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Impact of physical therapy techniques and common interventions on sleep quality in patients with chronic pain: A systematic review

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ABSTRACT

This systematic review aims to find effectful healthcare strategies, with special focus on drug-free interventions and physical therapy, as part of the treatment for sleep in patients with chronic musculoskeletal pain. Data search was conducted across seven scientific databases. This review is deposited in the Prospero International prospective register of systematic reviews (CRD42023452574). Seventeen RCTs from different healthcare fields complied with our inclusion criteria. Two RCTs investigated manual therapy, five RCTs therapeutic exercise, one RCT Fu's subcutaneous needling, two RCTs physical agents (one on balneotherapy and one on cryo-stimulation), two RCTs cognitive-behavioral therapy, and four RCTs pharmacological therapy and their effect on sleep quality and/or quantity in patients suffering from chronic pain. We included the four RCT's in this systematic review with the purpose to be able to compare natural interventions with allopathic ones. As allopathic interventions are more prone to have secondary negative effects than physical therapy, compare the two types of interventions could be in favor of choosing the most effective treatment with the least secondary negative effects. Additionally, two RCTs on neurofeedback and limbic neuromodulation were also included. The results of the included studies suggest that strategies such as manual therapy, therapeutic exercise, Fu's subcutaneous needling, balneotherapy, cryo-stimulation, neurofeedback, limbic neuromodulation, cognitive-behavioral therapy, and pharmacological therapies have positive effects on patients suffering from chronic pain and sleep disturbances, especially when they suffer musculoskeletal pain. Secondary negative effects were found for the possible overuse of certain medicines such as morphine, a huge problem in the United States. Sleep deficiency is an independent risk factor for many diseases, including chronic pain syndrome and therefore more studies are needed to find non-toxic interventions for people suffering sleep disorders associated with systemic diseases and pain.

Table of Acronyms/Abbreviations

BPI-SF	Brief pain inventory-shot form.
CNS	Central nervous system
CBT	Cognitive Behavioral Therapy.
HPA	Hypothalamic-Pituitary-Adrenal Axis.
ISI	Insomnia severity index.
IVP	Internal validity score.
MPQ	McGill pain questionnarie
MeSH	Medical subject headings.
MET	Muscle energy technique
NREM	Non-rapid eye movement.
NRS-11	Numeric rating scale for pain
PSQI	Pittsburgh sleep quality index.
PICO	Population, intervention, comparison and outcomes
PRISMA	Preferred reporting items for systematic reviews and meta-analyses.
ROM	Range of motion
RCT	Randomized controlled trial
REM	Rapid eye movement.
TENS	Transcutaneous electrical nerve stimulation.
VAS	Visual analog scale.

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1. Introduction

Sleep is a physiological and behavioral phenomenon characterized by a transient, periodic, and reversible decrease in the level of consciousness, accompanied by reduced responsiveness to external stimuli and associated with beneficial effects on the brain and all essential organs [1]. Borbely's model explains the latency, duration, organization, and quality of sleep [2]. It consists of a homeostatic process that corresponds to the need for sleep and the circadian rhythm associated with the control of the sleep-wake cycle by a biological clock [3].

Sleep is divided into two types. Non-Rapid Eye Movement (NREM) sleep is characterized by slow oscillations, sleep spindles, K complexes, and delta waves. Conversely, Rapid Eye Movement (REM) sleep is characterized by abundant brain activity and high blood flow, along with mixed-frequency and low-amplitude activity [2].

Various epidemiological studies have observed that poor sleep quality is a key factor for individuals suffering from chronic pain, such as fibromyalgia (FM) [4]. There is a strong association between the symptoms of FM, particularly pain, and sleep disturbances [5]. Sleep disturbances have been found to both contribute to and result from immune-neuro-endocrine disorders [6], which are also associated with the presence of chronic pain in general [4].

The circadian rhythm normally follows the light/dark cycle and is regulated by the endogenous biological clock located in the suprachiasmatic nucleus (Process C). Process C is influenced by our sleep/wake rhythm (Process S) as consequence of daily behavior. Process S and Process C, if in phase, produce physiological sleep pressure and optimal sleep physiology, giving rise to brain drainage, repair of tissues and regulation of the immune system. Both brain and immune system need non-REM sleep for the maintenance and further development of cognitive and immunological memory [7]. Modern life is characterized by exposure to excessive artificial light, social jet lags, jet lags and sometimes night shift. These factors can have prolonged negative effects on the circadian clock and clock disturbances can have severe negative health consequences, including the development of chronic musculoskeletal pain. The latter can be explained by the fact that circadian rhythm disruptions lead to an increase in excitatory glutamate activity, resulting in long-term pain potentiation and heightened sensitivity to pain [8].

Sleep disturbances encompass both sleep quality and disorders. Sleep quality refers to a multifactorial process encompassing both sleep duration and depth [9]. Sleep disorders are conditions that involve both subjective and objective symptoms, such as insomnia disorders, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, sleep-related movement disorders, parasomnias, and other sleep disorders [10].

There is substantial evidence supporting the association between chronic pain and sleep, as constant pain affects wakefulness and, consequently, sleep quality [11]. Hence, there is a close relationship between chronic pain and insomnia, and sustained sleep restriction further diminishes emotional and physical well-being, leading to depression, chronic fatigue and anxiety in many patients [12].

The opioid system, involved in the acute stress response, immune-emotional function, and pain modulation [13], is hypothesized to experience a reduction in opioid receptors in the Central Nervous System (CNS) when pain becomes chronic, leading to decreased pain inhibition [14]. Studies with rodents have demonstrated that the effects of the μ-opioid agonist morphine and enkephalinase inhibition result in a decline in analgesia over time, accompanied by REM sleep deprivation [15]. The monoaminergic system, consisting of dopamine, norepinephrine, and serotonin, is closely related to endogenous pain inhibition, analgesic effects, and direct involvement with inflammatory mediators. It is important to note that serotonin promotes wakefulness and inhibits REM sleep. The role of norepinephrine in wakefulness and its influence on the sympathetic system should also be emphasized [16].

The hypothalamic-pituitary-adrenal (HPA) axis, known for its role in the acute stress response and regulation of various physiological processes, is intricately involved in this complex interplay.

The hypothalamic-pituitary-adrenal (HPA) axis is partly responsible for the response to physical and psychological stress. The axis is closely linked to the immune system through the hormone cortisol, which inhibits the production of proinflammatory cytokines. In patients with chronic musculoskeletal pain, such as FM, dysfunction of the HPA axis has been found, leading to a weakened immune system and resulting in a state of low-grade inflammation [16]. Various studies demonstrate that sleep deficits lead to increased cortisol levels and dysregulation of the HPA axis in patients with FM, subsequently leading to low-grade inflammation [17,18].

Strategies to improve sleep can be both pharmacological and psychological. Often pharmacological interventions have negative secondary effects, whereas psychological treatment of sleep disorders is time and money consuming. Less toxic and faster interventions are needed and perhaps physical therapies could fill up the treatment gaps.

1.1. Main objective

To conduct a review of the current scientific literature on physical therapy focused healthcare strategies used as part of sleep treatment and their impact on patients with chronic musculoskeletal pain.

1.1.1. Secondary objective

To compare scientific information on the association between chronic pain and sleep, as well as to examine the methodological quality of the studies included in the review.

2. Methodology

2.1. Study design

This review included only studies with a clinical trial design. To ensure higher methodological quality, the PRISMA guidelines were followed as a reference for systematic review models [19]. Additionally, the PEDro scale, including the Internal Validity Score (IVS), was employed to assess the quality of clinical trials [20]. The literature review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO: CRD42023452574)

2.2. Sources of information and search strategy

The bibliographic search commenced on October 15 and concluded on December 24, 2022. Seven electronic databases were used to extract articles: Pubmed, CINAHL, Web of Science, Cambridge Core, Scopus, and Oxford Academy.

The search strategy was designed based on the PICO research questionnaire.

Intervention: Implementation of health care approaches such as physiotherapy with the following techniques: manual therapy, therapeutic exercise, subcutaneous puncture, physical agents (balneotherapy and cryoelectro-stimulation), cognitive-behavioral therapy, neurofeedback and limbic neuromodulation, psychology, and pharmacological therapy to reduce chronic musculoskeletal pain and simultaneously improve sleep quality or alleviate sleep disorders.

Comparison: Application of different treatments, including physical therapy techniques, psychology, and pharmacological therapies. The following variables were measured: Fatigue, chronic musculoskeletal pain, sleep quality, insomnia, depression, and anxiety.

Outcome: After the combined application of physiotherapeutic, psychological, and pharmacological treatments, a significant reduction in chronic musculoskeletal pain and improvement in sleep quality can be observed in patients suffering from both conditions.

Search strategies in the different databases are reflected in suppl. Material 1 (Table S1).

2.3. Study selection

2.3.1. Inclusion criteria

The inclusion criteria were as follows: Published from 2015 to 2022; clinical trials with free access and allowed by the University of Granada; adult individuals aged 18 years or older; experiencing chronic musculoskeletal pain and/or sleep disturbances or poor sleep quality.

2.3.2. Exclusion criteria

The exclusion criteria were as follows: Duplicates in the database; not meeting the inclusion criteria; studies focusing on patients with oncological pathology.

2.4. Article selection

The search yielded approximately one hundred thousand scientific articles on our study purpose. However, most trials solely focus on pain or sleep, independently and not combined. Only a few clinical trials, from a physical therapy perspective, address the interrelation between sleep and chronic musculoskeletal pain and the way improvement in one could improve the other. Data were so scarce that we decided to add psychological and medical interventions to our selection.

Then, two reviewers conducted an initial evaluation individually, beginning with a review of the titles, followed by a more comprehensive assessment involving both the titles and abstracts of the remaining studies. Subsequently, the complete texts of the articles that seemed to align with the inclusion criteria were meticulously reviewed. Oversight of the reviewers' decisions was entrusted to a third reviewer. The final number of selected studies included 17 clinical trials. Therapies varied from manual therapy, therapeutic exercise, Fu's subcutaneous puncture, balneotherapy, cryostimulation, neurofeedback, via limbic neuromodulation, cognitive-behavioral therapy, up to pharmacological therapies (duloxetine, pregabalin, buprenorphine, and naloxone).

2.4.1. Evaluation of methodological quality of RCTs

The methodological quality of RCTs has been assessed using the PEDro scale, translated and adapted to Spanish by Antonia Gómez-Conesa. This scale measures the internal and external quality of the trials. It consists of 11 items, each worth 1 point, except for item number 1, which is not counted as it assesses external quality. Thus, the overall score ranges from 0 to 10. Additionally, the internal quality of the clinical trials has been evaluated using the Internal Validity Score (IVS). This score belongs to the PEDro scale, and items 2, 3, 5, 6, 8, and 9 are scored [20].

2.4.2. Evidence quality

The tool used to assess the quality of evidence from the results reported by studies is the Grading of Recommendations, Assessments, Development and Evaluation (GRADE) system. This system defines the quality of evidence as the degree of confidence we have that the estimation of an effect is adequate to make a recommendation. The evaluation of evidence quality includes the risk of bias in studies, inconsistency, imprecision, publication bias, indirect outcomes, and other factors that may influence evidence quality.

2.4.3. Data extraction

For the data extraction, the PICOS strategy was employed. Data regarding the included articles were extracted, such as study characteristics (author, publication year and study design type), sample characteristics (size, age, gender), intervention characteristics (intervention type, sets, duration), and key outcomes (assessment tools, follow-up procedures, and intervention results).

2.5. Bibliography management

Literature has been managed through Mendeley.

3. Results

3.1. Article selection

The search was conducted in the 7 mentioned databases, yielding 542,648 articles. Trials that did not meet the inclusion criteria were eliminated. This review includes 17 clinical trials. The selection process is summarized in Fig. 1 using a flowchart according to the guidelines and criteria established by the PRISMA scale [19].

3.2. Methodological quality

The quality of the selected articles has been evaluated based on the PEDro and IVS scales, and the GRADE system, which are summarized in Supplemental Tables S2 and S3.

3.3. Study characteristics

The studies included in this review comprised of 17 articles [21–37]:

Nadal-Nicolás et al., 2020 [21]. The aim of this study was to assess the efficacy of moderate pressure manual therapy in women with fibromyalgia. The intervention involved treating the posterior neck musculature with digital pressures for 4 weeks. Two sessions were conducted per week, with a 48-h interval between them. The duration of each treatment session was 15 min.

Akodu et al., 2021 [22]. The purpose of this study was to evaluate therapeutic exercises for chronic neck pain. The exercises focused on neck stability and include a battery of Pilates-based exercises, isometric exercises, and neck stabilizer exercises.

Huang et al., 2022 [23]. The purpose of this study was to evaluate the effects of the FSN technique on people suffering from neck pain. The technique was applied on the forearm. The rocking time and frequency are set at 50 swings for 30 s each. Afterward, participants are asked to shrug their shoulders and lift their head for 10 s, followed by a rest. The cycle is repeated 3 times, with each cycle lasting 2 min.

Wiklund et al., 2018 [24]. The intervention was based on physical exercise and acceptance and commitment therapy. Physical exercise consisted of 1 h per day of aerobic exercise, twice a week, with minimal 2 resting days between sessions. Workload was progressive. The first part of the exercise program consisted of 30 min of resistance, coordination, functional strength, and flexibility exercises. The second part, also lasting 30 min, focuses on specific strength exercises for the back, neck, lumbar region, abdomen, shoulders, and arms. The acceptance and commitment therapy component involved 1 weekly session lasting 2 h each and during seven weeks, including lectures, role-playing, and mindfulness exercises.

Rapolienė et al., 2020 [25]. The study investigated the impact of different types of bathing on muscle pain. Mineralized bathing was compared with tap water bathing and doing nothing. Bathing lasted 20 min per session, 5 days a week, and 2 weeks in a row.

Mccrae et al., 2019 [26]. Cognitive-behavioral therapy was used for patients with chronic insomnia and fibromyalgia and the impact on sleep and pain. The therapy consisted of 8 sessions of 50 min each.

Sarmento et al., 2020 [27]. The intervention in this trial involved Qigong exercises, which consist of deep diaphragmatic breathing synchronized with upper body movements and accompanied by healing sounds meditation. The total duration of the intervention was 25 min per session.

Varallo et al., 2022 [28]. This trial compares conventional rehabilitation (exercise classes and physical therapy) with conventional

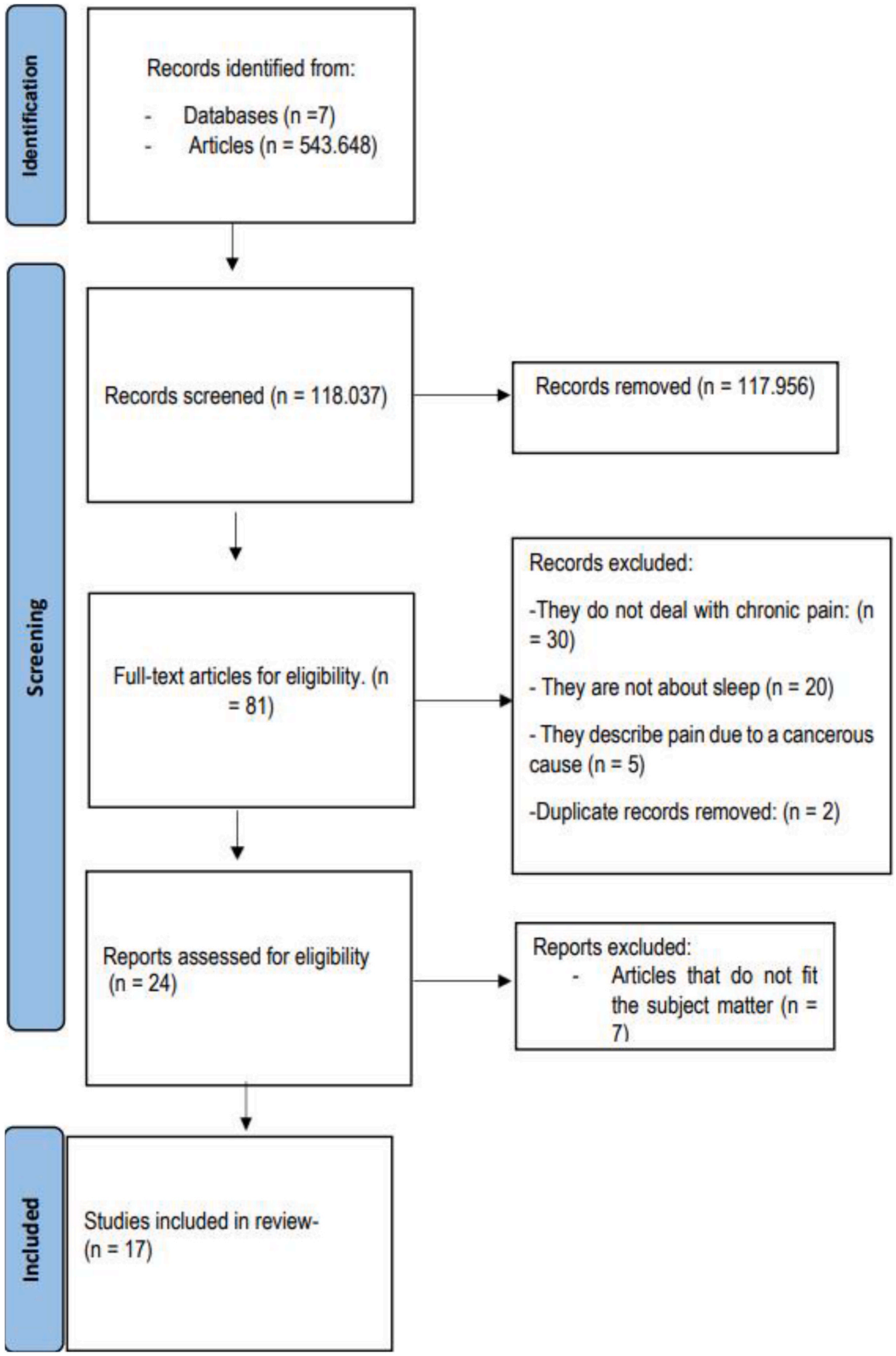

Fig. 1. Flow diagram.

rehabilitation plus cryostimulation sessions, lasting 2 min at a temperature of −110 °C, for patients with fibromyalgia and obesity. Additionally, they engaged in the use of a controlled hypocaloric diet.

Gilron et al., 2016 [29]. The effects of duloxetine and pregabalin use during 42 days on symptoms in patients with FM were investigated and compared with a placebo group.

Hadamus et al., 2021 [30]. Swedish massage on levator scapulae, lower trapezius fibers, neck erectors, and head erectors was performed in both groups as basic treatment. The experimental group received relaxation exercises as added intervention. The massage was administered for 2 weeks, with a total of 10 sessions. The duration of each session was approximately 30 min.

Berry et al., 2015 [31]. Randomized controlled clinical trial with an experimental group undergoing a cognitive-behavioral intervention focused on a 15-min didactic session on improving sleep, and a control group with no intervention. Sleep latency improved in the experimental group.

Goldway et al., 2019 [32]. Limbic neuromodulation, which includes an auditory interface and/or a 3D animated stage interface, was applied to a group of patients with FM and effects were compared with a control group.

Yarlas et al., 2016 [33]. Skin patches that delivered an average dose of 5, 10, or 200 mg/h of buprenorphine over 7 days for a period of 12 weeks, were used in patients with chronic low back pain and compared with a placebo group.

Wu et al., 2021 [34]. 20 Neurofeedback sessions were applied in a group of fibromyalgia patients. Each session lasted for 30 min, with 5 sessions conducted over 4 weeks and a follow-up period of 24 weeks. The first four sessions used alpha brainwaves, and the subsequent ones used sensorimotor rhythm brainwaves of 8Hz–12Hz. In the last four sessions, patients could choose their preferred brainwave type.

Block et al., 2015 [35]. Intrathecal morphine along with naloxone was administered to two groups, while the third group received a placebo.

Ahmed et al., 2016 [36]. Milnacipran or placebo in progressive doses (12.5 mg, 25 mg, and 50 mg) was used in a group of patients suffering from FMS over a period of 4 weeks.

Roseen et al., 2020 [37]. This triple clinical trial intervention had a duration of 12 weeks of treatment followed by a 40-week maintenance phase. It consists of two separate therapies: yoga (12 classes of 75 min each) and therapeutic exercise (15 classes of 60 min each). 127 patients with chronic low back pain performed yoga postures, breathing exercises, relaxation, and meditation. The therapeutic exercise group consisted of 129 patients engaging in aerobic exercise. The control group, comprising 64 patients, received pain reeducation and sleep problem resolution, with 15 classes of 60 min each.

Table 1 displays the main characteristics of the RCTs, such as the study type, group characteristics, intervention performed, variables, control/placebo groups and obtained results.

3.4. Results of studied interventions on pain and sleep in patients with chronic pain and specially suffering from FMS

3.4.1. Pain

Manual therapy showed a significant reduction in pain perception in women suffering from FM [21]. Pilates exercises and neck stabilizing also seems effective in pain reduction [22] and the same holds for the use of combined diaphragmatic breathing exercises, upper body movement and meditation in FM patients [27]. Subcutaneous Fu needling on the forearm significantly decreases pain in people suffering from chronic neck pain [23]. Balneotherapy with mineral essences has been shown to considerably reduce muscular pain [25]. Improvement in pain severity is demonstrated in patients with fibromyalgia after an intervention of exercise and cryostimulation, compared to exercise rehabilitation alone [28]. Cognitive-behavioral therapy appears to improve morning pain in patients with chronic insomnia and fibromyalgia [26,31]. Combined administration of pregabalin with duloxetine improves pain in patients, without affecting sleep patterns [33]. In patients receiving morphine for chronic pain, naloxone is added to avoid dosage overload. Positive results are observed in pain improvement, although not highly significant. The potential negative factor is excessive medication [35]. Limbic neuromodulation seems to be effective in reducing pain in patients with fibromyalgia within 90 min [32]. Another trial demonstrates its effectiveness in addressing all aspects of pain experienced by individuals with fibromyalgia [34]. In resume, all studies show significant positive effects of both physical, psychological and pharmacological interventions in patients suffering from chronic pain. This means that future studies should focus on the type of patient that is sensitive to the different treatment options.

3.4.2. Sleep

Sleep was not improved with manual therapy in patients suffering from FM [21]. Persons suffering from chronic neck pain do benefit from manual therapy as it optimizes sleep latency and reduces alterations in sleep [30]. Exercise therapy is another valid approach for addressing sleep issues. Better control of sleep disturbances is achieved through neck stabilizer exercises and isometric exercises. Qigong exercises result in improved sleep quality [27]. In another study involving patients with chronic low back pain [37], both yoga and aerobic exercise showed positive results in sleep quality. Additionally, positive results were observed in addressing insomnia in another study [24].

Regarding physical agents, mineralized water baths appear to be effective in improving sleep quality [25]. Low post-exercise cold exposures have been shown to enhance sleep quality compared to exercise alone [28]. Cognitive-behavioral therapy for chronic insomnia in patients with fibromyalgia yields good results, improving sleep onset latency, and lasting for 6 months [26,31].

In this clinical trial with patients receiving morphine, once again, the bidirectional relationship between chronic pain improvement and sleep quality improvement was observed [35]. Milnacipran has not been found to be useful in treating sleep issues in patients with fibromyalgia [36].

3.4.3. EVIDENCE quality

The quality of evidence in this review is moderate. The assessment has been largely based on the risk of bias of the included trials and their outcomes. For more detailed information, please refer to Table S4 in the supplementary material.

4. Discussion

The objective of this study was to find healthcare strategies with beneficial effects on sleep of patients suffering from chronic musculoskeletal pain and 17 RCTs complied with our inclusion criteria.

The studies examined were primarily focused on treating fibromyalgia, generalized chronic muscular pain, chronic neck pain, chronic lower back pain, and long-standing insomnia in patients with chronic musculoskeletal pain.

These clinical trials employed various therapies, including manual therapy, therapeutic exercise, Fu's subcutaneous puncture, cognitive-behavioral therapy, balneotherapy, cryostimulation, pharmacological treatments, limbic neuromodulation, and neurofeedback.

Regarding the trials targeting women with fibromyalgia treated with manual therapy, it was concluded that a painless massage with gradually increasing intensity, lasting for 15 min in multiple sessions, was beneficial in alleviating pain [21].

In studies conducted with patients suffering from chronic neck pain and treated with manual therapy involving painless massage sessions of progressive intensity lasting for 30 min each, it was determined that this approach achieved increased blood circulation, better oxygenation, improved mobility, greater muscle relaxation, and a reduction in the intake of analgesics to alleviate pain, which, in parallel, was accompanied by improvements in sleep quality and a decrease in sleep latency [30]. It appears essential to comprehensively address the evaluation of patients with chronic neck pain associated with sleep disorders, as there is a direct influence between both conditions, whether it be causative or consequential [38]. These trials support a positive influence on sleep by alleviating chronic muscular neck pain [39].

Pilates and neck stabilizing exercises, demonstrated improvement of overall body strength, CORE stability by strengthening abdominal and lumbar muscles, glutes, and deep spinal muscles. Pain reduction, improved circulation, relaxation, and, consequently, an improvement in sleep disturbances were the ultimate effects of these interventions [22,39].

The combined use of therapeutic exercises, gentle body movements, deep diaphragmatic breathing, and meditation with synchronized sound emission during 25-min sessions showed both subjective improvements of symptoms and biochemical parameters such as *C*-reactive protein [27]. This combined approach significantly reduced pain, stiffness, fatigue, and anxiety while enhancing sleep quality. Such positive effects may be attributed to the regulation of the HPA axis and modulation of the autonomic system, which helps to regulate and reduce inflammation, thereby alleviating pain [40].

However, in patients with chronic insomnia, it remains uncertain whether therapeutic exercises can effectively reduce symptoms. While some positive results have been reported, the scientific literature lacks conclusive evidence regarding the optimal frequency, intensity, duration, and specific type of therapeutic exercise most suitable for

Table 1
Development of the general characteristics of the selected studies.

Author	Year	Type of study	Experimental Group	Control Group	Interventions	Variables	Results
Nadal-Nicolás et al. [21]	2020	Randomized clinical trial	Number of people: 14 people. Average age: 53 ± 6 Sex: Female Pathology: Fibromyalgia	Number of persons: 10 persons Average age: 53 ± 6 Sex: Female Pathology: Fibromyalgia	Experimental group intervention: Moderate digital pressure massage on the dense connective tissue on the back of the neck. Control group intervention: Ultrasound performed without conductive gel and with the machine turned off in placebo mode.	Fatigue. Fatigue severity scale. Chronic musculoskeletal pain. Visual analog scale Sleep. Pittsburgh Sleep Quality Index.	Treatment with manual therapy: - Decreased chronic pain perception. - Fatigue was not reduced. Sleep and mood were positive, but not significant
Akodu et al. [22]	2021	Single blind randomized controlled tria	Number of people. Group of neck stabilization exercises: 17 Pilates group: 14 Pathology: Chronic neck pain.	Number of persons:14 Pathology: Chronic neck pain	Experimental group: Neck stabilization exercise group. Pilates exercises group. Control group: dynamic isometric neck exercise.	Chronic pain. Descriptive scale used to represent various levels of pain (NPRS-11). Sleep. Insomnia severity index (ISI).	Statistically significant improvement in sleep disturbance in the neck stabilization and Pilates exercise groups. In addition to a significant effect on chronic musculoskeletal neck pain.
Huang et al. [23]	2022	Randomized controlled trial	Number of patients: 30 Age: 52.73 ± 9.81 Gender, male/ female, number %: 10/20 (33 %/67 %) EVA (0–10): 5.95 ± 1.36 Pathology: Chronic neck pain	Number of patients: 30 Age: 52.16 ± 16.10 Gender, male/ female, number %: 8/22 (27 %/73 %) EVA (0–10): 6.71 ± 1.80 Pathology: Chronic neck pain	Experimental group: Fu subcutaneous puncture (FSN) treatment in the radial region of the extensor forearm muscle. Time and frequency of swinging were 50 times 30 s. Then they were asked to shrug their shoulders and raise their head 10 s and then rest. The cycle was repeated 3 times for 2 min. Control group: Treated with TENS. Connected in forearm for 20 min.	Pain intensity. Visual analog scale (VAS) Pressure to pain, myofascial trigger points. Pressure Algometry Sleep quality. Pittsburgh Sleep Quality Index	The results showed that FSN had significant benefits in VAS and sleep quality at 15-day follow-up compared to TENS treatment.
Wiklund et al. [24]	2018	Randomized controlled trial	Number of patients: 99 Age: 18–60 years. Chronic pain >3 months neck, low back and/or generalized pain. Pathology: Insomnia	Number of patients: 100 Age: 18–60 years. Chronic pain >3 months neck, low back and/or generalized pain. Pathology: Insomnia	Experimental group. Cognitive behavioral therapy group. Group treatment. 7 weekly sessions. 2h combination of lectures and experiential exercises: Role playing and mindfulness. Focus: Chronic pain and stress. Group Exercise. For 8 weeks. 1 h of exercise. 2 times per week. 2 days between sessions, rest. Same time of day. Focused exercise: neck, lumbar region and larger muscle groups. Training consists of: 30 min of group exercise and 30 min of exercise by stations. Control Group. Once a week. 2 h. For 7 weeks. Pain related topics to discuss patients' experiences.	Insomnia. Insomnia Severity Index (ISI). Pain intensity. Numerical rating scale (NRS-11)	Los grupos experimentales obtuvieron un efecto positivo sobre el insomnio en comparación con el grupo control y dicho efecto se mantuvo después de 12 meses. Se redujo el dolor significativamente tanto para el ejercicio como para el grupo control, pero no para terapia cognitiva conductual (ACT-bsm).
Rapolienė et al. [25]	2020	Single-blind randomized controlled study	Number of patients: 145 Age: 18–65 years old No history of diagnosed disease Have self-reported musculoskeletal pain of at least 1 point according to VAS	Number of patients:25 Age:18–65 years. No history of diagnosed disease Have self-reported musculoskeletal pain of at least 1 point according to VAS.	Treatment period 2 weeks. Follow-up period 3 months. Action protocol. 20 min daily 5 days a week Experimental group: 3 groups of water baths of different mineralization. 1 group of running water baths. Control group.	Musculoskeletal pain. EVA Sleep quality. Visual analog scale.	Both mineralized and tap baths reduced pain significantly. It had a greater effect in baths with 60 g/L mineralization. Better sleep quality was obtained with the 20 g/L and 40 g/L mineralization baths.

(continued on next page)

Table 1 (*continued*)

Author	Year	Type of study	Experimental Group	Control Group	Interventions	Variables	Results
					1 control group (without treatment)		
Mccrae et al. [26]	2019	Randomized clinical trial	Number of patients: 39 Age: Over 18 years old. Pain for at least 6 months. Pathologies: Chronic insomnia Fibromyalgia.	Number of patients: 39 Age: Over 18 years old. Pain for at least 6 months. Pathologies: Chronic insomnia Fibromyalgia.	Treatment: Cognitive-Behavioral Therapy. Number of sessions: 8 1 session lasts 50 min.	Pain. Mcgill pain questionnaire, EVA. Sleep. Polysomnography	. Significant effects on sleep quality, after sleep onset and sleep efficiency for 6 months¬. There were no significant interactions for pain and mood.
Sarmento et al. [27]	2020	Double-blind pilot randomized controlled trial	Number of persons: 10 Sex: Female Age: 18–70 years old Baseline pathology: Fibromyalgia. Body mass index: Equal to or greater than 30	Number of persons: 10 Sex: Female Age: 18–70 years old Baseline pathology: Fibromyalgia. Body mass index: Equal to or greater than 30	Grupo experimental: Movimientos corporales específicos de la técnica. Sonidos curativos. Respiración diafragmática y meditación. Grupo de control: Movimientos corporales específicos de la técnica. Sin sonidos curativos. Sin respiración diafragmática ni meditación.	Pain. McGill Pain Questionnaire and Visual Analog Scale (VAS). Sleep. Pittsburgh Sleep Quality Index. Fatigue. Fibromyalgia Impact of Fibromyalgia Revised (FIQR). Depression and anxiety. Hospital Anxiety and Depression Scale (HADS).	The 10-week Qigong exercise leads to improvements in most of the symptoms of fibromyalgia, which provided significant results: generalized pain, chronic fatigue, sleep disorders and anxiety
Varallo et al. [28]	2022	Randomized controlled trial	Number of patients: 20 Average age: 53 (18–65 years) Sex: female Body mass index: 38 Fibromyalgia diagnosed more than 1 year ago	Number of patients: 23 Average age: 56 (18–65 years) Sex: female Body mass index: 39.9 Fibromyalgia diagnosed more than 1 year ago	10 sessions during 2 weeks Rehabilitation program: 2 sessions composed of personalized progressive aerobic training, postural control exercises and progressive strengthening exercises. Duration: 60 min Individual nutritional intervention. Balanced hypocaloric diet: 18–20 % protein, 27–30 % fat, 50–55 % carbohydrates; 30g of fresh vegetable fibers. Energy distribution: breakfast 20 %, lunch 40 %, dinner 40 %. Experimental group. Intervention all of the above + cryostimulation. First session 1 min (−110 °C). Second session 2 min (−110 °C).	Pain severity. Numerical pain rating scale (NRS). Sleep quality. Visual Analog Scale.	. Both groups had changes after the rehabilitation period, but the magnitude of the changes was statistically greater in the multidisciplinary intervention and cryostimulation group.
Gilron et al. [29]	2016	4-period, randomized, double-blind, double-blind, crossover trial.	Number of patients: 41 Age: 18–70 years old Sex: 5 men and 36 women. Race: Caucasian Mean body weight: 81(18) Disease: Fibromyalgia.	Number of patients: 41 Age: 18–70 years old Sex: 5 men and 36 women. Race: Caucasian Mean body weight: 81(18) Disease: Fibromyalgia.	Intervention. 6 weeks per period. 4 periods characterized by: 1 placebo period, 2 periods with monotherapy and 1 period with both treatments. The dose was progressive towards the maximum dose.	Pain. McGill Pain Questionnaire and EVA. Sleep. Pittsburgh Sleep Quality Index	The combination has better results than placebo and monotherapy with respect to sleep. However, both duloxetine and pregabalin are frequent insomnia.
Hadamus et al. [30]	2021	Prospective, randomized, controlled trial.	Number of patients: 20 Mean age: 60.0 Mean body mass index: 25.9 Female to male ratio: 14/6 Chronic neck pain	Number of patients: 20 Mean age: 67.0 Mean body mass index: 24.7 Female to male ratio: 18/2 Chronic neck pain	Intervention lasted 2 weeks. Composed of 10 sessions, 30 min. Tests before and after the 2-week rehabilitation. Experimental group. Swedish massage + relaxation exercises on different musculature: scapula elevator, lower trapezius and erector of the head and spine. Control group. Only Swedish massage.	Sleep. Pittsburgh Sleep Quality Index.	All sleep components improved significantly in both groups. However, the experimental group specifically improved sleep latency and less sleep disturbance.

(*continued on next page*)

Table 1 (*continued*)

Author	Year	Type of study	Experimental Group	Control Group	Interventions	Variables	Results
Berry et al. [31]	2015	Randomized controlled trial	Number of patients: 44 Mean age: 50.4 Sex: predominantly female sample Illness: Fibromyalgia, high chronic pain condition.	Number of patients: 41 Mean age: 48.5 Sex: predominantly female sample. Disease: Fibromyalgia high chronic pain condition	Experimental group Cognitive behavioral intervention focused on a 15-min didactic session on better sleep. Control group no intervention was performed.	Sleep. Modified sleep apnea from the Berlin questionnaire.	Sleep latency improved in the experimental group
Goldway et al. [32]	2019	Randomized controlled trial	Number of patients:25 Average age:35 years Sex: 24 women and 1 man Medications administered: Analgesics, Gabapentinoids and Cannabis. Disease: Fibromyalgia	Number of patients: 9 Average age: 35 years old Sex: 7 women and 2 men. Medications administered: Analgesics, Gabapentinoids and Cannabis. Disease: Fibromyalgia	Experimental group: 1 night home sleep monitoring using an ambulatory sleep device. 10 real or simulated sessions. Two interfaces were used. 1st: Piano melody. 2nd: 3D audiovisual animated scenario correlated with the neural signal with the level of discomfort. Control group: Same simulated procedure.	Sleep. Pittsburgh Sleep Quality Index Chronic pain. McGill Pain Questionnaire and VAS. Anxiety. Trait Anxiety Inventory (STAI-T).	There were better results in amygdala regulation. Along with the homeostatic relationship of sleep-emotions. There was also palliation of chronic pain in a delayed form. It is worth mentioning that there were significant improvements compared to the pharmacology used.
Yarlas et al. [33]	2016	Randomized clinical trial	Trial I Number of patients: 541 Mean age: 49.4 Sex. Males: 243 Women: 298 Medications administered: No previous experience with opioids. Disease: chronic low back pain	Trial II Number of patients: 660 Mean age: 50 Sex. Males: 346 Women: 314 Medications administered: experience with opioids. Disease: chronic low back pain	Treatment protocol. Buprenorphine. Skin patch administering an average dose of 5,10 or 200 mg/h for 7 days over 12 weeks.	Dream. MOS-SS Pain. Visual Analog Scale (VAS)	The buprenorphine transdermal system improved sleep quality and disturbance in opioid-naive, opioid-experienced patients throughout the 12-week treatment period.
Wu et al. [34]	2021	Randomized clinical trial	Number of patients: 60 Average age: 48.6 Sex. Male: 3 Female: 57 BMI (mean ± SD): 21.9 Duration of pain (years; mean ± SD): 9.8 Disease: Fibromyalgia Duration of pain (years; mean ± SD): 9.8 Disease: Fibromyalgia	Number of patients:20 Mean age: 42.2 Sex. Males: 6 Female: 14 BMI: 23.8 Duration of pain (years; mean ± SD): 8.7 Disease: Fibromyalgia.	Experimental group. 20 sessions (600 min) of neurofeedback. During a period of 8 weeks. Each treatment session 30 min. The device used for biofeedback Pro-Com infinity. Transmits both alpha waves and 8–12 Hz sensorimotor rhythm waves. Control group. Educational material and telephone support consisting of 10 min divided into 5 min of questions or answers and 5 min of use of the material provided.	Pain. The BPI-Short Form (BPI-SF). Sleep. Pittsburgh Sleep Quality Index.	Fibromyalgia patients who received neurofeedback training exhibited significantly greater improvements in pain severity, pain interference, fibromyalgia symptom severity, sleep latency, and sustained attention compared to patients in the control group.
Block et al. [35]	2015	Randomized trial	Number of patients: 11. They suffered from chronic pain. Medication: long-term morphine infusion equal to or more than 2 years.	Number of patients:8 Suffered from chronic pain Medication: long-term morphine infusion equal to or longer than 2 years	3 weeks of 3 periods totaling 9 weeks of naloxone administration in the experimental group. Control group was administered placebo.	Pain. Scale of descriptives used to represent various levels of pain (NRS). Sleep. Visual analog scale (VAS)	Improvements in both pain and sleep were associated.
Ahmed et al. [36]	2016	Randomized clinical trial	Number of patients: 15 Fibromyalgia	Número de pacientes: 15 Fibromialgia	Two treatment periods of milnacipran or placebo administration	Sueño. Polisomnografía.	Administration of milnacipran did not show statistical improvements in the primary sleep maintenance parameters.
Roseen et al. [37]	2020	Randomized clinical trial	Number of patients: 256 Age range: 18–64 years old Pathology:	Number of patients: 64 Age range: 18–64 years old Pathology:	The intervention consisted of 12 weeks of therapy and 40 weeks of maintenance. Experimental group was divided into two therapies:	Sleep. Pittsburgh Sleep Quality Index (PSQI).	The experimental group improved sleep quality, according to the Pittsburgh Sleep Quality Index (PSQI) scale by 3 points or more. In

(*continued on next page*)

Table 1 (*continued*)

Author	Year	Type of study	Experimental Group	Control Group	Interventions	Variables	Results
			Nonspecific low back pain for more than 12 weeks.	Nonspecific low back pain for more than 12 weeks.	1°Therapy 12 yoga classes of 75 min duration. Where yoga postures, breathing, relaxation and meditation were included. 2nd Therapy. Therapeutic aerobic exercise. 15 classes of 60 min. Control group. 15 classes of 60 min Reeducation on pain and sleep problems.		contrast, the control group did not improve.

improving sleep disorders in these patients, leaving a research gap regarding their implication in sleep disturbances [41].

Regarding water therapy, a trial on balneotherapy showed significant pain reduction in patients suffering chronic pain [25]. Mineral baths proved to be as effective in alleviating pain as some oral anti-inflammatory medications [41]. This finding could be crucial for patients who frequently rely on analgesics, potentially providing an alternative to relieve their burden and avoid adverse effects [42].

Regarding cryostimulation, the included study demonstrated its effectiveness in alleviating pain and improving sleep in patients with fibromyalgia and obesity. This finding aligns with another study on cryostimulation by Rivera et al. [43] in the same population of fibromyalgia patients [43]. An important aspect of the study was the strong association between pain, mood, and sleep, all of which improved after cryostimulation sessions. However, further research is needed to explore the short and long-term clinical effects, as its impact on white blood cells remains unknown [28].

Cognitive-behavioral therapy appears to be a valid tool for treating insomnia and chronic pain, if it is tailored to each aspect separately to achieve favorable outcomes [26,31].

It is true that anticonvulsants and antidepressants alleviate pain in patients with fibromyalgia; however, a high percentage of somnolence leading to disrupted deep sleep has been observed as a side effect [29]. Therefore, alternative therapies such as the ones mentioned earlier would be a good option as complementary treatment for improving sleep.

The administration of buprenorphine in patients with chronic lower back pain appears to alleviate pain, but long-term use of certain opioids can cause drowsiness and poor sleep quality [33].

Morphine activates the opioid receptor, which inhibits pain reception. When administered chronically to treat pain, an effect called receptor coupling that can inactivate the opioid receptor. To counter this, naloxone is administered in low doses to prevent this inhibition. This drug administration approach seems to have positive outcomes in both sleep and chronic pain, but it involves a heavy medication burden [35]. Other drugs, such as milnacipran, improve pain but do not lead to an improvement in sleep quality and present adverse effects such as headaches and vomiting [36].

Training with limbic neuromodulation is effective in treating chronic pain and improving sleep quality. However, it should be noted that a considerable period must elapse for pain to be alleviated [32]. Ahmed et al., 's 2016 study demonstrates high clinical effectiveness compared to other pharmacological studies [36].

Goldway et al.'s [32] study supports the strong correlation between sleep disorders and amygdala activity. This could explain the association between sleep disturbances and emotional state. The study also demonstrated an improvement in brain waves, both alpha and sensomotor waves. Sensomotor waves are associated with a calm body while the mind remains active, while alpha waves are beneficial for relaxation and self-regulation, demonstrating a positive effect on the HPA axis [32].

The included studies in our review all communicate positive effects of the investigated interventions, anyway during the follow-up time used in those studies. We do not know if the mentioned improvements in both pain and sleep last longer than that follow-up period. The reviewed results all seem effective, which can also mean that every intervention influences the same, possibly, the universal mechanism behind sleep disturbances, pain, fatigue and depressive disorders which are all problems present in people suffering from FS.

Sleep, a recognized regulator of systemic inflammation, facilitates recovery from infections and diseases by influencing major CNS effector systems like the HPA axis, SNS, and the immune system [44]. Distinct sleep stages impact nocturnal inflammatory cytokine levels, establishing the foundation for daily inflammation patterns [45]. Sleep disruption, activating stress responses and inflammatory pathways, initially shifts the temporal pattern of inflammatory responses, increasing cytokine levels during the day. Even one night of partial sleep loss can induce these effects, while persistent sleep disturbance leads to prolonged inflammatory activation, resulting in chronically elevated systemic inflammation and associated health issues. Similar to stress, these connections are bidirectional and potentially cyclical, as changes in peripheral inflammatory status can influence sleep [46–49]. Furthermore, literature suggests a bidirectional relationship between sequential measures of pain and sleep, where daytime pain correlates with nighttime sleep deficit [50,51]. The sleep-wake cycle, controlled by hormones from the hypothalamus and circadian clock, is intertwined with pain regulation influenced by the circadian system [52]. Circadian rhythms, essential for health, undergo changes with age, impacting behavioral rhythms, temperature regulation, and hormone release [52,53]. Disruption of the circadian clock is associated with various health conditions, including metabolic syndromes and its characteristic insulin resistance, neurodegenerative diseases, chronic musculoskeletal pain, and inflammatory diseases [8,18,54]. Such disruptions are often associated with the presence of mitochondrial dysfunction [55], pathogenic gut microbiota, low-grade inflammation, and desynchronization of the sympathetic nervous system in relationship with the HPA-axis. All the mentioned health problems related to sleep, pain, depression, and fatigue seem to have one denominator: hippocampal atrophy [56–58]. The hippocampus is specifically susceptive to all kinds of stress factors, ranging from emotional and cognitive stress, via social and metabolic stress [56]. The metabolism of the hippocampus is unique because of the enormous energy demand needed for optimal functioning specially in humans (See Fig. 2).

Although similar across most mammalian animals, the size of the hippocampus varies between species, showing a two times greater hippocampus size to body size in primates compared to for instance the platypus [59]. Nevertheless, the neocortex to body size has increased much more, which means that the hippocampus size to neocortex size in rodents is significantly greater than in humans. The average size of the hippocampus on both sides of the brain in humans ranges from 3.0 to 3.5 cm whereas the neocortex volume averages 320–420 cm, producing an index between hippocampus neocortex of 1:100 [59]. Many functions

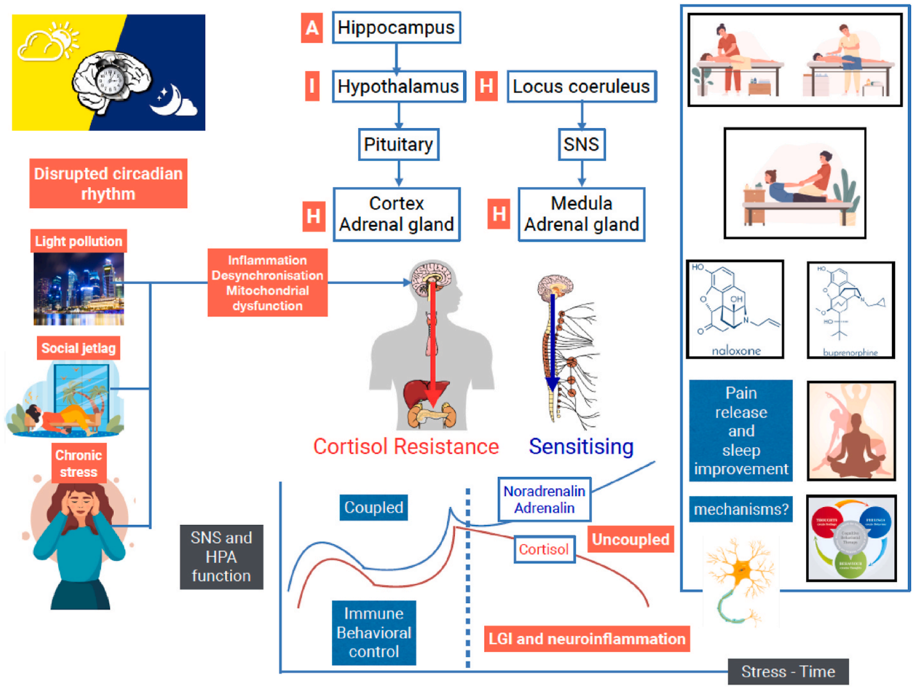

Fig. 2. Overview of the results in our systematic review. Left the risk factors related with sleep disturbances, fatigue and pain. Peripheral inflammation, neuroinflammation, mitochondrial dysfunction and desynchronization of stress axes (SNS $\gg$ HHPA) are all mechanisms related to the cluster of pain, fatigue and sleep disorders. The possible universal mechanism behind the development of this cluster, often accompanied with depressive mood, is hippocampal atrophy. The interventions used in the included studies all show some but significant improvement in pain and or sleep symptoms. Chronic stress (emotional, physical, mental, environmental) and disruption of the circadian rhythm leads to chronic activation of the sympathetic nervous system (SNA) and the HHPA-axis. Long term activation of both systems leads to cortisol resistance (acrophase of humoral axis) and sensitizing of the SNS (*C*-fibre), ultimately leading to low grade inflammation and neuroinflammation. A = Atrophy, I = Inflammation, H = Hyperactivity.

have been attributed to the hippocampus, ranging from spatial memory, via global memory and olfactory memory to navigation [60]. Functions and anatomy of the hippocampus, make this part of the brain susceptible to a metabolic catastrophe because of its high energy demand, hyperglycemia and insulin resistance [61,62]. We and others showed that the use of whole-body hyperthermia (WBH) in persons suffering from depression is highly effective [63–65]. It was shown that TRP 3 and 4 activity in the skin by WBH could have been responsible for neuroneogenesis of the hippocampus [66] and improvement of the cluster of pain, fatigue and depression in patients treated with WBH in psychiatry [66]. In this line, whole-body photobiomodulation (PBM) has recently shown promising results in terms of decreased pain and improved quality of life, as well as in psychological factors such as kinesiophobia, pain catastrophizing, and self-efficacy, in patients suffering from FM [67]. Furthermore, changes in circadian variations in blood pressure, pain pressure threshold and the elasticity of tissue, have been also observed [18]. Photobiomodulation encompasses Transcranial PBM, which has also been suggested to enhance neuronal bioenergetic processes, cerebral blood circulation, oxidative stress, neuroinflammation, neural cell death, neurotrophic elements, neurogenesis, and impacts on inherent brain circuits, thereby activating and regulating the central nervous system, and subsequently the peripheral nervous system, believed to play a crucial role in alleviating both central and peripheral sensitization symptoms observed in individuals with chronic pain. Once more, the underlying mechanisms proposed might be alike, ultimately promoting hippocampal neurogenesis; nevertheless, further research is required to corroborate this claim.

Studies included in this review, used several interventions that could have triggered TRP ¾ receptors in the skin [21,22,25,30], that leads to increase of serotonin production as a trigger for neuroneogenesis in the hippocampus [68]. Exercise, used as intervention in several included studies [22,27,28,30,37] can also induce hippocampal neurogenesis as evidenced in multiple studies reviewed in Liu et al. [69] Cognitive behavioral therapy, used as intervention in studies [24,26,31], in combination with environmental enrichment could also have induced neurogenesis of the hippocampus [70], leading to symptom improvement as documented [24,26,31]. The use of opioid influencing interventions [33,35] also show improvements in pain and sleep. Studies of the effects of opioids like buprenorphine on hippocampal neurogenesis show conflicting results. The study of Davila-Valencia et al. [71] shows that opioids can enhance neurogenesis in the hippocampus but only in males. Zhang [72] states that the use of opioids inhibits neurogenesis of the hippocampus and warns of these effects in patients addicted to it. Anyway, the hypothesis that hippocampal neurogenesis could serve as a possible explanation for the overall positive effects of the included studies in this review seems legitimate.

This hypothesis adds to the understanding of the impact of sleep quality and circadian rhythms on human development and health, particularly in musculoskeletal disorders, is crucial, although research in this area is currently limited [73,74]. In this regard, shoulder, neck and low-back disorders are being studied with great clinical and research interest [8,73,75,76].

Examining musculoskeletal health comprehensively poses a challenge due to the extensive array of potential contributing factors. While existing research has identified sleep that significantly affect inflammation, additional investigations are imperative to discern the clinical implications of sleep quality in the progression of chronic pain and connective tissue alterations in musculoskeletal conditions, such as to explore whether sleep quality has an accumulative or amplified effect on inflammation and overall musculoskeletal health [74].

4.1. Methodological quality of the gathered literature

The methodological quality was assessed using the PEDro and PVI scales, and the GRADE system. According to PEDro, 4 trials obtained a rating of excellent methodological quality [21,22,29,32]; 12 trials received a rating of good methodological quality [23,24,26–28,30,31,33–37]; and 1 trial received a rating of fair methodological quality [25].

According to PVI, the internal validity of the included studies was evaluated, showing that 5 trials achieved a high methodological quality rating [21,22,29,32,36]; 8 trials achieved a moderate methodological quality rating [23,24,26,28,31,33,34,37]; and 4 trials achieved a moderate methodological quality rating [25,27,30,35].

5. Conclusions

Strategies such as manual therapy, therapeutic exercise, balneotherapy, cryostimulation, cognitive-behavioral therapy, neurofeedback, and limbic neuromodulation could reduce the perception of chronic pain and improve sleep quality and quantity. Improving sleep quality (especially REM phase, sleep efficiency, and wakefulness) and reducing pain mechanisms enhances quality of life for patients. The quality of studies on different healthcare strategies for addressing sleep and chronic pain is good. However, more research is needed to analyze the impact of physical therapy on the sleep of patients with chronic musculoskeletal pain, as well as interventions to improve sleep as part of the treatment for patients with chronic pain. Ultimately, a possible universal mechanism behind the development of pain, fatigue, and sleep disorders, and hippocampal atrophy as the target for future interventions, is proposed for future research in this line.

5.1. Practice points

This review has several strengths, including the homogeneity of the included studies, which had RCT designs and utilized various validated objective scales and tools to ensure good methodological quality and reliable results. It offers a novel proposal by analyzing the impact of physical therapy techniques on sleep of patients with chronic pain, as well as other healthcare therapies, and proposes a universal mechanism in those with chronic pain and sleep disorders, opening future research and interventions. Additionally, it demonstrated homogeneity in the type of patients included with chronic musculoskeletal pain. Furthermore, seven databases were used to obtain the data.

However, there are limitations and weaknesses to consider. These include the diversity of treatments used in the different selected RCTs and limited scientific literature on sleep management from the perspective of physical therapy or its impact on sleep quality, especially regarding the specific type of therapeutic exercise to improve sleep.

5.2. Research agenda

Evidence regarding physical therapy and its use as treatment for managing sleep in patients with chronic pain is limited. Therefore, new lines of research are proposed: Investigate and conduct RCTs that incorporate physical therapy strategies for treating sleep and its disturbances in patients with chronic pain; investigate and conduct RCTs analyzing the physiology underlying the benefits of physical therapy strategies for managing sleep and its disturbances in patients with chronic pain; explore and conduct RCTs, from the perspective of physical therapy, in other areas such as sleep disturbances in oncological patients; investigate sleep cycles in relation to the HPA axis following a physical therapy intervention for sleep disturbances in patients with chronic musculoskeletal pain; study the impact of circadian rhythms disruption in patients with chronic pain; and finally to carry out meta-analysis to quantitatively assess the impact of different interventions, such as physical therapy techniques, on musculoskeletal chronic pain and sleep quality.

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Declarations of competing interest

None.

Appendix A. Supplementary data

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