope with"* *"I know that it's an absolute crucial thing to get a good night's sleep; to go to bed at the same time; eating on time... so everything has to be regular. And the more regular it is, the better I feel"*

	"I'll try anything to help me relax, deep breathing and visualization, anything to make me go to sleep. But nothing works"
	"I put ear plugs in and I find when I put ear plugs in I seem to sleep different . . . although I don't like things in my ears, if it means I'm going to sleep a bit better, so whether that's about noise, although it's very quiet where I live, so I don't know, I think I'm just looking for answers"
	"Sometimes I think I can get back to sleep, so I wait to see if I can and I think come on and I just lie there and hopefully I can get back to sleep easily again, um, but more often than not, I can't so after I try for about 15 to 20 minutes and if I can't get back to sleep after that time then as I say I put the television on and it'll refocus me and if I fall back to sleep, good"
	"Oh I just get up, it's just ridiculous trying to sleep and you can't sleep, you know you get to hate your bed after a while because you get fed up tossing around and trying to get to sleep the whole time"
Managing the consequences of a sleepless night	
Medication: finding the balance between benefits and side effects	*"I try to get out of bed every day regardless of how I feel. I'm trying to function, so I take the various medications . . . in the hopes that while it causes other problems it will at least allow me to continue to have a life"*
	"[…] When I have been resting a while and I sleep when I've taken a painkiller… and can sleep an hour and then it feels much better, then I can manage the afternoon"
Resting and relaxing during the day	*"I've been overworked, overstressed, and overtired. When I am fatigued I sleep, and that's what I've been doing in my spare time"*

"I'm at a place now where I, when I get tired, I say okay. And I'll go and lie down. And I may nap for half an hour, one hour, or three hoursy"

"If I can get sleep, I can fix all the rest"

"It can be up to an hour, at least an hour, even if I didn't sleep, I just have to get off my legs and just lie back and you know, very often I just lie back with nothing on, no television, nothing, just, just alone"

"I might have to go to bed for a couple of hours and then I'll be alright for the evening, because I know they advise you not to go to bed don't they, but I can't physically not and I find it makes me feel better actually if I do, so for me it works better, so you I've learnt to do what suits me rather than what I'm told to do you know they say you muck up your body clock up if you sleep in the day but for me it doesn't work that way"

"…lavender smell. Yes. So you're getting the olfactory there and it's got the, Epson salt-type stuff in it and you know, whatever. And it just, a warm bath sometimes will get me so I get over that stiffness, when I can't get out of bed…"

"You just have to lie down and rest, you can't do anything, can't go on or anything… it passes when you rest a moment… that total exhaustion […]"

Experience of poor sleep quality in FM

According to the SMT, symptom experience is determined by three major factors: symptom perception, evaluation, and response (224–226). The perception, evaluation and response to a symptom depend on the characteristics of each person, the physical, social, cultural environment, as well as their health and illness status. Likewise, it is important to highlight that these three processes show a bidirectional relationship as all of them can influence or be influenced by the others and do not necessarily have to follow a predictable pattern of behavior (224,226).

This overarching theme was organized into two sub-themes revolving around two of the major factors that determine the symptom experience as described in the SMT: 1) Evaluation of poor sleep quality and 2) Response to poor sleep quality

1. *Evaluation of poor sleep quality*

Based on the SMT, the evaluation of a symptom is understood as the meaning that a person attributes to the experienced symptom in terms of effects, severity, temporality, cause and treatability (224,226).

Poor sleep quality is a severe symptom of FM. People diagnosed with FM sometimes feel that poor sleep quality is the worst symptom of their health condition (274–276) which is associated with negative cognitive responses such as frustration and hatred towards life Being unable to sleep properly is perceived as a betrayal of the own body which may indicate that, at least in some cases, people suffering from FM consider that they have no control over the symptom (276). In other cases, participants reported that "sleep is such a gift" and that they "never take it for granted" reflecting that sleep problems are particularly severe in the context of FM.

"Sleep, or lack of it, is the worst thing about this condition for me […] It's just another way my body has betrayed me."

According to the reports of the participants, the most common sleep disturbances associated with FM are those related with the maintenance of sleep, which are also associated with the development of frustration and the feeling of being continuously deprived of sleep (274,275,277). While participants were arguing that their sleep problem is mainly related to sleep maintenance, others reported problems falling asleep (274). Besides, the participants described problems such as having spams in the lower extremities that may be indicative of an underlying sleep disorder (274).

"I can, initially, go to sleep, but it's staying asleep that's very hard. And then, I got to sleep tired and I wake up exhausted, and it's frustrating."

Perceived effects of poor sleep quality in other symptoms of FM. People diagnosed with FM commonly identify poor sleep quality as one of the symptoms that has the greatest impact on fatigue, pain, cognitive functioning, ability to manage symptoms, eating behavior, and symptoms flare-ups.

In general, people diagnosed with FM experience fatigue more acutely after a night of poor sleep quality making them feel intense sleep pressure. However, they must wake up in the morning despite feeling tired to fulfill their working schedules, and, consequently, fatigue ends up impacting their functional capacity at the workplace (272,285).

"Sleeplessness nights ... can you see the black circles under my eyes, because I wake up at 2 o'clock in the morning, then I wake up and feel right awake...and the next day I feel tired, I just want to sleep on but I have to get up and go to work ... I am extremely physically tired ... I am so tired I just can't function as a normal person."

Participants reported that when they are very tired they experience pain and small muscle cramps, being unable to fall asleep (275). In some cases, the participants considered that the only solution to reducing fatigue levels is having a good rest at night (286), whereas, in others, the participants indicated that fatigue is maintained or appears even when it is possible to have a satisfactory amount of sleep (271,277,286–288).

"The fatigue, it's number one, because I can deal with the pain, at least up to a certain point, but the fatigue there's nothing you can do besides sleep. There is no way to help that. There's no pill you can take, there's no medicine."

"I could sleep 20 hours and still be tired. That is terrible."

Regarding the sleep-pain relationship, the general belief was that there is a bidirectional relationship between poor sleep quality and pain, so that one night of not having sufficient sleep or a good sleep quality results in an increase of the intensity of pain the next day which, at the same time, prevents a good rest at night (274,289). One of the participants hypothesized that poor sleep quality affects her joints and muscles so that they do not "rest" properly increasing pain intensity (285).

"I feel constantly in pain, which obviously when I don't get enough sleep will aggravate that, and then because I've aggravated pain I don't get enough sleep. So I am on a vicious cycle, I can't sleep properly because of the pain, and I can't, because I am not sleeping, I then get in more pain."

Participants sometimes establish a direct connection between pain experience and poor sleep quality (275). However, it is also argued that experiencing pain prevents them from finding a resting position that facilitates sleep (275,277). Related to the latter, participants were concerned that the inability to finding a comfortable sleep position results in a constant movement that ends up impacting the quality of the sleep of their bedfellows. Consequently, it makes them barely able to share the bed with their partner (275).

"I don't hardly ever sleep with my husband anymore, because I disturb his sleep so much of the time with my tossing and turning, trying to get comfortable, getting in and out of bed, because I can't get comfortable."

Regarding the poor sleep-pain-fatigue cluster, it was described as a vicious circle in which insufficient sleep results in an increase of pain intensity the next day which, at the same time, leads to a state of fatigue that prevents a good rest at night (271). In other cases, it was reported that not moving during the night is the main cause of increases in pain intensity. Thus, staying awake favors a continuous movement that seems to decrease pain although, in consequence, increases fatigue (287).

"It's not just the pain and the fatigue...it's the nonrestorative sleep...it's a vicious circle because if you don't get enough sleep you feel pain more acutely...you're more tired and unable to sleep well."

In addition to fatigue and pain, people diagnosed with FM believed that poor sleep quality also affects cognitive functioning (285,289) and symptom management abilities (274). Likewise, poor sleep quality alters eating behaviors (285) and causes symptoms flare-ups (290).

"I will be thinking and, and trying to explain stuff to you, but my mind will just go completely blank. That gets worse on certain days, obviously with less sleep, but on other days I can sort of string together."

<u>Beliefs about the temporality and cause of poor sleep quality</u>. The perception of people diagnosed with FM is the sleep problems appeared simultaneously with other symptoms of FM (274). Regarding the cause of poor sleep quality, different beliefs were identified. While there were participants unable to identify a cause for their sleep problems (274), others pointed out that working on the night shifts during a long period derived in problems initiating and maintaining sleep (273).

"[After a night shift] I slept maybe an hour or hour and a half a day … you know how it is when you don't sleep practically at all for weeks and months … In fact, I was practically sleepless for years …"

<u>Meaning of good sleep quality.</u> For people diagnosed with FM good sleep quality is mainly related to feeling renewed upon waking and having the energy to face their daily tasks (285). Another important aspect that allows them to identify good sleep quality is the feeling of "disconnection" with the environment during the night or not remember waking up due to noise (285).

"It's that sensation of really I have switched off, I am not aware of anything. That you know, those three hours where maybe the following day my husband said to me, "Oh did you hear the thunderstorm last night?" "No," because it happened on those three hours and I didn't hear anything. I didn't hear the thunderstorm, I didn't notice the light, nothing, and that is for me a proper sleep. When I'm aware of everything else I'm not, and I get up noticing that I have not slept properly."

2. *Response to poor sleep quality*

The SMT describes the symptom response as a factor associated with the person's reactions to a symptom at physiological, psychological and social levels (224,226). In this metasynthesis, and in accordance with the results, only the psychosocial factors were explored and described.

<u>Feeling frustrated and like a failure</u>. People diagnosed with FM consider that constantly waking up is the worst thing about their health condition (274,275) and usually develop feelings of frustration and despair.

Participants argue that sleep problems affect their functional capacity in the workplace, which causes them anxiety and a feeling of constant failure (274). Other factors that lead to a feeling of frustration are not getting enough sleep (274), the inability to fall asleep, and extreme daytime fatigue due to poor sleep quality (277). In some cases, participants even express hatred towards their health condition, being the inability to satisfy their sleep needs a central factor contributing to this feeling (275).

"The not sleeping and then not being able to function the next day when you need to perform at work… - when you're being paid and you're meant to work and you can't function, it's horrible, it's really horrible because you feel like a failure."

Participants believe that lack of sleep is aging them which leads to feelings of hatred towards their life (275). Besides, they believe that there is no possible solution for their sleep problems (276) and that the impact of poor sleep quality on their functionality is an "absolute nightmare" (291).

"I don't feel like I can sleep. ... This is aging me, I can feel it. Sometimes I just hate life."

<u>Fear of going to bed</u>. According to the participants' reports, people diagnosed with FM can develop a fear of not sleeping. This factor has a direct impact on their personal life, leading them to consider motherhood for that fear of not being able to meet their sleep needs (274). The participants also develop a fear of the bedroom and fear of going to bed (274,276), reflecting the great impact of poor sleep quality at the emotional level.

"Sleep, or lack of it, is the worst thing about this condition for me. I have christened my bedroom "the torture chamber."

Concerns about poor sleep quality were reported to manifest constantly, generating ruminating thoughts and fear of going to bed (274).

"If there's something on my mind, that makes me a bit worried about sleeping, I don't know what it is but I sort of need to try and get to the bottom of it, but I sort of have this fear of going to bed."

Poor sleep quality management strategies in FM

Developing symptom management strategies is not only about preventing, diminishing, or delaying the occurrence of negative outcomes, but it is also about controlling and influencing the whole symptom experience (224,226).

This overarching theme was organized into two sub-themes: 1) Management strategies to favor sleep and 2) Managing the consequences of a sleepless night

1. *Management strategies to favor sleep*

This sub-theme describes the strategies that people diagnosed with FM employ to initiating and maintaining sleep during the night.

Medication: from dependency to rejection. Taking medications is one of the most frequent strategies among people diagnosed with FM to fall asleep and some of the participants report not taking (sleep) medication prevents them to fall asleep (274,275,287). While drug dependency behaviors can be intuited (274,292) participant also reported that they resort to taking medications occasionally when they feel they need them (272). However, it also seems that there are attitudes of rejection towards sleeping medications, mainly due to side effects (273) and to the low effectiveness favoring a good sleep quality (274).

"I am on Amytriptiline to help with my sleep and other tablets... I only take them when it is right for my body. I don't like to be taken as a guinea pig. I don't trust staff to deal with me in that way. I am the only person who knows what it feels like to be ill, and what is good for my body, I don't like other people to tell me and to control me."

Self-management: behavioral adaptations. A common strategy that favors sleep, and that participants recognize as essential, is to establish regular sleep schedules (274,293). However, in some cases having to constantly monitor the organization of sleep schedules and their ADLs generates anxiety (274).

"I know that it's an absolute crucial thing to get a good night's sleep; to go to bed at the same time; eating on time... so everything has to be regular. And the more regular it is, the better I feel."

Participants also adopt other strategies such as the use of earplugs (274) or relaxation techniques (276). However, these strategies are perceived as ineffective and, sometimes, unjustified.

"I put earplugs in and I find when I put earplugs in I seem to sleep different . . . although I don't like things in my ears, if it means I'm going to sleep a bit better, so whether that's about noise, although it's very quiet where I live, so I don't know, I think I'm just looking for answers."

In dealing with awakenings during the night two opposite strategies were identified (274). While participants were reporting that they get out of bed to avoid developing attitudes of rejection towards the bed; others stay in bed and try to fall asleep again. Regarding the latter strategy, it is usually perceived as ineffective and the participants end up turning on the television to try to refocus their attention.

"Sometimes I think I can get back to sleep, so I wait to see if I can and I think come on and I just lie there and hopefully I can get back to sleep easily again, um, but more often than not, I can't so after I try for about 15 to 20 minutes and if I can't get back to sleep after that time then as I say I put the television on and it'll refocus me and if I fall back to sleep, good."

2. *Managing the consequences of a sleepless night*

Managing the consequences of a sleepless night described how people diagnosed with FM cope with the impact of poor sleep quality during the daytime.

Medication: finding the balance between benefits and side effects. The participants usually reported relying on drugs in the hope that they will help them to "*continue to have a life*" even if they cause side effects (271). In other cases, it was commented that taking analgesics help them to fall asleep during the day, providing a boost of energy to face ADLs during the afternoon (288).

> *"I try to get out of bed every day regardless of how I feel. I'm trying to function, so I take the various medications...in the hopes that while it causes other problems it will at least allow me to continue to have a life."*

Resting and relaxing during the day. The most generalized strategy is daytime rest which helps in decreasing fatigue and allows them to cope with evening tasks (274,275,287,288). However, it was also reported that daytime rest could be more a necessity than a strategy due to the extreme fatigue experienced after a sleepless night (288). Besides, the use of lavender scent while taking a hot bath in the morning helps to reduce morning stiffness and better cope with the day (294).

> *"I might have to go to bed for a couple of hours and then I'll be alright for the evening, because I know they advise you not to go to bed don't they, but I can't physically not and I find it makes me feel better actually if I do, so for me it works better, so you I've learnt to do what suits me rather than what I'm told to do you know they say you muck up your body clock up if you sleep in the day but for me it doesn't work that way."*

STUDY III. 'Sleeping is a nightmare': a qualitative study on the experience and management of poor sleep quality in Spanish women with fibromyalgia

The study participants ranged in age from 44 to 75 years. The characteristics of the participants are presented in Table 8.

Table 8. Characteristics of the Participants (N = 21)

PARTICIPANT	AGE	EDUCATIONAL LEVEL	EMPLOYMENT STATUS	CIVIL STATUS	MEMBER OF FM ASSOCIATION
1	53	Secondary	Full-time employment	Registered partner	No
2	59	Tertiary	Medically retired	Married	Yes
3	72	Primary	Retired	Married	No
4	61	Secondary	Retired	Married	No
5	68	Primary	Retired	Married	No
6	56	Primary	Part-time employment	Divorced	No
7	65	Secondary	Retired	Married	No
8	61	Secondary	Full-time employment	Divorced	No
9	66	Secondary	Part-time employment	Divorced	No
10	45	Tertiary	Full-time employment	Married	No
11	68	Secondary	Retired	Married	No
12	58	Primary	Full-time employment	Divorced	No

13	59	Secondary	Medically retired	Registered partner	No
14	59	Primary	Medically retired	Registered partner	No
15	44	Secondary	On sick leave	Married	Yes
16	54	Secondary	Medically retired	Married	Yes
17	61	Secondary	Medically retired	Divorced	Yes
18	55	Secondary	Full-time employment	Married	Yes
19	44	Secondary	Medically retired	Divorced	Yes
20	75	Primary	Retired	Married	Yes
21	67	Primary	Retired	Married	Yes

The results were organized in two themes: Experience of Poor Sleep Quality and Poor sleep quality Management Strategies. The subthemes, categories and quotations can be consulted in Table 9 and Table 10, respectively.

Experience of Poor Sleep Quality

1. Evaluation of poor sleep quality

Main sleep problems

Women with FM complained about not being able to sleep more than 5-6 hours at a time, waking up several times during the night. Then, participants felt that they did not have a recovering sleep.

They would wake up after a very short period of time asleep and have difficulty falling asleep again. Participants reported waking up during the night feeling pain (in any body part such as arms, hands), experiencing light sleep or feeling the need to visit the toilet.

They also mentioned difficulty falling asleep at night or even being unable to sleep for days.

It was common among participants to relate their difficulty falling asleep with being very sensitive to noise. Women with FM experienced other difficulties in falling asleep, such as finding a comfortable body position free of pain.

The women mentioned that their sleep problems fluctuated: there were nights in which their main problem was that they had difficulties falling asleep and other night in which they would wake up several times during the night. One participant thought that the variability of her sleep problems makes difficult for her to find an effective solution to improve her sleep quality.

Aggravating factors of poor sleep quality

The participants reported that menopause-related hot flashes and other comorbidities (for example, restless leg syndrome, sleep apnea, tinnitus) prevented them to fall asleep or produce awakenings during the night. They also mentioned that they sleep worse on days in which they engaged in less physical activity.

Factors that positively influence sleep

The participants also identified factors that favored the reconciliation of sleep or facilitated better sleep at night. These factors included to get tired during the day, to sleep in a place without noise (for example, another house in a quiet place) or on vacation not having to work or get up early.

Perspectives on good sleep quality

The participants described good sleep as waking up feeling refreshed and energized. Although some considered getting 8 hours of sleep per night beneficial, the group generally considered it more important to wake up feeling like they had obtained restful and uninterrupted sleep (even if they had only slept for 3 or 4 hours).

They considered a good night's sleep to be a night of sleep without experiencing pain during the night and waking up without pain. For example, one participant indicated that for her, a good night's sleep would be waking up in the morning without thinking to herself "even my soul hurts" (P7). Participants also commented that good sleep involved falling asleep rapidly, forgetting about the problems of daily life and feeling peaceful, and waking up with a clear mind, which they described as if they were disconnected or not remembering what they had dreamt.

Beliefs regarding the causes of poor sleep quality

The participants identified pain, FM itself, ageing, genetic factors, stress, and mental health problems (such as depression or obsessive thinking) as the main causes of poor sleep quality. In terms of

temporality, they mentioned that the initiation of their sleep problems or changes in sleep patterns from deep to light sleep coincided with maternity, menopause, and periods characterized by work overload or problems with their partner. However, there were also participants that did not relate their sleep problems to a specific cause.

Consequences of poor sleep quality

Complaints derived from having a poor sleep quality among the interviewed women included waking up feeling fatigue, stiffness, pain, mood alterations, and attention and concentration difficulties. One participant reported waking up feeling as if she had been "run over by a truck" (P14). Participants emphasized that they feel tired all throughout the day and that even performing simple tasks required great effort. They mentioned that after a bad night's sleep, they experience more intense pain, which also affects their functional capacity. Likewise, they reported that coping with pain becomes more difficult after not having a restful sleep. The women also reported waking up feeling as if their whole body were completely stiff and having to stretch for a while before being able to get out of the bed.

Poor sleep quality was perceived as being directly associated with mood alterations, as the participants felt very nervous and emotional. They reported getting upset easily. They also indicated that poor sleep quality affected their executive functions, perceiving a decreased capacity for attention and concentration. They believed that poor sleep quality affected their general health status and quality of life. Furthermore, they felt that the consequences of poor sleep quality are unpredictable and that did not follow a consistent pattern.

2. Response to poor sleep quality

Worries, nocturnal intrusive thoughts, and rumination

Participants reported being concerned about not sleeping, especially if they were required to work the next day. When experiencing problems falling asleep, they would start analyzing their diurnal behaviors to determine what was impairing their sleep, such drinking coffee after noon or feeling more nervous than usual. Having intrusive, recurring, and even irrational thoughts when they went to bed and when the awoke during the night was commonly reported. During this time, they usually thought about the past, their daily life problems, and the possibles consequences of not sleeping that could occur the next day. Despite experiencing intrusive thoughts that prevent them from falling back to sleep, they would try to relax and not to obsess over the situation.

Desperation and anticipation of poor sleep quality

It was common for participants to experience frustration and despair at not being able to sleep, which could even lead them to think about suicide. One woman informed that the impact of her pain on her sleep was so unbearable that she would cry out of anger. It was identified a possible process of anticipation of a sleepless night, as they reported knowing or feeling when they are going to have difficulty sleeping.

Future expectations

The participants expressed differing beliefs regarding the consequences of poor sleep quality in the future. Some women were not worried about the future and they believed that their sleep could be managed and improved, whereas others were convinced that poor sleep quality would worsen over time, which had a significant impact on their health status.

Table 9. Theme 1. Experience of Poor Sleep Quality

Subtheme	Category	Quotations
Evaluation of poor sleep quality	Main Sleep Problems	"I never sleep, never ever, I never sleep the whole night, never ever" (P8) "I go to sleep around 10:30p.m. or 11:00 p.m. and I am always waking up. And after 12:30-3:00a.m. I no longer sleep" (P16) "The problem is that I wake up, the problem is that when I sleep, I don't sleep. I am sleeping, but it is as if I am awake" (P11) "There are times when my problem is that I can't sleep. And other times the problem is that I wake up" (P15) "I didn't know how to place myself, because if I would place myself like this my shoulder would hurt, if I would place myself like this... my hip would hurt, and you go around and around" (P16) "Sometimes because of the arms and hands, because of the pain. And other times I go to the bathroom" (P6)
	Aggravating Factors of poor sleep quality	"When you are silent is when you hear them (the tinnitus) the most. Then this... and of course, if you wake up at two and you have this, it is very difficult to go back to sleep" (P11) "Now I have realized that, if I am not tired and have a more active day, I also sleep worse" (P14)
	Factors that positively influence sleep	"I sleep better in the village, there is no noise" (P14)
	Perspectives on good sleep quality	"Getting up in the morning and feeling rested, I do not care about the hours, at least open my eyes and say, "I have slept, I feel rested, come on, let's start the day" (P15)

		"That you can wake up without any pain, this would be good for me... the best" (P20) "That you do not remember what you have dreamed about, that you do not remember anything and get up and say: I feel so rested, I got up feeling so well!" (P7)
	Beliefs regarding the causes of poor sleep quality	"[...] everything happened more or less when my period stopped, and so I said, "This is menopause". Sometimes you say, "This must be caused by the menopause"... you always look for the solution or attribute the problem to something else, yes" (P20)
	Consequences of poor sleep quality	"it is that you wake up in the morning already with fatigue that looks like you have been run over by a truck, and you cannot handle your life. You get up already holding on to the wall. And you say: I am going to get dressed, I am going to go out and I think: where am I going, if I just can't?" (P14) "In the morning everything is stiff, when I wake up, I am like a stick, all stiff" (P15) "Then you get up and you [feel]... super sore, like you have been beaten up, with a stick, that's how I got up" (P19) "I think I am very hysterical, and I answer back, and I was not like that before. I get upset over nothing, I answer badly, which I never did before, and now I do" (P3) "Sometimes I have to do like this (rubs the eyes) because I feel that my eyes… I am not clear. And, with the car, I already had a couple of scares [...] the other day I almost caught a guy on a motorcycle and that scared me" (P15) "[...] there is nothing constant, it may be normal one day, and another day I can feel very tired or very nervous. The next night, I may sleep, or I may not sleep again... It changes every night, there is nothing constant" (P9)
Response to poor sleep quality	Worries, nocturnal intrusive thoughts, and rumination	"I'll be sleepy, that's what I think. I do think about it because I know that tomorrow... it will be hard for me to get up" (P6) "And I say, "How strange! Why don't you sleep?" Then I wonder if I had a coffee or a drink at noon that day, "Well, that's it" (P5) "Sometimes I fall asleep quickly, but if I have occasional concerns, like everyone else, that sleepless night will catch you" (P8)

	Desperation and anticipation of poor sleep quality	"I would go to the balcony at night when I could not sleep, and say: "and from here down, four floors, I would come down in a huff and puff!" I have thought about it many times" (P7) "How are you going to start your dream? How are you going to cope with sleeping today? It was torture for me to go to sleep because I knew that I would have nightmares, I would have aches that I could not sleep at all... […] Initially, before going to sleep, I was already worried about what was going to happen to me in the dream" (P13)
	Future expectations	"[I fear] that I will go a little crazy, that I will go a little crazy, because not sleeping gives you a lot of problems, gives you a lot of anxiety, you do not live your life with peace of mind, you have a very bad temper, and then it gives me the feeling that my whole body is trembling" (P11)

Poor sleep quality management strategies

1. Management strategies suggested by health care professionals

Health care professionals' awareness of sleep in the context of fibromyalgia

It was common among participants to report that they never received information about sleep problems related to FM, even when they complained about sleep problems during a medical consultation. Only one woman reported being informed about sleep disturbances related to FM by a health care provider (a psychologist). Consequently, participants used the internet and attended seminars to learn about sleep in the context of FM.

Self-management advice from health care professionals

In general, women diagnosed with FM believed that they did not receive enough information from health professionals about strategies to effectively manage poor sleep quality. Examples of health professionals' recommendations were to have a light dinner, to use the bed only for sleeping, and to not watch television or use electric devices at night. However, one of the women stated that she did not follow the advice because she believed that general recommendations are not always useful for everybody.

Pharmacological treatment as the main approach

The participants generally believed that health professionals preferred to treated poor sleep quality through pharmacological methods. Medications prescribed to improve sleep included sleeping pills, antidepressants, and anxiolytics. Participants were divided among those who mentioned that the medication was effective and helped them to fall asleep quicker and sleep longer, and those who found medication ineffective. The first group of women explained that taking sleeping pills helped them to sleep for at least a few hours straight and to wake up feeling more refreshed. Taking antidepressants or anxiolytics made them feel relaxed and allowed them to fall asleep quicker. However, there were also women who recognized that they became dependent on their medication because they assumed that they would not be able to sleep without it. These women worried about the possibility of needing stronger medication in the future.

The second group of women refused sleeping pills and antidepressants, and tended to also refuse other medications, such as pain killers, because their taking these medications had not resulted in better sleep. For these women, the medications had only been effective at the beginning of use or for a short period of time, the effects did not last throughout the night, and there were negative side effects (e.g. general discomfort, feeling drugged or paraesthesia in the extremities). In addition, these women worried about the long-term effects of the medications. It was common among these women to take medication only as an exception, as a last resort when they felt desperate.

2. Self-management strategies

General strategies for improving sleep quality

Although taking melatonin, performing mindfulness techniques, and undergoing acupuncture was generally considered effective strategies, taking valerian supplements did not help to improve sleep quality. Other strategies mentioned were engaging in physical activities during the day (e.g. walking), avoiding naps, not drinking coffee or limiting the intake of coffee after noon, trying to feel tired at night, using articulated beds or cervical pillows, and having a daily scheduled routine. However, strategies tended to work one day but not the next, making it difficult to cope with poor sleep quality.

Strategies for falling asleep and for dealing with interrupted sleep or waking up too early

The strategies employed to induce sleep when going to bed were watching television or using the computer or laptop, although participants recognised that these actions contradicted professional recommendations. They also counted sheep, prayed, or used painkillers or topical ointments to relieve

pain or to induce relaxation. One strategy employed by participants who were waking up too early in the morning was to rearrange their sleep schedules in order to go to sleep later.

When dealing with difficulties falling asleep at the beginning or during the night, two differing main strategies emerged: getting out of the bed and staying in the bed. However, the participants recognised that neither strategy was effective for preventing waking up in the middle of the night. During their time awake, instead of or in addition to taking medication, the participants usually employed relaxation techniques to avoid overthinking and worrying, such as listening to music or the radio, and/or drinking a hot beverage.

Coping with the consequences of poor sleep quality during the day

Participants usually coped with poor sleep quality at night by napping, resting and relaxing, drinking coffee or tea, and/or taking energy supplements, such as ginseng, during the day. Nevertheless, some participants recognised that some of the strategies could negatively affect their sleep at night, and that they could still have trouble falling asleep despite feeling tired, whereas others tried to continue performing their daily activities without a concrete compensating strategy.

Needs

Participants missed the sleep quality that they once had and/or envied those who had no sleep problems. They were motivated to improve their sleep, obtain more knowledge about sleep problems in the context of FM, receive more information from health professionals about effective self-management strategies, and obtain prescriptions for medications that could improve their sleep (e.g. assist them in falling asleep or allow them to sleep longer without interruption).

Table 10. Theme 2. Poor sleep quality management strategies

Subtheme	Category	Quotations
Management strategies provided by health care professionals	Health care professional's awareness of sleep in the context of fibromyalgia	"They haven't explained anything else to me, all I know is through the computer" (P9)
	Self-management advice from health care professionals	"Well, you may have been advised to try not to eat too much or not to eat too much at night [...] if you want to read, do it on the sofa, don't go to bed [...] If I do that [...] on the way from the sofa to the bed, I would lose my sleep. Everyone is different. So, each one of us must have our own tactics" (P12)

	Pharmacological treatment as the main approach	"Now I am already taking Zolpidem, I do not sleep, I pass out for a while. Four hours, I am gone, that's it [...] once I fall asleep, I stay asleep, I say, rest the body I [...] I am rested, because with other medicines, with other drugs that I have taken, I could not sleep" (P18) "(with the tablet) It usually takes me half an hour to fall asleep. And I cannot be without it (...) I want the medication to take away my anxiety, my fears and to be able to fall asleep" (P13) "I took valerian, and nothing happened, and then I took a tablet of these and after three hours I was exhausted, it was when I had to get up that I got sleepy" (P12) "I think that if I take it, it hurts me even more. Not in terms of sleep, but I feel worse. [...] And it is horrible. You are full of drugs, it is not you, you are a vegetable. No, no, not this, and on top of that, you also feel bad. They take away a... I don't know what they take, but they put you to sleep, but to sleep, you'd better die now" (P3) "You get used to the drugs and after a while they no longer work" (P9) "I'm telling you, so much medication in my body, that's what I think that will affect me in the long run" (P15)
Self-management strategies	General strategies for improving sleep quality	"If I am not tired, for spending all day without much activity, I also sleep worse. So, I try to get a little more tired [...] to get physically tired helps me. I do not take a nap, I cannot sleep. If I take a nap, then at night I do not sleep at all, for sure" (P14) "Sometimes I try to sleep thinking that I'm resting. Sometimes I try not to sleep, to sleep more at night. Nothing is constant, neither one nor the other helps me [...] There are days when one thing works for me but then the next day I am no longer doing well.

		There are periods when I feel better [...] A week goes by and gets terrible again" (P9)
	Strategies for falling asleep and dealing with interrupted sleep or waking up too early	"I stay there, I go around or whatever, but I stay there. I say wait, I close my eyes, I do not think about anything, to see if I fall asleep. I try to relax so that I can fall asleep" (P6) "I play with the computer and they already told me that I shouldn't do it because this is bad for sleeping" (P11) "I don't go to sleep before one [...] I don't want to go at eleven or twelve because then I would already be awake at three or four" (P17)
	Coping with the consequences of poor sleep quality during the day	"And you say "I can go and lay down"; I have to lay down because if I don't, I can't stand it, and sometimes I leave them food and go to lay down because my body can't stand it, and you say "But I can lay down and take a little nap, hopefully", and when I see that my husband stays there, sometimes I say "Wake up, I can't" (P16) "I do nothing, I remain the same, I have not slept because I have not slept, life remains the same, I continue with my life the same way" (P7)
	Needs	"I would say that it would be like a fantasy to be able to sleep well, because I sleep very badly" (P18) "[I would need] something to help me sleep and not wake up at night, those eight hours a day, so that I could sleep more comfortably" (P6)

STUDY IV. Patient Reported Outcome Measures of Sleep Quality in Fibromyalgia: A COSMIN Systematic Review

Study selection

The electronic literature search yielded 3042 records in total and 1410 duplicates were removed. During the process of study selection, 1632 records were analyzed by title and abstract, and 1620 were excluded. Finally, 12 records were selected for the full text analysis, and 6 studies met the inclusion criteria. The manual search based on the bibliographic references of the included studies yielded one study. Therefore, seven studies were included in the narrative synthesis and five instruments were described (Figure 13: Process of Study Selection (PRISMA Flow Diagram) (282).

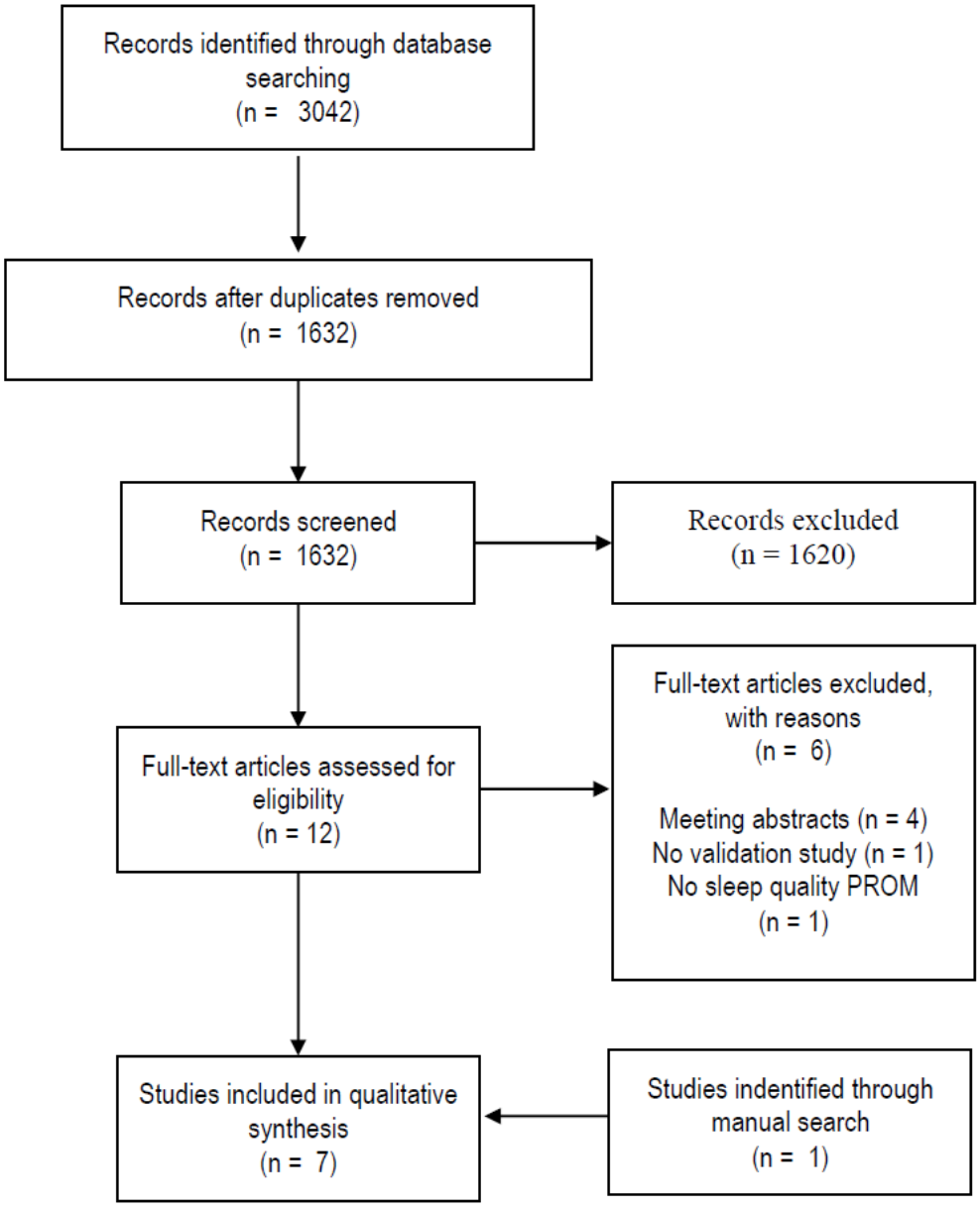

Figure 13. Process of Studies Selection (PRISMA Flow Diagram)

Risk of Bias

All the included studies (249,277,289,295–298) showed a very good methodological quality for assessing the measurement properties of the selected PROMs in accordance with the COSMIN criteria. Therefore, the RoB was rated as low for all the studies. The results from the risk of bias assessment can be consulted in Table 11.

Table 11. Risk of Bias Assessment

PROM	Measurement properties assessed	Risk of Bias
PSQI	Internal Consistency	Low
	Reliability	Low
	Structural validity	Low
	Hypothesis testing	Low
JSS	Internal Consistency	Low
	Reliability	Low
	Structural validity	Low
	Responsiveness	Low
SQ-NRS	Content validity	Low
	Reliability	Low
	Hypothesis testing	Low
MOS-SS	Content validity	Low
	Internal Consistency	Low
	Reliability	Low
FSD	Content validity	Low

Characteristics of the included PROMs and the study populations

The characteristics of the included PROMs and the characteristics of the study populations can be consulted in Table 12 and Table 13, respectively.

The included studies reported the following PROMs for sleep quality in patients with FM: 1) Pittsburgh Sleep Quality Index, 2) Jenkins Sleep Scale (alternative scoring method), 3) Sleep Quality-Numeric Rating Scale, 4) Medical Outcomes Study-Sleep Scale, and 5) Fibromyalgia Sleep Diary.

For those of the included PROMs that were not originally developed as specific tools for assessing sleep quality in patients with FM, the characteristics of the PROM and the study populations of the original development studies were also included in Tables 12 and 13.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI was developed with the understanding that the essential elements that characterize good sleep are mainly subjective and may vary between individuals. Accordingly, Buysse et al. (150), pointing out that poor sleep quality was a highly prevalent problem in people with psychiatric problems, developed the first version of this index in 1989 with the objective of assessing in a reliable and valid way the quality of sleep from the perspective of patients.

Objective of the tool (150): The PSQI assesses the sleep quality of the month prior to the evaluation since, as the authors stated in the "Consensus Conference of Insomnia, 1984," it was established that the assessment of 2-3 weeks of sleep is the ideal minimum time for being able to discern between transient and persistent sleep problems. Accordingly, the PSQI allows the latter distinction to be made if it is applicable twice with one month of separation.

Number of items and response options (150): To assess the described components, the PSQI is composed of 19 self-rated questions and 5 questions that are answered by the roommate or bedmate, although the latter are only used for clinical purposes and are not included in the final score. The items of the PSQI are organized into seven components: 1) Subjective sleep quality, 2) Sleep latency, 3) Sleep duration, 4) Habitual sleep efficiency, 5) Sleep disturbances, Use of sleeping medication, and 7) daytime dysfunction. The first four items are answered by providing some data related to the usual time of sleep, time to fall asleep, time awake at night, and hours of sleep per night. The other 12 items to be filled out by the patient plus the items to be filled in by the roommate or bed partner use the previous set of answers, and the respondent is asked to mark an X for the option that most corresponds to their experience. There are four possible answers, for example: 1) Not during the past month, 2) Less than once a week, 3) Once or twice a week, or 4) Three or more time a week. In one of the items the possible answers are: 1) Very good, 2) Fairly good, 3) Fairly bad or 4) Very bad. Another item has the following answers: 1) No problem at all, 2) Only a very slight problem, 3) Somewhat of a problem, or 4) A very big problem. Finally, the last question has also four possible answers: 1) No bed partner or roommate, 2) Partner/roommate in other room, 3) Partner in the same room, but not same bed, or 4) Partner in same bed.

Administration method and time of response: The PSQI is self-completed by the respondent, and it takes 5–10 minutes to complete the questionnaire.

Scoring (150): The total score of the questionnaire is derived from the sum of the seven components of the questionnaire. Each of the items has, as explained above, four possible answers, so the scoring varies between 0 and 3. In this way, the maximum final score is 21 points and the minimum score is 0.

Score interpretation (150): According to the authors, a score lower than 5 points would indicate that the respondent is a "good sleeper" while ratings greater than 5 points would be indicative of poor sleep quality and moderate difficulties in three components or serious difficulties in at least two components of the seven that are evaluated.

Method of development (150): The PSQI was developed based on the clinical experience of the authors with patients with sleep disorders and the results of a review of the previous literature through which the authors identified the already developed tools for the assessment of sleep quality. This process ensured that prior to the development of the PSQI, there were already different sleep measurement tools. However, there were very few that had been developed with clinical subjects. In addition, the PSQI allows the assessment of the sleep quality of the previous month, unlike other scales that only permit the assessment of the previous night or sleep problems during the year prior to the evaluation.

The authors defined four objectives (150): 1) to develop a standardized, reliable, and valid tool to assess the quality of sleep, 2) to differentiate good and bad sleepers, 3) to develop an easy-to-complete and easy-to-interpret tool, 4) to develop a short and clinically useful tool to assess a series of sleep problems that can interfere with the quality of it.

For the development of the PSQI, the authors recruited a sample composed of 52 healthy subjects defined as "good sleepers", who formed control group I, 34 patients admitted to or outpatients of a psychiatric center diagnosed with major depressive disorder and considered "bad sleepers" who formed group II, and finally, 62 patients with sleep disorders referred by a physician from another psychiatric center formed group III.

After the development of the PSQI, an 18-month field testing was carried out to assess the clinical experience of its use.

Translations/adaptations in patients with FM: According to the results of our review, the PSQI was also validated in a sample of people diagnosed with FM in Spain (249) (more details in Table 12 and Table 13).

Jenkins Sleep Scale (JSS)

The development of the JSS was based on the absence of brief and easy-to-use sleep evaluation scales in the field of epidemiological research. In addition, the available tools only allowed the assessment of

very specific sleep conditions. Thus, the main objective of the JSS was not to serve as a tool for assessing specific sleep problems such as narcolepsy or sleep apnea, but to allow evaluation of the most common symptoms in the general population (299).

Objective of the tool (299): The JSS permits the assessment of the most common symptoms of insomnia (difficulty falling asleep and maintaining sleep, as well as the sensation of fatigue upon awakening) during the previous month.

Number of items and response options (299): The scale consists of four items: 1) Do you have trouble falling sleep? 2) Do you wake up several times per night? 3) Do you have trouble staying asleep? (Including waking far too early), and 4) Do you wake up after your usual amount of sleep feeling tired and worn out?

Each of the items is classified on a Likert scale of 6 points based on the frequency with which the respondent experiences each of the evaluated symptoms (0 = not at all, 1 = 1–3 days, 2 = 4–7 days, 3 = 8–14 days, 4 = 15–21 days, and 5 = 22–31 days).

Administration method and time of response (299): The JSS is a self-administered, brief, and quick-filling scale.

Scoring (299): According to the response options previously presented, the results of the JSS can vary from 0 to 20 in the total sum of the items.

Score interpretation (299): 0 points are indicative that there are no sleep problems and 20 points indicate significant sleep problems.

Method of development (299): The scale was developed within the framework of two other larger projects, the “Air Traffic Controller (ATC) Health Change Study” and the “Recovery Study” (RS). In the former, 300 questionnaires were sent by post, of which 250 were completed and returned. The sample consisted mainly of men between 25 and 49 years of age and the average age of respondents was 37.1 years. In the case of the RS, 467 subjects admitted for cardiac valve surgery or coronary bypass were included. 80% of the sample consisted of white men between the age of 25–69 years, although most were between 50 and 60 years old.

Although the JSS was used for both studies, in the ATC study all four items that make up the scale were included, but in the RS the item “waking up several times per night” was omitted, and the last two categories of responses were also modified and grouped into one, so that the last answer option was “15-31 days” and the total score could range between 0 and 12 points.

In the ATC study the scale was administered only once, while in the RS study it was completed before the surgery and at 6 and 12 months after the same.

Translations/adaptations in patients with FM: Crawford et al. (295) validated a JSS version with an alternative method of scoring in a sample of patients diagnosed with FM. The authors hypothesized that using a scoring method in which the patients must recall the exact number of nights they had sleep disturbance could increase the likelyhood of incurring a recall bias. Therefore, an alternative scoring method was proposed in which the respondent must select a period of time instead of an exact number of days: 1) not at all (score = 0), 2) less than half the time (score = 1), and 3) greater than half the time (score = 2). Hence, the total score ranges from 0 to 8, higher scores being indicative of greater severity of sleep problems (more details in Table 12 and Table 13).

Sleep Quality-Numeric Rating Scale (SQ-NRS)

The Sleep SQ-NRS was developed in order to collect relevant and appropriate information for a generic approach to the global impact of sleep problems in patients with FM (289).

Objective of the tool (289): The NRS is eligible in evaluations that require a daily record of the quality of sleep, offering the patient an element with little time burden.

Number of items and response options (289): It is a tool with a single element. The patient is asked to choose the one that best describes their sleep quality during the last 24 hours on a numerical scale of 11 points (0-10).

Administration method and time of response: Self-managing scale and quick response. The patient is instructed to complete the tool just after waking up.

Scoring and score interpretation (289): The scoring scale fluctuates in a range between 0 “best possible sleep” and 10 “worst possible sleep”.

Translations/adaptations in patients with FM: no validations were found in other languages.

Medical Outcomes Study-Sleep Scale (MOS-SS)

The development of the MOS-SS was derived from the results of a larger research project called the Medical Outcomes Study (MOS) (300), which consisted of a longitudinal descriptive observational study linked to the health outcomes in patients with chronic diseases. In this study, the authors concluded that sleep is a key factor for the functionality and well-being of people with chronic health conditions. In addition, the authors stated that sleep assessment could be key to understanding the health problems associated with chronic health conditions and developing more effective treatments.

Objective of the tool: The MOS-SS allows the assessment of sleep quality.

Number of items and response options (260,301): The MOS-SS is composed of 12 items that evaluate 6 sleep domains: initiation (time to fall asleep), quantity (hours of sleep each night), maintenance, respiratory problems, perceived adequacy, and drowsiness.

The sleep scale uses a wide variety of response sets. The first item: 1) 0-15 minutes, 2) 16-30 minutes, 3) 31-45 minutes, 4) 46-60 minutes, 5) More than 60 minutes. The second item is an open question allowing a response that ranges from 0–24 h. The remaining 10 items use a set of 6-point answers based on the following values: 1) All of the time, 2) Most of the time, 3) A good bit of the time, 4) Some of the time, 5) A Little of the time, 6) None of the time.

There is a nine-item version of the MOS-SS, named Sleep Problems Index II, and a 6-item version defined as the Sleep Problems Index I. Neither of the scales excludes any item from the original scale, but rather groups them in unique items so that the only difference is that these two scales are shorter.

Administration method and time of response (296): The MOS-SS is a self-administered scale and takes about 2-3 minutes to complete.

Scoring (289): Each of the response options described above is accompanied by a numerical index. The sum of the scores of the items and domains becomes a numerical scale of 0-100 in all the items. Two exceptions are contemplated: the score of the item “quantity” ranges between 0–24 and the score of the item “adequacy of sleep” ranges between 0–1. Regarding the interpretation of the score, higher scores indicate greater affectation of the variable that is being measured. In relation to sleep maintenance, it is considered optimal if the patient reports 7–8 hours of sleep, assessed as 1, otherwise the score is 0.

Score interpretation (260): According to the authors, high scores indicate worse sleep problems. The exceptions are the items “sufficiency of sleep” and “quantity” where lower scores indicate worse sleep problems.

Translations/adaptations in patients with FM : According to the results of this systematic review, the are three studies evaluating the content validity (289), the psychometic properties (296) and the test-retest reliability (297) of the MOS-SS in patients with FM (more details in Table 12 and Table 13).

Fibromyalgia Sleep Diary (FSD)

Objective of the tool (277): In contrast with the above presented PROMs, the FSD was the first tool originally developed for evaluating sleep quality in people diagnosed with FM in a dialy basis.

Number of items and respons options (277): The FSD is composed of 8 items: 1) How difficult was it to fall asleep last night?, 2) How restless was your sleep last night?, 3) How difficult was it to get comfortable last night?, 4) How diffciult was it to stay asleep last night?, 5) How deep was your sleep last night?, 6) How rested were you when you woke up for the day?, 6) How difficult was it to begin your day?, 8) Did you have enough sleep last night?. The responsed options are base on a numerical scale of 11 points ranging from 0 to 10.

Score and score interpretation (277): not reported.

Method of development: The FSD was developed by Kleinman et al. (277) in 2014 through a multi-staged process including a review of the literature, different qualitative approaches with experts and patients such as semi-structured interviews and focus groups, development of the conceptual framework and the first version of the FSD, and cognitive interviews so as to analyze the content validity and comprehensiveness of the PROM. The psychometric properties of the FSD were not analyzed.

For the development of the items the authors used the terminology that emerged from the focus groups with the patients so as to ensure the adequacy of the content to peolple diagnosed with FM.

Translations/adaptations in patients with FM: no validations were found in other languages.

Table 12. Characteristics of the included PROMs

PROM* (reference to first article)	Construct(s)	Target population	Mode of administration (e.g. self-report, interview-based, parent/proxy report etc)	Recall period	(Sub)scale (s) (number of items)	Response options	Range of scores/scoring	Original language	Available translations
Pittsburgh Sleep Quality Index [24]	Sleep Quality	Patients diagnosed with major depressive disorder	Self-completed by the respondent	One month	Subscales: 1) subjective sleep quality, 2) sleep latency, 3) sleep duration, 4) habitual sleep efficiency, 5) sleep disturbances, 6) use of sleeping medication, and 7) daytime dysfunction. Items: 19 self-rated questions and 5 questions that are answered by the roommate or bedmate	The first four items are answered by providing some data related to the usual time of sleep, time to fall asleep, time awake at night, and hours of sleep per night. The other 12 items to be filled out by the patient plus the items to be filled in by the roommate or bed partner use the previous set of answers, and the respondent is asked to mark an X for the option that most corresponds to their experience: 1) Not during the past month, 2) Less than once a week, 3) Once or twice a week, or 4) Three or more time a week. In one of the items the possible answers are: 1) Very good, 2) Fairly good, 3) Fairly bad or 4) Very bad. Another item has the following answers: 1) No problem at all, 2) Only a very slight problem, 3) Somewhat of a problem, or 4) A very big problem. Finally, the last question has also four possible answers: 1) No bed partner or roommate, 2) Partner/roommate in other room, 3) Partner in the same room, but not same bed, or 4) Partner in same bed.	The total score of the questionnaire is derived from the sum of the 7 components of the questionnaire. Each of the items has, as explained above, four possible answers, so the scoring varies between 0 and 3. In this way, the maximum final score is 21 points and the minimum score is 0. a score lower than 5 points would indicate that the respondent is a “good sleeper” while ratings greater than 5 points would be indicative of poor sleep quality and moderate difficulties in 3 components or serious difficulties in at least 2 components of the 7 that are evaluated.	English	Spanish with a sample of people diagnosed with FM

Table 12. Characteristics of the included PROMs (cont.)

PROM* (reference to first article)	Construct(s)	Target population	Mode of administration (e.g. self-report, interview-based, parent/proxy report etc)	Recall period	(Sub)scale (s) (number of items)	Response options	Range of scores/scoring	Original language	Available translations
Jenkins Sleep Scale [25]	Symptoms of insomnia	Patients 6 months after cardiac surgery Air traffic controllers	Self-administered	One month	The scale consists of 4 items: 1) Have trouble falling sleep? 2) Wake up several times per night? 3) Have trouble staying asleep? (Including waking far too early), and 4) Wake up after your usual amount of sleep feeling tired and worn out?	Each of the items is classified on a Likert scale of 6 points based on the frequency with which the respondent experiences each of the evaluated symptoms (0 = not at all, 1 = 1–3 days, 2 = 4–7 days, 3 = 8–14 days, 4 = 15–21 days, and 5 = 22–31 days).	According to the response options previously presented, the results of the JSS can vary from 0 to 20 in the total sum of the items. 0 points are indicative that there are no sleep problems and 20 points indicate significant sleep problems.	English	An alternative scoring method for the JSS was validated in Spanish with a sample of people diagnosed with FM.
Sleep Quality Numeric Rating Scale [19]	Sleep Quality	People diagnosed with FM	Self-administered	Daily record of the quality of sleep	It is a tool with a single element. The patient is asked to choose the one that best describes their sleep quality during the last 24 hours on a numerical scale.	A numerical scale of 11 points (0-10).	The scoring scale fluctuates in a range between 0 “best possible sleep” and 10 “worst possible sleep”.	English	-

Table 12. Characteristics of the included PROMs (cont.)

PROM* (reference to first article)	Construct(s)	Target population	Mode of administration (e.g. self-report, interview-based, parent/proxy report etc)	Recall period	(Sub)scale (s) (number of items)	Response options	Range of scores/scoring	Original language	Available translations
Medical Outcomes Study-Sleep Scale]	Sleep quality and quantity	Healthy adults and adults diagnosed with neuropathic pain	Self-administered	One month	The MOS-SS is composed of 12 items that evaluate 6 sleep domains: initiation (time to fall asleep), quantity (hours of sleep each night), maintenance, respiratory problems, perceived adequacy, and drowsiness.	The first item: 1) 0-15 minutes, 2) 16-30 minutes, 3) 31-45 minutes, 4) 46-60 minutes, 5) More than 60 minutes. The second item is an open question allowing a response that ranges from 0–24 h. The remaining 10 items use a set of 6-point answers based on the following values: 1) All of the time, 2) Most of the time, 3) A good bit of the time, 4) Some of the time, 5) A Little of the time, 6) None of the time.	According to the authors, high scores indicate worse sleep problems. The exceptions are the items “sufficiency of sleep” and “quantity” where lower scores indicate worse sleep problems.	English	English with a sample of people diagnosed with FM]
Fibromyalgia Sleep Diary	Sleep quality	People diagnosed with FM	Self-administered	Daily record of the quality of sleep	The FSD consist of 8 items: 1) How difficult was it to fall asleep last night?, 2) How restless was your sleep last night?, 3) How difficult was it to get comfortable last night?, 4) How difficult was it to stay asleep last night?, 5) How deep was your sleep last night?, 6) How rested were you when you woke up for the day?, 7)How difficult was it to begin your day?, and 8) Did you have enough sleep last night?	A visual analogue scale of 11 points ranging from 0 to 10.	Not provided	English	-

Table 13. Characteristics of the included studies populations

	Population			Disease characteristics			Instrument administration			
PROM	**N**	**Age Mean (SD, range) yr**	**Gender % female**	**Disease**	**Disease duration mean (SD) yr**	**Disease severity**	**Setting**	**Country**	**Language**	**Response rate**
Pittsburgh Sleep Quality Index	Sample 1 = 34 Sample 2= 45 Sample 3 = 17 Sample 4 = 52	Sample 1: 50.9 (range: 21-80) Sample 2: 44.8 (range: 20-80) Sample 3: 42.2 (range: 19-57) Sample 4: 59.9 (range: 24-83)	Sample 1: 26.4% Sample 2: 64.4% Sample 3: 52.9% Sample 4: 23.07%	Sample 1: Major depressive disorder Sample 2: Disorder of Initiating and Maintaining Sleep Sample 3: Disorders of Excessive Somnolence Sample 4: Healthy subjects	-	-	Psychiatric Clinics	United States of America	English	93.67%
	138	52.83 (±9.32)	100% women	Fibromyalgia	15.77 years (±9.76)	Moderate: FIQ <70 N = 68 FIQ score (51.02 ± 16.28) Severe: FIQ ≥70 N= 70 FIQ score (80.44 ± 6.20)	Community (FM association)	Spain	Spanish	Test: 100% Retest: 69.56%
Jenkins Sleep Scale	Sample 1 = 300 Sample 2 = 467	Sample 1: 37.1 (25-49) Sample 2: 54.9 (25-69)	Sample 1: 0% Sample 2: 20%	Sample 1: Air Traffic Controllers Sample 2: Cardiac valve surgery or coronary bypass	Sample 1: - Sample 2: -	Sample 1: - Sample 2; -	Sample 1: community Sample 2: Secondary health care	United States of America	English	Sample 1: 83.33% Sample 2: Test: 100% Retest: 91.22%
	195	46.5 (±11.35)	94.4%	Fibromyalgia	~9 years	-	Clinical setting (unspecified)	United States of America	English	97.95%

Table 13. Characteristics of the included studies populations (cont.)

	Population			Disease characteristics			Instrument administration			
PROM	**N**	**Age Mean (SD, range) yr**	**Gender % female**	**Disease**	**Disease duration mean (SD) yr**	**Disease severity**	**Setting**	**Country**	**Language**	**Response rate**
Sleep Quality Numeric Rating Scale	Sample 1 = 748 Sample 2 = 745	Sample 1: 48.8 (± 10.9) Sample 2: 50.1 (± 11.4)	Sample 1: 94.4% Sample 2: 94,5%	Fibromyalgia	Sample 1: ~9 years Sample 2: ~10 years	Mean pain score (0-10) Sample 1: 7.1 (± 1.3) Sample 2: 6.7 (± 1.3)	Clinical setting (unspecified)	United States of America	English	-
	20	50.3 (29-64)	80%	Fibromyalgia	8.9 (-1-18)	Pain level (0-10) (SD) 6 (1.6)	Community	United States of America	English	
Medical Outcomes Study Sleep Scale	Sample 1 = 1011 Sample 2 = 173	Sample 1: 46 (18–94 range) Sample 2: 72 (31–100 range)	Sample 1: 51% Sample 2: 53%	Sample 1: Healthy subjects Sample 2: Postherpetic neuralgia	Sample 1: - Sample 2: 33.8 months (35.9)	-	Clinical Setting (unspecified)	United States of America	English	Sample 1: - Sample 2: Test: 100% Re-test: 51.44%
	20	50.3 (29-64)	80%	Fibromyalgia	8.9 (-1-18)	Pain level (0-10) (SD) 6 (1.6)	Community	United States of America	English	
	Sample 1: 748 Sample 2: 745	Sample 1: 48.8 (± 10.9) Sample 2: 50.1 (± 11.4)	Sample 1: 94.4% Sample 2: 94,5%	Fibromyalgia	Sample 1: ~ 9 years Sample 2: ~ 10 years	Mean pain score (0-10) Sample 1: 7.1 (± 1.3) Sample 2: 6.7 (± 1.3)	Clinical setting (unspecified)	United States of America	English	-
	129	49.4 (± 11.0)	91.3%	Fibromyalgia	≥ 2 years	moderate-to-severe in 88.1% of the sample	Community	United States of America	English	100%
Fibromyalgia Sleep Diary	FM experts = 4 FM patients = 34	FM patients: 47.8 (±11.9)	FM patients: 88.2%	Fibromyalgia	Not reported	Not reported	community-based clinical sites	United States of America	English	100%

Results of studies on measurament properties in people diagnosed with FM

Non of the included studies reported all the measurement properties established by the COSMIN guidelines (281).

For the PSQI, the authors (249) reported data regarding internal cosistency, reliability and hipotheses testing and were rated as positive (more details in Table 14: Results of studies on measurement properties (PSQI))

The reported measurament properties for the JSS with an alternative scoring method (295) were internal consistency, criterion validity, test-retest reliability, and responsiveness. The results from internal consistency and responsiveness were rated as positive, while structural validity, criterion validity and reliability obtained moderate quality of the results as some of them did not achieve the minimun standarts established by the COSMIN guidelines (281) (more details in Table 15. Results of studies on measurement properties (JSS))

The SQ-NRS content validity was evaluated by Martin et al. (289) showing favorable results for patients with FM. Cappelleri et al. (298) analyzed the criterion validity, the test-retest reliability and the responsiveness of the SQ-NRS showing positive results (more detail in Table 16. Results of studies on measurement properties (SQ-NRS))

Regarding the MOS-SS the results obtained by Martin et al. (289) provided strong evidence for validating the content of the tool in people diagnosed with FM. Cappelleri et al. (296) reported the structural validity and the internal consistency of the MOSS-SS, while the 1-week reliability of the scale was assessed by Sadosky et al. (297). The results were positive for the internal consistency and for the reliability. However, the structural validity was rated as negative (more details in Table 17. Results of studies on measurement properties (MOS-SS))

Addtionally, Cappelleri et al. (296) stimated that a change of 7.9 of the total score represents the minimal clinical important change of the MOS-SS.

In relation to the FSD, the included study (277) aimed to develop and to analyze the content validity of the tool trought a qualitative approach. The qualitative results showed that the FSD strongly represents the elements of sleep quality as a construct in the context of FM. As the psychometric evaluation of the FSD was not performed there were no statistical data to summarize.

Table 14. Results of studies on measurement properties (PSQI)

PROM	***Country (language) in which the PROM was evaluated***	***Internal consistency***			***Test-retest reliability***			***Hypotheses testing***		
		n	Meth qual	Result (rating)	n	Meth qual	Result (rating)	n	Meth qual	Result (rating)
Pittsburgh Sleep Quality Index	Spain (Spanish)	138	+	α = 0.805	96	+	ρ = 0.806 for the PSQI total score (p<0.001). Lowest value ρ = 0.356 "daytime dysfunction" Highest value ρ = 0.718 "use of sleeping medication"	96	+	FIQ (total score) ρ = 0.304 (p < 0.01) SF-36 Physical functioning ρ = -0.372 (p < 0.01) Role physical ρ = -0.217 (p < 0.05) Role emotional ρ = -0.254 (p < 0.01) Vitality ρ = -0.247 (p < 0.05) Mental Health ρ = -0.208 (p < 0.05) Social functioning ρ = -0.426 (p < 0.01) Bodily pain ρ = -0.351 (p < 0.01) General Health NS
Pooled or summary result (overall rating)		*138*		*0.805*	*96*		*0.806*	*96*		*FIQ: ρ = 0.304 (p < 0.01) SF-36: General Health NS Social functioning ρ = -0.426 (p < 0.01)*

KMO: Kaiser-Meyer-Olkin, ρ: Spearman's rank correlation coefficient, FIQ: Fibromyalgia Impact Questionnaire, SF-36: Short-Form health survey-36, NS: nonsignificant

Table 15. Results of studies on measurement properties (JSS)

PROM	***Country (language) in which the PROM was evaluated***	***Internal consistency***			***Criterion validity***			***Reliability***			***Responsiveness***		
		n	Meth qual	Result (rating)	n	Meth qual	Result (rating)	n	Meth qual	Result (rating)	n	Meth qual	Results (rating)
Jenkins Sleep Scale	United States of America (English)	195	+	α = 0.70	195	+/-	FIQ item 16 r=0.68 FIQ item 17 r=0.72 Pain VAS r=54 Fatigue VAS r=57 ESS r=0.43 FOSQ total score r=-0.57 SF-36 Vitality score r=-0.66	195	+/-	FIQ total score ICC 0.70 FIQ item 17 ICC 0.72 ESS ICC 0.69 Fatigue VAS ICC 0.66 Pain VAS ICC 0.61	R: 38 NR: 115	+	R: Pain VAS + FIQ total score SES = 1.62 NR Pain VAS + FIQ total score SES = -1.33
Pooled or summary result (overall rating)		*195*		*0.70*			*0.43-0.72*	*195*		*0.61-0.72*	*R: 38* *NR: 115*		*R: 1.62* *NR: -1.33*

r: Pearson Correlation Coefficient, ICC: Intraclass Correlation, α: Cronbach's alpha, SES: Standardized effect sizes, FIQ: Fibromyalgia Impact Questionnaire, FOSQ: Functional Outcomes of Sleep Questionnaire, SF-36: Short-Form health survey-36, ESS: Epworth Sleepiness Scale, VAS: Visual Analogue Scale, R: Responders, NR: Nonresponders

Table 16. Results of studies on measurement properties (SQ-NRS)

PROM (ref)	***Country (language) in which the PROM was evaluated***	***Criterion validity*** n	Meth qual	Result (rating)	***Test-retest reliability*** n	Meth qual	Result (rating)	***Responsiveness*** n	Meth qual	Result (rating)
Sleep Quality Numeric Rating Scale [20]	United States of America (English)	Sample 1 = 748 Sample 2 = 745	+	PNRS Sample 1 r = 0.64, p <0.001 Sample 2 r = 0.58, p <0.001 MOS-SS Sample 1 Sleep disturbance r = 0.45, p <0.001 Snoring r = 0.01, p = 0.884 Awaken Short of breath of with headache r = 0.21, p <0.001 Quantity of sleep r = -0.31, p <0.001 Sleep adequacy r = -0.21, p <0.001 Somnolence r = 0.11, p = 0.004 Sample 2 Sleep disturbance r = 0.42, p <0.001 Snoring r = 0.00, p = 0.993 Awaken Short of breath of with headache r = 0.14, p <0.001 Quantity of sleep r = -0.34, p <0.001 Sleep adequacy r = -0.32, p <0.001 Somnolence r = 0.15, p <0.001	Sample 1 = 748 Sample 2 = 745	+	Sample 1 ICC 0.90 Sample 2 ICC 0.91	Pregabalin treatment Sample 1: 300mg (n = 368) Sample 2: 450mg (n = 373) Sample 3: 600mg (n = 378)	+	Sample 1: SES = 0.46-0.52 Sample 2: SES = 0.59 Sample 3: SES = 0.73
Pooled or summary result (overall rating)		*1493*		*PNRS 0.58-0.64* *MOS-SS 0.00-0.45*	*1493*		*0.90-0.91*			*0.46-0.73*

PNRS: Pain Numerical Rating Scale, MOS-SS: Medical Outcomes Measures-Sleep Scale, r: Pearson Correlation Coefficient ICC: Intraclass Correlation

Table 17. Results of studies on measurement properties (MOS-SS)

PROM	***Country (language) in which the PROM was evaluated***	***Structural validity***			***Internal consistency***			***Test-retest reliability***		
		n	Meth qual	Result (rating)	n	Meth qual	Result (rating)	n	Meth qual	Result (rating)
Medical Outcomes Study Sleep Scale	United States of America (English)	Sample 1 = 748 Sample 2 = 745	-	CFA Bentler's comparative fit index Baseline: 0.88 Week 5: 0.93 Week 9: 0.91 Week 13: 0.92	Sample 1 = 748 Sample 2 = 745	+/-	Sample 1: Week 1/ week 13 Sleep disturbance subscale α=0.78 / α=0.87 Somnolence subscale α=0.72 / α=0.86 Sleep adequacy subscale α=0.36 / α=0.74 Sample 2: Week 1/ week 13 Sleep disturbance subscale α=0.80 / α=0.87 Somnolence subscale α=0.71 / α=0.75 Sleep adequacy subscale α=0.61 / α=0.74			
Medical Outcomes Study Sleep Scale	United States of America (English)							140	+	Week 1 = ICC 0.81 Week 4 = ICC 0.89
Pooled or summary result (overall rating)		*1493*		*0.88-0.93*	*1493*		*0.36 - 0.87*	*140*		*0.81- 0.89*

CFA: Confirmatory Factor Analysis, α: Cronbach's alpha, ICC: Intraclass Correlation

DISCUSSION

Study II. Poor Sleep Quality Experience and Self-Management Strategies in Fibromyalgia: A Qualitative Metasynthesis

The objective of this research was to metasynthesize the available qualitative studies exploring how people diagnosed with FM experience and manage poor sleep quality. The overall methodological quality of the included studies was good according to the CASP qualitative checklist.

In this metasynthesis the authors took the SMT as a conceptual framework and the two overarching themes were pre-established in accordance with two of the domains of the theory "Symptom Experience" and "Symptom Management Strategies": 1) Experience of poor sleep quality in FM and 2) Poor sleep quality management strategies in FM. The sub-themes were also organized taking into account the concepts nested within each of the domains. The results related to the experience of poor sleep quality were classified into two sub-themes: 1) Evaluation of poor sleep quality and 2) Response to poor sleep quality. The results related to poor sleep quality management strategies in FM were classified into three sub-themes: 1) Management strategies to favor sleep and 2) Managing the consequences of a sleepless night.

The present analysis showed that poor sleep quality is perceived as a severe symptom of FM and that the most troublesome problems are those related to the maintenance of sleep throughout the night, indicating the experience of fragmented sleep. Likewise, complaints about superficial and non-restorative sleep were common among the participants. When people diagnosed with FM were asked about the meaning of good sleep quality usually report that it is related to having uninterrupted sleep, the feeling of "disconnection" during the night, and waking up feeling refreshed. Therefore, our results showed that for people diagnosed with FM the most important aspects of sleep that contribute to defining good sleep quality are those related to sleep continuity, perception of disengagement from the environment, and waking up feeling refreshed in the morning. According to a panel of experts assembled by the National Sleep Foundation (302) the concept of sleep quality is mainly related to sleep continuity, sleep maintenance, sleep initiation, and sleep efficiency. However, because of the subjectivity linked to sleep quality and that its meaning can vary among individuals (303) it is important to continue exploring the meaning that people with different health conditions attach to sleep quality. Moldofsky et al. (304) investigated the meaning of sleep quality among people suffering from insomnia in comparison with good sleepers and concluded that, in general terms, the meaning of sleep quality is very similar between them. However, the lack of quantitatively and qualitatively oriented research comparing the meaning of sleep quality between healthy sleepers, people with other sleep disorders, and people suffering from FM, highlight the need to further investigate on this subject to provide the most appropriate assessment and management approaches.

Although the beliefs regarding the cause of poor sleep quality have been hardly explored in the available qualitative literature, the results indicated that people diagnosed with FM appear to believe that poor sleep quality development depends on external factors given that most of the participants rely on aspects related to working conditions.

Another aspect that highlights the severity of poor sleep quality in the context of FM is the perceived effect on other symptoms commonly associated with FM such as pain, fatigue, poor functionality, mood states alterations, and cognitive problems. Particularly, it seems that the most complex relationship for people diagnosed with FM is that of poor sleep quality with fatigue and pain. Those beliefs are supported by scientific evidence demonstrating that poor sleep quality correlates with reports of increased fatigue (264). Likewise, participants argued that fatigue is not alleviated after having a satisfactory quantity of sleep which may be indicative that the sleep-fatigue relationship could be mediated by other sleep aspects rather than by the total amount of sleep.

The sleep-poor functionality relationship is perceived as having a negative impact on managing work-related demands which ultimately leads to a feeling of frustration and failure. The qualitative literature exploring how poor sleep quality affects work performance in people diagnosed with FM is insufficient. However, Litwiller et al. (305) suggested that the consequences of poor sleep quality on affect and cognition mediate the impact of poor sleep quality on task and contextual performance and impair the ability to develop safety behaviors. The authors also highlighted the relevance of including a measure of sleep quality in surveys of well-being and satisfaction at the workplace. This information would facilitate the implementation of poor sleep quality management programs that could help employees develop effective coping strategies.

Regarding the sleep-pain cluster, the results of this metasynthesis suggest that the interaction of these two symptoms is perceived as bidirectional. In this regard, there is an increasing amount of scientific evidence showing that there is a bidirectional relationship between pain and sleep (175,180,196,306–309). The proposed underlying physiological mechanisms of sleep-chronic pain relationship involve multiple brain structures and systems such as the monoaminergic system (308,310), opioid and endocannabinoid systems, the orexinergic system, the immune system, the hypothalamus-pituitary-adrenal axis, and the pineal melatonin system among others (308).

Other important factors mediating the sleep-pain relationship are psychological processes. Results of a review (180) showed that the cognitive factors associated with pain may be key in the sleep-pain relationship. In 2012, Buenaver et al. (186) investigated whether pain catastrophizing was linked to greater severity of pain and if this relationship could be mediated by sleep problems including a sample of 214

participants with temporomandibular myofascial disorder. The results showed that pain catastrophizing was, directly and indirectly, related to greater severity of pain. Sleep problems can mediate the indirect relationship between pain catastrophizing and pain intensity, although the mechanisms of this association have not yet been elucidated. Smith et al. (187) postulated that this relationship could derive from the development of ruminative and catastrophic thoughts related to pain just at bedtime. In their research, they found that people with chronic pain think more often about their pain in the previous moments of going to sleep and that a higher incidence of such thoughts can affect the onset and maintenance of sleep. Likewise, people with chronic pain develop negative presleep cognitions related to sleep although in this case, the authors did not found them to be correlated with problems in sleep continuity.

Concerning the latter, our results showed that, in some cases, people diagnosed with FM respond to poor sleep quality by developing ruminating thoughts about sleep, generating fear of going to bed. Other notable responses are related to the development of negative thoughts as well as feelings of frustration and hopelessness. A repetitive thought is a well-known perpetuating factor in patients with insomnia and Galbiati et al. (311) investigated whether worry and rumination were related with subjective and polysomnographic indices of sleep disruption comparing a sample of patients with insomnia and a sample of healthy subjects. The results suggested that repetitive thought affected the subjective sleep quality in both samples. However, the results from polysomnographic measures indicated that worry and rumination affected sleep differently in the sample of patients with insomnia. Worry was significantly correlated with problems maintaining sleep, lower sleep efficiency, and decreased total sleep time, while rumination was correlated with an augmented sleep-onset latency and lower sleep efficiency. It seems that perceived stress and dysfunctional beliefs and attitudes about sleep are factors that also affect subjective sleep quality in patients with FM in comparison with healthy people according to the results of Theadom and Cropley (312). Therefore, exploring in deep the cognitive processes associated with sleep in the context of FM could be key for developing educational materials that respond to the actual needs of these patients and help them to change maladaptive sleep cognitions and to develop effective symptom management strategies.

Regarding poor sleep quality management strategies our results highlighted that people diagnosed with FM commonly reject pharmacological treatments for both improving sleep quality and dealing with daytime consequences of poor sleep quality. However, there were also participants reporting drug dependency attitudes to fall asleep. The most common worries regarding pharmacological approaches are fear of addiction and side effects. Scientific evidence demonstrated that most of the drugs prescribed in chronic pain patients with concomitant insomnia have several side effects, risk of addiction, cause premature drug withdrawal and even impact negatively on sleep measures (196). In this regard, Haack et al. (308) recently

investigated the clinical implications of pharmacological and non-pharmacological approaches for the management of the chronic pain-poor sleep quality cluster, highlighting the importance of being cautious in the prescription of sleep-disturbing medications for the treatment of chronic pain. They propose that clinicians must consider the timing of pain medication intake to reduce their detrimental effects on sleep and emphasize the importance of promoting good sleep quality in chronic pain patients through biopsychosocial interventions.

Our results also showed that, although it seems that some people diagnosed with FM have knowledge about basic principles of sleep hygiene and resort to them to improve their sleep quality, the vast majority tend to develop desperate management strategies. The latter may indicate that, at least in some cases, these patients do not receive enough information from health professionals that allow them to develop effective strategies for managing poor sleep quality.

Another important aspect to be investigated in future research involving people diagnosed with FM is if the beliefs and cognitive responses related to sleep quality affect how they manage poor sleep quality. Research including a sample of people suffering from medically unexplained symptoms, as is the case of FM, found that those people reporting greater understanding of the illness and perceiving that their symptoms are controllable were more prone to develop effective management strategies. Besides, the development of effective management strategies was correlated with less disability. However, participants showing threat beliefs associated with the illness presented a decrease in coping active responses and were more dependent on external support. Furthermore, those two aspects were significantly correlated with worse disability (313).

Consequently, educational interventions focused on changing the beliefs and cognitive responses of people diagnosed with FM regarding poor sleep quality may be essential to help them to develop effective management strategies. However, our results showed that further qualitative research comprehensively exploring how patients with FM experience and manage poor sleep quality is needed to conceptualize and contextualize sleep education interventions that respond to their needs.

Engaging in physical exercise practice could also provide an effective strategy not only for improving sleep but also in motivating patients with FM to change maladaptive lifestyle habits. In this regard, a recently published systematic review with meta-analysis (314) analyzed the effects of exercise on fatigue and sleep in FM and which type of exercise is more effective. The results suggested that including meditative exercise programs in the management of FM could provide beneficial effects on sleep quality.

Rigour

In accordance with Sandelowski and Barroso (315) and to fulfill the fifth step of a qualitative metasynthesis "Maintaining quality control" we used established methods for the methodological quality assessment (CASP approach) and the analysis of the findings (metasynthesis). The authors also employed a pre-planned and comprehensive search utilizing electronic and manual searches. Additionally, a peer-review procedure was implemented in the processes of studies screening and data extraction.

To enhance the rigor of the data analysis process two authors highlighted the participants' quotations of the included reports that were relevant for responding to the objective of this metasynthesis. Consequently, a meeting with the rest of the research team was organized to reach a consensus regarding the codes and themes that emerged, and the final transcript was modified accordingly.

Limitations of the study

This qualitative metasynthesis presents some limitations that could have affected the results obtained. The authors did not search grey literature and only included qualitative studies published in English or Spanish language, which could have precluded the inclusion of relevant research responding to the objective of this metasynthesis.

Study III. 'Sleeping is a nightmare': a qualitative study on the experience and management of poor sleep quality in Spanish women with fibromyalgia

Study III showed that the main sleep problems reported by women diagnosed with FM were those related to the initiation and maintenance of sleep, and inadequate total sleep time. They did not receive information from health care professionals about sleep in the context of FM or about how to effectively manage their sleep problems. They reported the treatment approach of most health professionals to be mainly pharmacological and unsatisfactory. Consequently, women resorted to improvised self-management strategies to improve their sleep, which were also ineffective or even detrimental to their sleep.

The results of the present study support those of previous studies in which the participants reported that the main sleep problems experienced were difficulty falling and maintaining asleep, and constantly waking up during the night (274). In fact, sleep disturbances are usually perceived as the worst symptoms of FM and a betrayal of the body (274–276).

The participants also mentioned other sleep problems that could be indicative of sleep apnea syndrome. Köseoğlu et al. (2017) observed that obstructive sleep apnea is considerably prevalent among people with FM, and that it is correlated with greater intensity of pain and severity of FM.

Similar to a previous study (274), symptoms of restless leg syndrome were also reported by our participants. Restless leg syndrome negatively affects sleep quality and quality of life in patients with FM, and some antidepressants commonly prescribed to these patients (e.g. fluoxetine, sertraline, and amitriptyline) may increase limb movement (317).

Our results confirmed the existence of two differing attitudes towards medication in FM patients: dependency and rejection. Not taking sleep medication leads to not being able to fall asleep (274,275,287,292) and patients usually complain of not having the tolerance level for the majority of drugs to treat insomnia, which makes them susceptible to the more common side effects, including falls and cognitive disturbances (273,318–320). Attitudes of rejection towards sleeping medications are primarily due to their short-term effectiveness or lack of effectiveness (274). A recent article in Spain demonstrated that patients with FM are unsatisfied with the pharmacologic treatments received because these treatments do not provide clinical benefits even when the patient is overtreated (318,319).

Participants in the present study attempted to find a balance between medication benefits and side effects. For example, some took melatonin or valerian supplements. The available evidence shows a positive effect of melatonin on FM symptoms (318). Similar to other studies, one strategy used by the participants was to take medication occasionally, as a last resort only when they felt it was absolutely needed, and even if the medication caused side effects (272). For example, taking painkillers during the day could allow them to perform activities of daily living without pain (271), and painkillers can help participants to fall asleep during the day (288).

With regards to self-management strategies used by participants, some were in line with the principles of cognitive-behavioral therapy for the treatment of insomnia, such as establishing regular sleep schedules, obtaining physical exercise, practicing relaxation techniques, avoiding naps, and not drinking coffee after noon (321). Although organizing regular sleep schedules is a common strategy, it is known to generate anxiety (274,293). One strategy that emerged in our study that has not been reported in previous studies was using cervical pillows or articulated beds to reduce pain during the night.

Getting out or staying in bed were the two main strategies for returning to sleep when experiencing awakenings during the night, and one previous study indicates that patients could try to avoid developing attitudes of rejection towards the bed when they got out of bed (274). However, our results identified other strategies not found in previous literature, such as watching television, listening to music or the radio, using the computer, avoiding overthinking, drinking a hot beverage, praying, and applying topical ointments for pain.

Daytime rest and relaxation came up as a strategy to cope with the consequences of poor sleep quality. This finding was in line with those of previous qualitative studies (274,275,287,288). In the present study,

participants also mentioned drinking stimulants and taking ginseng to perform their activities of daily living with more energy.

Participants reported that physical activity acted as a moderator of sleep quality. In line with our results, Borges-Cosic et al. (2019) revealed that women diagnosed with FM who showed lower sedentary time and greater engagement in daily physical activity had better sleep.

With regards to beliefs about the cause of their sleep problems, the participants mentioned ageing, menopause, and stress, among other factors. It has been observed that ageing is related to dysregulation of neurotransmitters implicated in the regulation of sleep-wake cycles, such as orexin, adenosine, galanin, and serotonin, a degeneration of the white matter, and a dysfunction of the suprachiasmatic nucleus, which could lead to sleep disturbances (274). In the present study, the participants perceived that the initiation of their sleep problems coincided with menopause. A recent systematic review found that in 65% of the cases, FM is diagnosed after menopause and that sleep problems linked to menopause may be predisposing factors for the development of FM. The rapid hormonal decline after surgical menopause is also associated with FM symptoms, including poor sleep quality (323).

Although the role of stress as an underlying mechanism for developing sleep problems in the context of FM is still open for scientific debate, high levels of perceived stress are correlated with greater sleep disturbances and poorer daily function in patients with FM (312).

Similar to the present study, other studies have demonstrated that poor sleep quality is also perceived as negatively affecting other symptoms of FM, such as pain, fatigue, and cognitive function (271,272,274,275,285,287,289). Available scientific evidence (324) indicates that pain and sleep interact in a bidirectional manner; patients with greater pain intensity experience more sleeping problems and vice versa. However, one previous study suggests that poor sleep quality affects pain more than pain affects sleep (131).

Additional consequences not found in the present study include changes in eating behaviors (285,325), symptoms flare-ups (290) and an impaired ability to manage other symptoms (274). Participants in the present study reported that poor sleep quality also worsens stiffness, quality of life, and general health status, which were not observed in previous qualitative studies. Because of these negative consequences, sleep problems affect the functional capacity of patients with FM in the workplace, which causes them to experience anxiety and a feeling of constant failure (274).

It is well understood that poor sleep quality generates negative responses, such as feelings of helplessness, despair, and frustration (274,275,277); the present study adds to the previous knowledge that not being able to sleep can even provoke suicidal thoughts. Participants in other studies expressed hatred towards their health condition, and the inability to satisfy their sleep needs was a major contributing factor to this feeling (275). Previous studies have also demonstrated fear of not sleeping or even going to

the bed (274,276). The original contribution of the present study is related to catastrophic thoughts regarding the consequences of poor sleep quality in the future. In line with our results, other studies have demonstrated that it is common among patients with FM to be resigned to sleep disturbances (276). This attitude could be used by patients as a strategy to cope with FM limitations (326,327).

One of the main findings of the present study is that participants expressed the need to receive more information about sleep in the context of FM and advice on how to manage poor sleep quality. The latter can explain why patients with FM look for information on the internet or other sources of information that may be unreliable and negatively affect how they manage poor sleep quality. In this regard, the European League Against Rheumatism recommends patient education as an initial approach to the management of FM (189). However, education interventions for sleep problems are very limited in chronic pain management programs (196).

Patient education about sleep should be an essential part of the treatment of FM and, therefore, health care professionals should include this education in their daily clinical practice (328). However, carrying out education interventions in medical consultation is, in most cases, non-viable, given the evident time restraints that accompany health care practice (329,330). Web-based education interventions could be useful tools for educating patients without consuming time during consultations (278).

Study IV. Patient Reported Outcome Measures of Sleep Quality in Fibromyalgia: A COSMIN Systematic Review

Study IV aimed to describe the available PROMs for assessing sleep quality in people diagnosed with FM and to present and analyze their psychometric properties. A total of 7 studies (249,277,289,295–298) and 5 PROMs were included in this systematic review: 1) Pittsburgh Sleep Quality Index, 2) Jenkins Sleep Scale, 3) Sleep Quality Numeric Rating Scale, 4) Medical Outcomes Study-Sleep Scale, and 5) Fibromyalgia Sleep Diary. All of the included studies presented low RoB for the analyzed psychometric properties according to the COSMIN RoB checklist, indicating very good methodological quality (283). Likewise, the quality of the results ranged from moderate to high in accordance with the established COSMIN standards (281). Although not all of the included studies conducted an analysis of the content validity of the PROMs, this systematic review found that the concept of sleep quality in the context of FM is homogeneous across included studies.

The PSQI showed high quality results for internal consistency, test-retest reliability, and hypotheses testing. For the JSS, the results were high quality for internal consistency and responsiveness and moderate for criterion validity and test-retest reliability as some of the items analyzed did not achieve the minimum pre-established standards. The SQ-NRS showed high quality for content validity, criterion validity, test-retest reliability, and responsiveness. For the MOS-SS, the results for structural validity,

content validity, internal consistency, and test-retest reliability were rated as high quality. With regard to the FSD, the authors analyzed only the content validity, which demonstrated high quality results. Therefore, the PSQI, the JSS, the SQ-NRS, and the MOS-SS present satisfactory psychometric properties and are valid and reliable tools for assessing sleep quality in the context of FM.

Interestingly, the FSD is the only PROM specifically developed for evaluating sleep quality in patients with FM and is also the only one in which the psychometric properties were not analyzed. The latter highlights the need for future studies investigating if the FSD is a valid and reliable PROM in the context of FM.

In the context of clinical practice the SQ-NRS is likely the most adequate measure for a rapid visual analogue scale-format evaluation of global severity of poor sleep quality, due to time restraints that usually accompany healthcare practice (329,330). However, because the subjective perception of poor sleep quality in people diagnosed with FM is associated with alterations to different aspects of sleep (e.g., problems falling and staying asleep), tools allowing for a more comprehensive assessment of those sleep aspects could provide valuable information on how poor sleep quality impacts the general health of patients with FM and guide the development of more individualized treatment approaches. The PSQI, the JSS, and the MOS-SS permit the assessment of various components of sleep during the month prior to their completion, which provides concrete information on those aspects of sleep that are most affected.

At the research level, using valid and reliable PROMs for sleep quality in the context of FM could improve the quality of the studies' results and increase knowledge of the relationship between poor sleep quality and other FM symptoms. Moreover, when investigating new treatment approaches, using PROMs for sleep quality that have been validated in people with FM could provide more reliable conclusions about their effectiveness (10). Although the SQ-NRS is as valid and reliable as the other included PROMs, using tools such as the PSQI, the JSS, and the MOS-SS which permit a more comprehensive evaluation of sleep quality could provide more accurate information on the effects of new interventions on specific sleep quality aspects and how these aspects relate with other FM symptoms. In this regard, the PSQI is the most widely used PROM among the existing literature in the field of FM providing relevant information about both the relationship of poor sleep quality to other symptoms of this health condition (11,324,331) and the effects of different treatment approaches (332–335).

CONCLUSIONS

The conclusions derived from the studies included in the present research document are:

- The Symptom Management Theory provided a well-founded framework to conceptualize poor sleep quality in the context of FM from a biopsychosocial perspective. Integrating the domains of "symptom experience", "management strategies", and "outcomes" of the theory helped to comprehensively understand how women diagnosed with FM evaluate and respond to poor sleep quality, how they manage this symptom and their perceptions of the treatment approaches provided by health care professionals. Likewise, the Symptom Management Theory provided guidance to identify the needs of women diagnosed with FM to develop effective management strategies to cope with poor sleep quality.
- For people diagnosed with FM the most important aspects of sleep that contribute to define good sleep quality are those related to sleep continuity, perception of disengagement from the environment and waking up feeling refreshed in the morning. Poor sleep quality is perceived as a severe symptom of FM and the most troublesome problems are those related with the initiation and maintenance of sleep throughout the night -indicating the experience of a fragmented sleep- as well as not having a satisfactory total sleep time. Another aspect that highlights the severity of poor sleep quality in the context of FM is the perceived impact on other symptoms commonly associated with FM such as pain, fatigue, poor functionality, mood states alterations and cognitive problems. Particularly, it seems that the most complex relationship for people diagnosed with FM is that of poor sleep quality with fatigue and pain. In addition, people diagnosed with FM respond to poor sleep quality developing ruminating thoughts about sleep, generating fear of going to bed. Other relevant responses are related with the development of negative thoughts as well as with feelings of frustration and hopelessness.
- Women diagnosed with FM perceive that they did not receive enough information from health care professionals about sleep in the context of FM, nor about how to effectively manage their sleep problems, being their approach mainly pharmacological and unsatisfactory. As a consequence, women resort to improvised self-management strategies trying to improve sleep quality, which are also ineffective or even detrimental for sleep quality. In addition, this research revealed that receiving more information about poor sleep quality in the context of FM and being educated on how to develop effective management strategies is an essential need for women suffering from this health condition. Therefore, the results could be useful for healthcare professionals that include sleep education when assisting women with FM and will help for future research to develop patient education interventions aimed at changing the cognitive and

behavioral factors that are causing or maintaining poor sleep quality in people diagnosed with FM.

- The Patient-Reported Outcomes Measures for assessing sleep quality in people diagnosed with FM are valid and reliable. However, this subject remains a vital field of research as none of these tools reported the complete list of psychometric properties established in the COSMIN guidelines. In particular, the Fibromyalgia Sleep Diary, which is the only Patient-Reported Outcomes Measure specifically developed for people diagnosed with FM, should be analyzed for its validity and reliability in future studies.

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