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REVIEW ARTICLE

Effectiveness of health education interventions in patients with fibromyalgia syndrome: an umbrella review

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ABSTRACT

Background: Fibromyalgia syndrome (FMS) is characterized by chronic widespread pain that is accompanied by emotional distress, fatigue, tender points of pain, sympathetic nervous system disturbances, and alterations in the quality of sleep.
Aim: The main aim of this umbrella review was to assess the effectiveness of health education interventions (HEI) in patients with FMS.
Methods: We searched in PubMed, PEDro, EMBASE, CINAHL, Psicodoc, and Google Scholar (August 6, 2022). The outcomes measures were pain intensity, quality of life, functionality, anxiety, and pain catastrophizing. This review was previously registered in the international prospective register of systematic reviews (SR) PROSPERO (CRD42022368068). Methodological quality was analyzed using AMSTAR and ROBIS scale, and the strength of evidence was established according to the guidelines advisory committee grading criteria.
Results: Five SR with and without meta-analysis were included in the study. The results were pooled to assess the effects of HEI in isolation and to assess the effects of HEI in combination with other interventions (multicomponent approach based on therapeutic exercise or pharmacological). The results showed that HEI combined with other interventions was effective in improving pain intensity, quality of life, functionality, and anxiety compared to minimal intervention/usual care or no intervention, although mixed evidence was found improving pain catastrophizing, all with a limited quality of evidence. Regarding HEI in isolation, contradictory evidence was found for pain intensity and quality of life variables with a limited quality of evidence. Finally, no significant results were found in improving functionality, anxiety, and pain catastrophizing variables also with a limited quality of evidence.
Conclusions: Overall, it seems that the addition of HEI to other interventions, mostly therapeutic exercise although we could refer to it in terms of a multimodal approach, leads to greater clinical improvements than HEI in isolation. We have seen this especially in some clinical variables of interest such as pain intensity or quality of life. It seems that the main strength of the HEI is the interaction with other interventions to enhance its efficacy with respect to the outcomes assessed. Further research is needed especially ensuring the correct comparison when combining HEI with other interventions to obtain more consistent results.
Relevance for Patients: Adding therapeutic education programs to the management of patients with FMS seems to have a clinically important effect. However, the application of therapeutic education in isolation does not appear to be effective in the management of these patients. More research is needed in this field.

1. Introduction

Fibromyalgia syndrome (FMS) is characterized by chronic widespread pain that is accompanied by emotional distress, fatigue, tender points of pain, sympathetic nervous

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system disturbances, and alterations in the quality of sleep [1]. Several investigations have suggested that one of the mechanisms that may be involved in the FMS is a process of central hyperexcitability [2,3]. This process involves an amplification of signaling at the neuronal level in the medullary and supramedullary centers, which may lead to increased sensitivity to pain, lowering the excitability threshold of afferent sensory inputs with painful information [4]. On an epidemiological level, FMS has a prevalence in the general population between 0.5% and 5% [5]. The prevalence is higher in women than in men [5]. Regarding mortality, the recent study conducted by Treister-Goltzman and Peleg [6] showed that FMS is associated with an increased mortality rate from all causes, especially suicidal ideation, accidents, and the presence of infections.

Nowadays, there seems to be no objective test that can help clinicians make an accurate pathophysiological diagnosis of FMS [7]. To date, most of the tools and criteria used for the diagnosis of FMS are vaguely specific [8]. This situation, together with the difficulty of subclassifying patients with FMS, poses a huge challenge when treating patients with FMS [8]. Despite this, in 2016 the American College of Rheumatology (ACR) established some criteria [9]. In the revised 2016 ACR criteria, generalized pain (rather than widespread pain) in at least four of five distinct body regions is required for a diagnosis of FMS along with persistent symptoms for more than 3 months, and also high scores on indices of widespread pain and symptom severity [9].

Regarding the treatment of FMS, the effectiveness of some treatments has been evaluated. For example, previous systematic reviews (SR) have assessed the effectiveness of some important interventions such as pharmacological treatment [10,11], psychological therapies [12,13] as well as exercise-based interventions [14,15] to manage the described main symptoms of FMS. However, most of the clinical interventions evaluated do not incorporate educational features in them. Education is fundamental in the management of patients with persistent pain, as it improves the influence of psychosocial variables that can modulate pain perception [16]. Within the biopsychosocial perspective, some health educational interventions (HEI) have been proposed as an alternative, with the aim of reconceptualizing the pain experience, improving coping strategies toward pain, or improving knowledge regarding the disease process to improve some clinical variables of interest such as disability and quality of life in patients with FMS. Educational strategies such as pain neuroscience education (PNE) or pain neurophysiology education (PNpE) are among the most studied educational interventions for patients with persistent pain [17,18]. The number of research studies evaluating the effect of HEI on patients with FMS has grown in recent years [19-23], and so far, no research studies have pooled and analyzed these results. Moreover, the SR published so far are not consistent with the results obtained. We believe that a general overview that encompasses all of them allows us to analyze the effectiveness of these interventions in depth, as well as to analyze and extract possible lines of improvement so that research may continue to be carried out in the near future.

It is therefore that the main aim of this umbrella review was to assess the effectiveness of HEIs in patients with FMS.

2. Methods

This study was conducted in accordance with the Preferred Reporting Items for Overviews of SR including harm checklist (PRIO-harms), which consists of 27 items (56 sub-items), followed by a 5-stage process flow diagram (identification, screening, eligibility, inclusion, and separation of relevant studies) [24]. This review was previously registered in the international prospective register of SR: PROSPERO (CRD42022368068).

2.1. Review inclusion criteria

The inclusion criteria employed in this article were based on methodological and clinical factors such as population, intervention, control, outcomes, and study design [25].

2.1.1. Population

The participants selected for the articles were patients with FMS. Included SR had to explicitly state that they included patients with FMS in their inclusion criteria. We excluded all SR that include patients with other chronic conditions with persistent pain.

2.1.2. Intervention and control

The intervention consisted of HEI (PNE) *(i.e.: Neurophysiology of pain, differences between "pain" and "nociception", factors contributing to the perpetuation of pain, or the influence of thoughts (cognitions) or emotions on pain experience)*, PNpE *(i.e.: neurophysiology of the central nervous system, central/peripheral hyperexcitability or sensitization/habituation concepts)*, and therapeutic education (TE) *(i.e.: FMS symptoms information, active coping strategies, or self-management strategies)* conducted in isolation, in conjunction or combined with other treatments. The education sessions could be individual or group-based and could contain any semantic resources for a better understanding (such as the presence of metaphors). Interventions based on psychological treatment or cognitive behavioral therapy were excluded from the study. The comparator groups used the following interventions: no intervention, minimal interventions in isolation or combined to form a multicomponent approach. (e.g.: information about relaxation, analgesic drugs, therapeutic exercise, or exercises information booklets), or waiting list.

Regarding the intervention studied:

- TE is a therapeutic modality that explicitly involves a non-directional dynamic interaction with the patient, based on a biobehavioral paradigm, which includes educational or training activities that promote learning and acquisition of adaptive skills to improve self-management and knowledge that facilitate changes in beliefs, attitudes, and behaviors associated with disability. TE aims to change maladaptive beliefs, reconceptualize aspects related to pain, implement educational processes on the importance of therapeutic

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exercise, improve adherence, active coping skills training, and sleep regulation strategies. It may also include techniques such as sensory retraining, sensory reinterpretation, experiential motor restructuring, activity and exercise, and graded exercise exposure as part of TE.

- PNE corresponds to educational processes that focus on a broad, multidisciplinary understanding of pain, including neuroanatomical, neurochemical, cognitive emotional, and social aspects that relate to the perception of the pain experience.
- Finally, PNpE corresponds to educational aspects that focus on a more specific understanding of the neurophysiological and neurobiological processes underlying pain perception, also including the transmission of the nociceptive signal, its processing at the central nervous system level and pain modulation systems.

2.1.3. Outcome measures

The outcomes employed to assess the effectiveness of HEI were pain intensity, quality of life, functionality, anxiety, and pain catastrophizing.

2.1.4. Study design

We selected SR (with or without a meta-analysis) of randomized controlled trials (RCTs) or controlled clinical trials (CCTs) and excluded SR that included RCTs or CCTs in combination with non-experimental designs. There were no restrictions for any specific language, as recommended by the international criteria [26].

2.2. Search strategy

We conducted the search for published scientific articles between 1950 and August 6, 2022, in the following databases: MEDLINE (PubMed), EMBASE, PEDro, CINAHL, Psicodoc, and SPORTDiscus. An additional manual search was realized in Google Scholar. The reference sections of the included studies and original studies were screened manually, and the authors were contacted for further information if necessary. The search strategy combined Medical Subjects' Headings (MeSH ["Fibromyalgia"]) or ["Patient Education as topic"], and non-MeSH terms ("fibrositis", "fibromyositis", "rheumatism muscular", "fibromyalgias", "fibromyalgia secondary", "fibromyalgia primary", "PNE", "therapeutic neuroscience education", "pain neurophysiology education", or "patient education") adding a Boolean operator (AND and/or OR) to combine them. Appendix 1 shows the search strategy, which was adapted for each database. The search was conducted by two independent reviewers using the same methodology. Differences that emerged during this phase were resolved by consensus. The reference sections of the original studies were screened manually, and the authors were contacted for further information if necessary.

2.3. Selection criteria and data extraction

Initially, the two independent reviewers conducted a screening assessing the relevance of the SR (with and without a meta-analysis) regarding the studies' questions and objectives. The first screening was based on each study's title information, abstract, and keywords. The full text was reviewed if there was no consensus or if the abstracts contained insufficient information. In the second phase of the screening, the full text was assessed if the studies met all of the inclusion criteria. Differences between the reviewers were resolved by a discussion and consensus process mediated by a third reviewer. The data described in the results section were extracted by means of a structured protocol that ensured that the most relevant information was obtained from each study.

2.4. Methodological quality assessment

The two independent reviewers assessed the methodological quality of the SR (with or without meta-analysis), assessing each of the selected studies based on the Modified Quality Assessment Scale for SR (AMSTAR) developed by Barton *et al.* [27] a scale shown to be a valid and reliable tool for assessing the methodological quality of SR. With a total of 13 items, each worth 2 points (with "yes" scoring 2; "in part" scoring 1; "no" scoring 0), the maximum possible score is 26. A high-quality cutoff of 20 or more points was provided by the developers. The exclusion and keyword criteria were modified to better evaluate the selected SR of this study. In addition, we calculated the kappa coefficient (κ) and percentage (%) agreement scores to assess reliability before any consensus.

2.5. Risk of bias assessment

We assessed the risk of bias with the Risk of bias in SR tool (ROBIS) [28], which consists of three phases: (1) Relevance assessment (optional); (2) identification of concerns with the review process through four domains related to study eligibility criteria, identification and selection of studies, data collection and study appraisal and synthesis and findings; and (3) judgment on the risk of bias.

2.6. Grading of evidence

The physical activity guidelines advisory committee grading criteria (PAGAC) were used to assess the grading of evidence. The criteria used to assess the quality of the evidence were as follows: (1) Applicability of the study sample, exposures, and outcomes to the research question, (2) generalizability to the population of interest, (3) risk of bias/study limitations, (4) quantity and consistency of findings across studies, and (5) magnitude and precision of the effect. With these data, final evidence grades and conclusion statements for each research question were developed [29].

3. Results

3.1. Study selection

The initial search revealed 99 records. Through the title and abstract screening and the full-text assessment, five SRs were eligible according to our criteria. The study screening strategy is shown in the form of a flow chart **(**Figure 1**)**.

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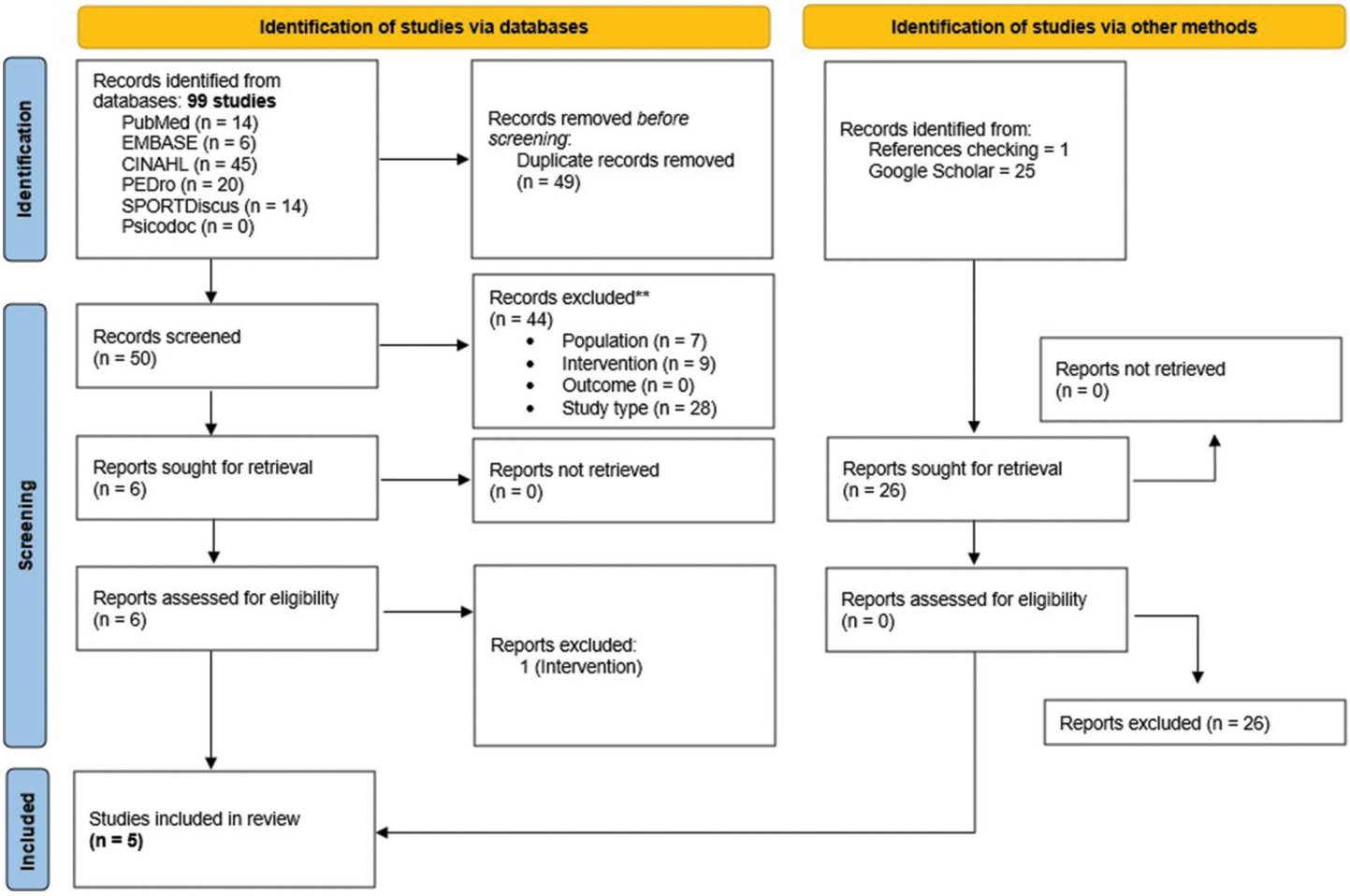

Figure 1. PRISMA Flowchart of studies selection.
*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org.

3.2. Characteristics of the included SR

Table 1 lists the characteristics of the SR included (study design, original studies included, demographic characteristics, interventions, variables, and results). Antunes *et al.* [19] conducted a SR that included two RCTs only, of which only one primary study evaluated the effect of TE (FMS symptoms information, active coping strategies) as a form of HEI in combination with a multicomponent approach (therapeutic exercise, relaxation techniques or pharmacology) versus no intervention. The study conducted by Elizagaray-García *et al.* [20] analyzed a total of five RCTs. Two of the five primary studies compared HEI (PNE, PNpE, and TE) in isolation against minimal intervention (including information leaflets on stretching, relaxation, or general pain management strategies). Two further studies had at least one study arm that performed some model of HEI in isolation for comparison against no intervention or waiting list. Finally, three RCTs combined HEI with a therapeutic exercise-based approach (aerobic, strengthening, or flexibility exercise) and compared it against waiting list, information leaflet, or no intervention. The study carried out by García-Ríos *et al.* [21] analyzed a total of 12 RCTs. In six studies, FMS patients received HEI as the only form of intervention (including PNE, PNpE, and TE). In the remaining studies, HEI was combined with other interventions such as therapeutic exercise, including pool exercise. Saracoglu *et al.* [22] included only four primary studies where the PNE-based intervention was added to a multicomponent approach (including cognitive-behavioral therapy, mindfulness training, or therapeutic exercise) and compared it to a minimal intervention. Suso-Martí *et al.* [23] analyzed eight RCTs. They included primary studies where the role of HEIs (PNE and PNpE) was assessed in isolation or if combined with an intervention, it had to be in the control group to ensure correct comparison between groups and to be able to attribute clinical differences to HEIs. In fact, only two RCTs combined HEI with therapeutic exercise and relaxation exercises, but these interventions were also in the comparison group.

Table 1. Characteristics of the reviews included in the umbrella review

Study	Studies k (n) Types	Meta-analysis (k)	Population	Intervention	Control	Outcomes (instruments)	Author's conclusions
Antunes *et al*. [19]	2 RCTs (65)	No	FMS FMS (Diagnosis based on 1990/2010ACR criteria)	HEI - TE in FMS (FMS symptoms information and active coping strategies) (+ Multicomponent approach in 1/1 RCT)	Comparator - No intervention	- Pain intensity (NHP subscale) - Quality of life (NHP)	An interdisciplinary health education program can improve pain and quality of life in people with FMS
Elizagaray-García *et al*. [20]	5 RCTs (611)	No	FMS (Diagnosis based on 1990 ACR criteria)	HEI - PNpE - PNE - TE in FMS (FMS symptoms information, SM skills education or active coping strategies) (+TEx in 3/5 RCT)	Comparator - Information about relaxation - Stretching exercises information booklets - No intervention - Waiting list	- Pain intensity (PPT, TS, SSP, CPM, FIQ subscale and number of tender points) - Quality of life (SF-36 and SV-QOLS) - Functionality (FIQ subscale, SF-36 subscale and 6MWT)	HEI, in itself, has not proved to be effective for pain intensity, quality of life or functionality in patients with FMS. However, HEI in combination with TEx showed effectiveness on the variables analyzing.
García-Ríos *et al*. [21]	12 RCTs (1389)	No	FMS (Diagnosis based on 1990 ACR criteria)	HEI - PNpE - PNE - TE in FMS (FMS symptoms information, SM skills education or active coping strategies) (+ Multicomponent approach in 6/12 RCT)	Comparator - Information about relaxation - Relaxation breathing - Stretching exercises information booklets - FMS information booklets - Waiting list - Usual practice - TEx	- Pain intensity (VAS, PPT, SSP, PCI, MPI-S and PVAQ) - Quality of life (FIQ, IPQ-R, EQ-5D, SF-36, NHP and SV-QOLS) - Functionality (FIQ subscale, SF-36 subscale, 6MWT and AIMS) - Anxiety (PGWB and GADS) - Pain Catastrophizing (PCS)	The scientific evidence that supports the effectiveness of HEI in the reduction of pain intensity, quality of life, functionality, anxiety, and pain catastrophizing is limited.
Saracoglu *et al*. [22]	4 RCTs (612)	Yes (4)	FMS (Diagnosis based on 2010 ACR criteria)	HEI - PNE (+ Multicomponent approach in 2/4 RCTs)	Comparator - Minimal intervention (patient information about the disease, recommendations on aerobic exercise, and pharmacological treatment)	- Pain intensity (VAS and NPRS) - Quality of life (FIQ)* - Anxiety (HADs) - Pain Catastrophizing (PCS)	Adding PNE to a multimodal treatment including TEx might be an effective approach for improving functional status, pain-related symptoms, anxiety, and depression for patients with FMS.
Suso-Martí *et al*. [23]	8 RCTs (738)	Yes (8)	FMS (Diagnosis based on 1990/2010/2016 ACR criteria)	HEI - PNE (+TEx in 1/8 RCT)	Comparator - Relaxation - Breathing exercises - Minimal intervention (pharmacological usual care or general advice) - No intervention - TEx	- Pain intensity (VAS, SF-BPI, NPRS) - Quality of life (FIQ) - Anxiety (PASS-20, HAQ, and HADS) - Pain Catastrophizing (PCS)	In patients with FMS, PNE can decrease the pain intensity in the post-intervention period and the quality of life in the follow-up period (3 m). However, it appears that PNE showed no effect on anxiety and pain catastrophizing.

Notes. FMS: Fibromyalgia syndrome; ACR: American college of rheumatology; RCT: Randomized controlled trial; PNpE: Pain Neurophysiology Education; SM: Self-management; PNE: Pain neuroscience education; TE: Therapeutic education; PPT: Pressure pain threshold; TS: Temporal summation; CPM: Conditioned pain modulation (CPM); FIQ: Fibromyalgia impact questionnaire; SF-36: 36-Item Short Form Health Survey; QOLS: Swedish version quality of life scale; 6MW: 6 minutes walking test; HEI: Health education interventions; PT: Physical Therapy; m: months; PCS: Pain catastrophizing scale; VAS: Visual analogue scale; SF-BPI: Short form of brief pain inventory; NPRS: Numeric pain rating scale; HAQ: Health assessment questionnaire; PASS-20: Pain anxiety symptoms scale-20; HADS: Hospital anxiety and depression scale; TEx: Therapeutic exercise; SSP: Spatial summation of pain; PCI: Pain coping inventory; PVAQ: Pain and awareness surveillance questionnaire; MPI-S: Swedish version of the Multidimensional pain inventory; IPQ-R: Revised illness perception questionnaire; EQ-5D: EuroQoL-5D questionnaire; AIMS: Arthritis impact measurement scales; NHP: Nottingham health profile. PGWB: Psychological general well-being and GADS: Goldberg scale of anxiety and depression.

*The quality of life variable was reinterpreted for this study. In the original review, it is found as: severity of FMS

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Table 2. Quality assessment scores (AMSTAR)

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	Score
Antunes *et al*. [19]	2	1	0	1	1	2	2	2	2	0	0	1	0	14
Elizagaray-García *et al*. [20]	2	2	0	2	1	2	2	2	2	0	0	2	1	18
García-Ríos *et al*. [21]	2	2	0	2	1	2	2	2	2	0	0	1	1	17
Saracoglu *et al*. [22]	2	2	2	2	1	2	2	2	2	2	2	2	0	23
Suso-Martí *et al*. [23]	1	2	2	0	2	2	1	2	2	2	2	2	2	22

Notes: 1. Explicitly described to allow replication; 2. Adequate number and range of databases; 3. Alternative searches; 4. Adequate range of key words; 5. Non-English-language papers included in the search; 6. Inclusion criteria explicitly described to allow replication; 7. Excludes reviews which do not adequately address inclusion and exclusion criteria; 8. Two independent reviewers assessing selection bias; 9. Quality assessment explicitly described to allow replication; 10. Meta-analysis conducted on only homogeneous data or limitations to homogeneity discussed; 11. Confidence intervals/effect sizes reported where possible; 12. Conclusions supported by the meta-analysis or other data analysis findings; 13. Conclusions address levels of evidence for each intervention/comparison

Table 3. Summary of findings and quality of evidence (PAGAC)

	2018 PAGAC				Magnitude and precision of effect	Overall grade
Systematic review research questions	Applicability	Generalizability	Risk of bias or study limitations	Quantity and consistency		
Pain intensity	Strong	Limited	Limited	Limited	Not assignable	Limited
Quality of life	Strong	Limited	Limited	Limited	Not assignable	Limited
Functionality	Moderate	Limited	Limited	Limited	Not assignable	Limited
Anxiety	Moderate	Limited	Limited	Limited	Not assignable	Limited
Pain catastrophizing	Moderate	Limited	Limited	Limited	Not assignable	Limited

PAGAC: Physical activity guidelines advisory committee grading criteria

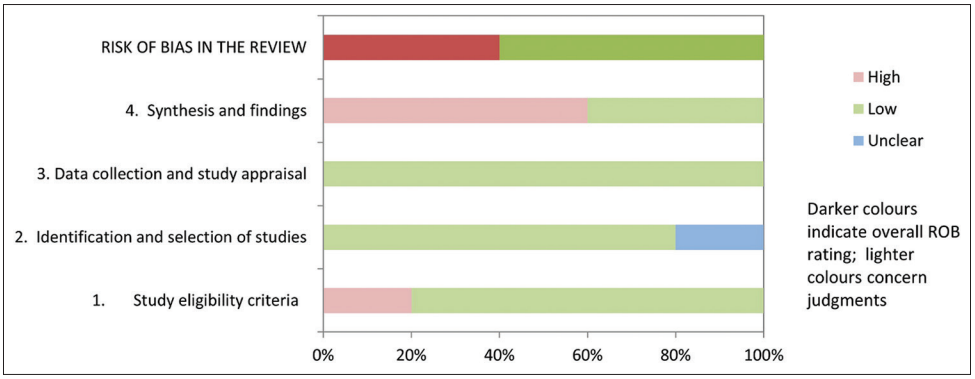

Figure 2. Graphical representation for risk of bias in SR tool results.

Finally, Suso-Martí *et al.* [23] included primary studies that used the ACR criteria from 1990, 2010, and 2016 as the diagnosis for FMS. Antunes *et al.* [19] included studies that used the ACR criteria from 1990 and 2010. Saracoglu *et al.* [22] included only the ACR 2010 diagnosis. García-Ríos *et al.* [21] and Elizagaray-García *et al.* [20] used the ACR 1990 criteria.

3.3. Results of AMSTAR and ROBIS

The scores ranged from 14 to 23 points out of a possible 26, with a mean score of 18.8 points. Only two (40%) study scored above 20 points and were considered high-quality **(**Table 2**)**. The inter-rater reliability of the methodological quality assessment was high ($\kappa = 0.91$). Figure 2 shows the results of the risk of bias assessment using ROBIS. About 60% of studies had a low risk of bias.

3.4. Grading of evidence results (PAGAC)

Table 3 shows the findings regarding the quality of evidence for each outcome of research question. The quality of evidence found for all outcome measures was limited.

3.5. Qualitative synthesis of HEI (in isolation)

3.5.1. HEI (in isolation)

3.5.1.1. Pain intensity

A total of three SR offered at least one outcome for the pain intensity variable [20,21,23]. Elizagaray-García *et al.* [20] found strong evidence ($n = 4$) of HEI, in isolation, did not show significant improvements in reducing pain intensity in the short, medium, or long term. However, García-Ríos *et al.* [21] found statistically significant differences in the pain

intensity variable in favor of HEIs. In addition, Suso-Martí *et al.* [23] found that PNE showed statistically significant differences reducing post-intervention pain intensity with a moderate clinical effect (n = 7, SMD = −0.76; 95% CI: −1.33 – −0.19, P < 0.05, I^2 = 92%) but not at 3 months of follow-up (n = 7, SMD = −0.42; 95% CI: −0.93 – 0.08, P > 0.05, I^2 = 89%).

3.5.1.2. Quality of life

A total of two SRs offered at least one outcome for the quality of life variable [20,23]. Elizagaray-García *et al.* [20] found strong evidence (n = 5) of HEI, in isolation, did not show significant improvements in improving quality of life in the short, medium, or long term. Finally, Suso-Martí *et al.* [23] found that PNE did not show statistically significant post-intervention improvements in quality of life (n = 8, SMD = −0.37; 95% CI: −0.85 – 0.11, P > 0.05, I^2 = 91%). However, Suso-Martí *et al.* [23] found statistically significant improvements in quality of life at 3 months of follow-up with a small clinical effect (n = 8, SMD = −0.44; 95% CI: −0.73 – −0.14, P < 0.05, I^2 = 89%).

3.5.1.3. Functionality

One SR offered at least one outcome for the functionality variable [20]. Elizagaray-García *et al.* [20] found controversial evidence (n = 3) of HEI, in isolation, did not show significant improvements in improving functionality in the short term.

3.5.1.4. Anxiety

One SR offered at least one outcome for the anxiety variable [23]. Suso-Martí *et al.* [23] found no statistically significant differences in anxiety improvement either at post-intervention (n = 5, SMD = −0.06; 95% CI: −0.67 − 0.55, P > 0.05, I^2 = 85%) or at 3-month follow-up (n = 5, SMD = −0.07; 95% CI: −0.69 to 0.82, p>0.05, I^2=85%).

3.5.1.5. Pain catastrophizing

One SR offered at least one outcome for pain catastrophizing variable [23]. Suso-Martí *et al.* [23] found no statistically significant differences in pain catastrophizing improvement either at post-intervention (n = 8, SMD = −0.10; 95% CI: −0.52 – 0.32, P > 0.05, I^2 = 89%) or at 3-month follow-up (n = 8, SMD = −0.16; 95% CI: −0.52 – 0.19, P > 0.05, I^2 = 86%).

3.5.2. HEI (in combination with other interventions)

3.5.2.1. Pain intensity

A total of four SR offered at least one outcome for the pain intensity variable [19-22]. Antunes *et al.* [19] found in one primary study that HEI plus multicomponent approach significantly reduced pain intensity. Elizagaray-García *et al.* [20] found moderate evidence (n = 2) of HEI plus therapeutic exercise showed significant improvements in reducing pain intensity in the medium term although mixed results were found in the short term. García-Ríos *et al.* [21] found that studies analyzing the impact of HEI, in combination with other approaches, showed a significant improvement in pain intensity variable (n = 8). Finally, Saracoglu *et al.* [22] also found that adding PNE to a multicomponent approach resulted in a statistically significant decrease in pain intensity with a moderate clinical effect (n = 3, standardized mean differences (SMD) = −1.05; 95% confidence interval (CI): −1.4 – −0.69, P < 0.001, I^2=37.7%).

3.5.2.2. Quality of life

A total of four SRs offered at least one outcome for the quality of life variable [19-22]. Antunes *et al.* [19] found in one primary study that HEI plus multicomponent approach significantly improved quality of life. Elizagaray-García *et al.* [20] found strong evidence (n = 4) of HEI plus therapeutic exercise significantly improved quality of life in the short, medium, and long term. García-Ríos *et al.* [21] reported that the best results in improving quality of life were found when a multicomponent approach was added to HEIs. Finally, Saracoglu *et al.* [22] found that adding PNE to a multicomponent approach resulted in a statistically significant improve in quality of life with a moderate clinical effect (n = 4, SMD = −1.05; 95% CI: −1.3 – −0.79, P < 0.001, I^2 = 86%).

3.5.2.3. Functionality

A total of two SRs offered at least one outcome for the functionality variable [20,21]. Elizagaray-García *et al.* [20] found strong evidence (n = 3) of HEI plus therapeutic exercise significantly improved functionality in the short and the medium term. Finally, García-Ríos *et al.* [21] found that adding HEI to a multicomponent approach resulted in a statistically significant improve in functionality (n = 3).

3.5.2.4. Anxiety

A total of two SRs offered at least one outcome for the anxiety variable [21,22]. García-Ríos *et al.* [21] found that adding HEI to a multicomponent approach resulted in a statistically significant improve in anxiety (n = 4). Finally, Saracoglu *et al.* [22] found that adding PNE to a multicomponent approach resulted in a statistically significant improve in anxiety with a moderate clinical effect (n = 4, SMD = −0.711; 95% CI: −0.86 – −0.55, P < 0.001, I^2 = 51.6%).

3.5.2.5. Pain catastrophizing

A total of two SRs offered at least one outcome for pain catastrophizing variable [21,22]. García-Ríos *et al.* [21] showed contradictory results with regard to the improvement of pain catastrophizing variable (n = 2). Finally, Saracoglu *et al.* [22] found that adding PNE to a multicomponent approach resulted in a statistically significant improve in pain catastrophizing with a moderate clinical effect (n = 3, SMD = −0.89; 95% CI: −1.43 – −0.34, P = 0.001, I^2 = 70.5%).

4. Discussion

The main aim of this review was to assess the effectiveness of HEI in patients with FMS. We divided the results into two groups: When HEI were evaluated in isolation and when HEI

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were evaluated in combination with other interventions, which were not present in the comparator group.

4.1. Summary results

Analyzing the outcome for each variable, for pain intensity, we found mixed evidence in favor of HEI alone, as we found significant and non-significant post-intervention results. However, in the short- to medium-term, no significant differences were found in favor of HEI. When HEI was combined with other interventions, the results showed significant effects on the reduction of pain intensity in the short and even in the medium term. With respect to quality of life, HEI in isolation did not lead to significant improvements in the short term; however, mixed evidence was found in the short- to medium-term. When HEI was combined with other interventions, the results showed significant effects on improving quality of life in the short, medium, and even long term. On the variables functionality and anxiety, the HEI alone did not show any significant effect on the improvement of these variables. However, when analyzing the combination of HEI with other interventions, we found significant improvements in both functionality and anxiety symptoms in favor of HEI combined with other interventions. Finally, with regard to the pain catastrophizing variable, the results showed that the HEI alone did not lead to any significant improvement. When evaluating the combination of the HEI with other interventions, the evidence found was mixed.

4.2. Strengths and weaknesses of HEIs

Overall, it seems that the addition of HEI to other interventions, mostly therapeutic exercise although we could refer to it in terms of a multimodal approach, leads to greater clinical improvements than HEI in isolation. We have seen this especially in some clinical variables of interest such as pain intensity or quality of life. It seems that the main strength of the HEI is the interaction with other interventions to enhance its efficacy with respect to the outcomes assessed. HEI are clinical interventions that has the communication process as a key point of its application and where the patient feels listened to, cared for and, in addition, allows patients to better understand their clinical condition process [30]. This increased knowledge from a patient perspective, together with an adequate context promoted by empathy, shared understanding between health professional and patient, and increasing social support, seems to help improve the influence of psychological variables that are widely present in chronic pain processes. However, despite this, a clinical approach based on HEI in isolation may be insufficient to provide clinically relevant and meaningful outcomes in patients with FMS, and we believe that HEI should be combined with an active and/or passive intervention (such as exercise-based interventions, manual neuro-orthopedic physiotherapy, or pharmacological) to improve its efficacy. Positive effects on decreasing pain intensity, disability levels, or catastrophic thoughts have been described when researchers combined PNE together with an exercise-based intervention compared to exercise-based intervention alone in patients with chronic musculoskeletal pain [31] or in patients with chronic non-specific spinal pain [32]. Given that exercise has already shown positive results in pain patients such as FMS [33,34] or chronic non-specific low back pain [35,36] in the scientific literature, it seems that future studies should address whether HEI could improve the efficacy of therapeutic exercise-based interventions. It is important to highlight at the clinical level the dosage of HEIs in the patient with persistent pain, in this case, applied to FMS. Recently, the study conducted by Salazar-Méndez *et al.* [37] aimed to evaluate how long it is necessary to perform PNE and PNpE in patients with chronic pain to obtain a clinical change in psychosocial variables. The authors found very interesting results. For example, they found that the longer the HEIs time, the greater improvements were found in variables such as anxiety, catastrophizing, or movement-related fear. In fact, it was estimated that a dose of 100, 200, and 400 min of HEIs exceeded the clinically relevant difference in the improvement of the three variables mentioned above.

Finally, as a practical recommendation for implementing HEI in patients with FMS, the authors of this article propose that HEI should be implemented in combination with other clinical interventions (such as therapeutic exercise) to achieve a stronger clinical effect. The application should be individualized and person-centered. Consideration should be given to the application of not only educational aspects but also processes focused on changing dysfunctional behaviors to have a greater impact on the person and be applicable to the person's daily life. Finally, dosage matters and clinicians must deliver the number of sessions (or intervention time) necessary to have an influence on the clinical variables of interest in FMS patients.

4.3. Study limitations

This review has some limitations that need to be taken into consideration. First, a great deal of heterogeneity has been found with education models, which makes it difficult to draw solid conclusions. Studies are needed to define well what each intervention is and how to implement it so that it has its own name. Second, the results were categorized into "HEI in isolation" and "HEI combined with other interventions". We included in the first those studies where only the role of HEI was evaluated or if HEI was combined with an intervention, the latter should also be in the comparator group to ensure correct comparability between the groups. The group "HEI combined with other interventions" was created when HEI was combined with other interventions which were not found in the comparison group. This is a relevant methodological problem because the clinical effect cannot be attributed to HEIs completely. In addition, the quality of evidence was low for most of the included studies. This is an issue to be considered, as more studies in this field could probably change the results of the outcome measures. Future studies should ensure proper comparability to draw more robust conclusions. Finally, as no statistical aggregation could be performed due to the low number

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of included studies, the conclusions are somewhat ambiguous as they satisfy a qualitative analysis, and not a quantitative one (which would be more robust).

5. Conclusion

Overall, it seems that the addition of HEI to other interventions leads to greater clinical improvements than HEI in isolation. We have seen this especially in some clinical variables of interest such as pain intensity or quality of life. It seems that the main strength of the HEI is the interaction with other interventions to enhance its efficacy with respect to the outcomes assessed. Further research is needed especially ensuring the correct comparison when combining HEI with other interventions to obtain more consistent results.

Finally, we could raise public awareness through informative campaigns, and on the health-care front, we can implement educational programs for health-care professionals with the aim of improving the understanding and management of FMS.

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Conflicts of Interest

None declared.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

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Appendix

Appendix 1. Database search strategies

-PubMed (Medline) (14 articles retrieved)

((“fibromyalgia”[MeSH Terms] OR “fibromyalgia”[All Fields] OR “fibromyalgias”[All Fields] OR (“fibromyalgia”[MeSH Terms] OR “fibromyalgia”[All Fields] OR (“fibromyalgia”[All Fields] AND “fibromyositis”[All Fields] AND “syndrome”[All Fields])) OR (“fibromyalgia”[MeSH Terms] OR “fibromyalgia”[All Fields] OR (“syndrome”[All Fields] AND “fibromyalgia”[All Fields] AND “fibromyositis”[All Fields])) OR (“fibromyalgia”[MeSH Terms] OR “fibromyalgia”[All Fields] OR (“rheumatism”[All Fields] AND “muscular”[All Fields]) OR “rheumatism muscular”[All Fields]) OR (“fibromyalgia”[MeSH Terms] OR “fibromyalgia”[All Fields] OR “fibrositis”[All Fields]) OR (“fibromyalgia”[MeSH Terms] OR “fibromyalgia”[All Fields] OR (“diffuse”[All Fields] AND “myofascial”[All Fields] AND “pain”[All Fields] AND “syndrome”[All Fields])) OR (“fibromyalgia”[MeSH Terms] OR “fibromyalgia”[All Fields] OR (“fibromyositis”[All Fields] AND “fibromyalgia”[All Fields] AND “syndrome”[All Fields])) OR (“fibromyalgia”[MeSH Terms] OR “fibromyalgia”[All Fields] OR (“fibromyalgia”[All Fields] AND “secondary”[All Fields]) OR “fibromyalgia secondary”[All Fields]) OR (“fibromyalgia”[MeSH Terms] OR “fibromyalgia”[All Fields] OR (“fibromyalgia”[All Fields] AND “primary”[All Fields]) OR “fibromyalgia primary”[All Fields])) AND (((“pain”[MeSH Terms] OR “pain”[All Fields]) AND (“neuroscience s”[All Fields] OR “neurosciences”[MeSH Terms] OR “neurosciences”[All Fields] OR “neuroscience”[All Fields]) AND (“educability”[All Fields] OR “educable”[All Fields] OR “educates”[All Fields] OR “education”[MeSH Subheading] OR “education”[All Fields] OR “educational status”[MeSH Terms] OR (“educational”[All Fields] AND “status”[All Fields]) OR “educational status”[All Fields] OR “education”[MeSH Terms] OR “education s”[All Fields] OR “educational”[All Fields] OR “educative”[All Fields] OR “educator”[All Fields] OR “educator s”[All Fields] OR “educators”[All Fields] OR “teaching”[MeSH Terms] OR “teaching”[All Fields] OR “educate”[All Fields] OR “educated”[All Fields] OR “educating”[All Fields] OR “educations”[All Fields])) OR (“patient education handout”[Publication Type] OR “patient education as topic”[MeSH Terms] OR “patient education”[All Fields]))) AND (meta-analysis[Filter] OR systematicreview[Filter])

-EMBASE (6 articles retrieved)

‘fibromyalgia’/exp AND (‘pain education’/exp OR ‘pain neuroscience education’/exp) AND (‘systematic review’/exp OR ‘review, systematic’ OR ‘systematic review’ OR ‘meta analysis’/exp OR ‘analysis, meta’ OR ‘meta analysis’ OR ‘meta-analysis’ OR ‘metaanalysis’)

Mapped terms ‘’meta analysis” mapped to ‘meta analysis’, term is exploded

-PEDro (20 articles retrieved)

1. Abstract and Title: Pain Neuroscience Education AND Fibromyalgia. (seven articles retrieved)
2. Abstract and Title: Pain Neuroscience Education AND Fibromyalgia. Method: systematic review (one article retrieved)
3. Abstract and Title: Pain Neurophysiology Education AND Fibromyalgia. Method: systematic review (0 articles retrieved)
4. Abstract and Title: Pain Education AND Fibromyalgia. Method: systematic review (12 articles retrieved)

-CINAHL (45 articles retrieved)

-(pain neuroscience education or pain neurophysiology education) AND (fibromyalgia or fibromyalgia syndrome or fms or fm)
-(pain neuroscience education or pain neurophysiology education) AND (fibromyalgia [mesh] or fibromyalgia or fibromyalgia syndrome or fms or fm)
-(pain neuroscience education’ or ‘pain education’ or ‘pain neurophysiology education’ or ‘therapeutic neuroscience education) AND fibromyalgia syndrome)
-(pain neuroscience education’ or ‘pain education’ or ‘pain neurophysiology education’ or ‘therapeutic neuroscience education) AND fibromyalgia syndrome AND (systematic review or meta-analysis)

-Psicodoc (0 articles retrieved)

Terms employed:
-Pain neuroscience education
-Pain education
-Pain neurophysiology education
-Therapeutic neuroscience education
-Fibromyalgia

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-SPORTDiscus (14 articles retrieved)

-pain neuroscience education' or 'pain education' or 'pain neurophysiology education' or 'therapeutic neuroscience education) AND (fibromyalgia [mesh] or fibromyalgia or fibromyalgia syndrome or fms or fm) AND (systematic review or meta-analysis
-pain neuroscience education' or 'pain education' or 'pain neurophysiology education' or 'therapeutic neuroscience education) AND (fibromyalgia [mesh] or fibromyalgia or fibromyalgia syndrome or fms or fm)

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