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Effectiveness of a structured group intervention based on pain neuroscience education for patients with fibromyalgia in primary care: A multicentre randomized open-label controlled trial

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Abstract

Background: There has been increased interest in pain neuroscience education (PNE) as a therapeutic approach for the management of fibromyalgia (FM).

Methods: A multicentre randomized, open-label, controlled trial was conducted to assess the effectiveness of a structured group intervention based on PNE in patients with FM. A total of 139 patients were included in the study and randomized to the intervention group (7 group sessions of education in neurobiology of pain) or to the control group (treatment as usual only). The primary outcome was the improvement

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of functional status and pain measured with the Fibromyalgia Impact Questionnaire (FIQ), and secondary outcomes were the reduction in the impact of pain and other symptoms (catastrophizing, anxiety and depression) and number of patients reaching no worse than moderate functional impairment (FIQ score <39). Differences between groups were calculated by linear mixed-effects (intention-to-treat approach) and mediational models through path analyses.

Results: At 1 year, improvements in FIQ scores were higher in the intervention group with moderate or high effect size, and decreases of ≥20% in 69.1% of patients (20.9% in the control group) and of ≥50% in 39.7% (4.5% in the control group). Also, 52.9% of patients had a FIQ <39 points (13.4% in the control group).

Conclusions: In this sample of patients with FM, the improvement in quality of life and control of symptoms obtained by adding a PNE intervention showed promising results, equalling or surpassing previously reported outcomes.

Significance: A structured group intervention based on pain neuroscience education for 1 year in patients with fibromyalgia was associated with significant amelioration of the impact of the disease on scores of the Fibromyalgia Impact Questionnaire, the Health Assessment Questionnaire, the Hospital Anxiety and Depression Scale, the Pain Catastrophizing Scale and the Polysymptomatic Distress Scale as compared with only treatment as usual. These findings are clinically relevant considering the challenges posed by fibromyalgia to clinicians and patients alike.

1 | INTRODUCTION

Fibromyalgia (FM), a disorder of chronic widespread pain accompanied by numerous other symptoms that causes significant functional impairment, is currently considered to fall under the umbrella of central sensitivity syndromes. In these syndromes, there is an amplification of sensory stimuli and a permanent activation of the alarm system, with sustained motor, autonomic and neuroendocrine reactions (Hawkins, 2013; Yunus, 2007). At present, there are no medications with FM-specific approval in Europe, and therapies are focused on the relief of symptoms and improvement of quality of life and functioning (Macfarlane et al., 2017). Nonpharmacological interventions, such as physical exercise (Bidonde et al., 2017) and cognitive behavioural therapy (Bernardy et al., 2018), have provided evidence-based benefits (García et al., 2018) and are recommended by guidelines (Macfarlane et al., 2017).

Recently, growing evidence supports the use of pain neuroscience education (PNE) as an educational strategy that focuses on teaching subjects especially those with chronic pain, about the neurobiological and neurophysiological processes involved in their pain experience (Brodal, 2017; Butler & Moseley, 2003; Geneen et al., 2015; Gifford, 1998; Gomez-Arguelles et al., 2018; Moseley, 2003b). Knowing and understanding the mechanisms behind the perception of pain may reduce the assessment of threat and change the patient's cognition of the pain process and the attitudes related to it (Moseley, 2003a, 2003b). The use of PNE in patients with FM has shown promising results (Amer-Cuenca et al., 2019; Van Ittersum et al., 2014; Van Oosterwijck et al., 2013) but the reported experience is still limited. This randomized controlled clinical trial investigated the effectiveness of a structured group intervention based on PNE for improving pain and functioning in patients with FM as compared with treatment as usual.

2 | METHODS

2.1 | Trial design

We conducted a multicentre, randomized, open-label, controlled trial in the primary care setting at the Basque country in Spain. The main goal of the study was to evaluate the effectiveness at 1 year of a structured education intervention in neurobiology of pain in patients diagnosed with FM as compared with a control group of patients that continued only with their usual treatments. The time frame of the study was 1 year. All patients provided written informed consent before enrolment. The study protocol was designed following the SPIRIT statement (https://www.spirit-statement.org/) and was approved by the Ethics Committee of the Basque country (file no. PI2016097). This trial was registered at ClinicalTrials.gov (identifier NCT03947502).

2.2 | Patients

Participants in the study were male and female patients aged 18 years or older who had been previously diagnosed with FM by their attending physicians (e.g. rheumatologists, specialists in internal medicine, general practitioners, etc.) in any health care setting. The electronic databases of patients with FM included in the waiting lists for appointments in five primary health care centres in the area of Bilbao (Basque country, Spain) were used for the selection of patients. Eligible patients were initially contacted by telephone and were informed regarding the purpose and characteristics of the study; those who agreed were appointed for an initial (enrolment) visit at the primary health care centre. At this visit, a member of the research team confirmed the diagnosis of FM according to 2010 diagnostic criteria of the American College of Rheumatology (Wolfe et al., 2010) (i.e. widespread pain index (WPI) ≥ 7 and symptom severity (SS) score ≥5 or WPI 3–6 and SS ≥9, presence of symptoms at a similar level for at least 3 months and absence of any disorder that would otherwise explain the pain) and reviewed the exclusion criteria, which were cognitive impairment or psychiatric disorders that prevented to complete the study questionnaires. Full details of the study were provided and enrolled patients signed the written informed consent.

2.3 | Randomization

After written informed consent was obtained, enrolled patients were randomized to 1 of 2 treatment groups. Randomization was performed by the statistical team with the software nQuery Advisor version 7.0 (Statistical Solutions, Boston, MA, USA). The randomization list generated by this process was concealed and safeguarded by the statistical team. The research team and treating physicians did not have access to this list. Allocation concealment was maintained by the use of sequentially numbered opaque envelopes containing a letter A (experimental group) or B (control group), following the randomization list and were opened by the therapists who performed the intervention after enrolment. Each study arm was subsequently subdivided into five subgroups, each of them (an intervention subgroup and control subgroup) assigned to the five participating centres. Patients assigned to the intervention arm received a structured pedagogical group intervention based on PNE and patients randomized to both groups (intervention and control) continued with their usual treatments. Neither the patients nor the evaluators were blinded to the treatment allocation. However, data managers and the statistical team were blinded.

2.4 | Intervention

The theoretical framework of the educational intervention is based on PNE to address chronic pain, providing extensive explanations of neurobiology and neurophysiology adapted for FM patients (Butler & Moseley, 2003; Goicoechea & Echávarri, 2009; Goicoechea & Goicoechea, 2019; Louw Pt et al. 2016). Briefly, the purpose is to make the person aware that there are unconscious automatic mechanisms involved in the learning processes, sensitization and acquisition of beliefs about pain that can be modulated through conscious behaviour. Active participation of the patient is proposed in the process of central nervous system (CNS) desensitization with his/her attention fostered with the aim of weakening the neuronal connections that comprise the pain neuromatrix, and establishing new connections thanks to neuroplasticity. Likewise, improvement of proprioception was attempted with exercises of conscious movement. Work was based on the hypothesis of the importance of the information handled by the CNS in the threat assessment process as a determining factor in the appearance and maintenance of the pain disorder. This threat assessment is favoured by unconscious nociceptive learning throughout life, such as the alarmist culture, the presence of pain models in the surroundings and the information given by expert professionals as sensitizing factors.

Patients were divided into five subgroups of 14 patients each. The intervention consisted of six 2-hr weekly classes taught by a multidisciplinary team of two or three experienced therapists trained in teaching educational interventions to patients with FM, followed by a seventh reinforcement class a month later. Therapists who delivered the intervention taught the content of each class with the aid of audio-visual material. Interspersed in the neurobiology topic were short exercises of conscious movement. After each class, supporting material was sent to patients by email. The content of the classes (Barrenengoa, Gracia, & Martínez de la Eranueva, 2020) is summarized in the Supplementary material. PNE was not associated with physical therapy or use of physical exercises and sport, although patients were motivated in this direction during the sessions.

Patients both in the intervention and control groups continued with their usual treatments, with medication adjustments made at follow-up visits when necessary by their attending physicians (different from the researchers of the study). In Spain, the usual treatment for patients with FM is mainly pharmacological and adjusted to the symptomatic profile of each individual patient, mostly including antidepressants, antiepileptics and opioid and nonopioid analgesics. Exercise tailored to the patients' physical limitations are usually recommended based on recommendations of scientific societies summarized in a document issued by the Spanish Ministry of Health (Ministerio de Sanidad, 2011).

2.5 | Study procedures and data collection

The study included a baseline visit, a visit after treatment (1 month) and follow-up visits at 6 and 12 months. At the baseline visit, clinical history of pain was made, demographics and clinical data were recorded, and the study questionnaires were completed. At follow-up visits, clinical data were recorded and study questionnaires were also completed. Visits lasted about 45 min except for the baseline visit in patients assigned to the intervention arm, in which personal and familial history of pain was specifically recorded and lasted about 90 min.

Data collected for each patient included demographics (age, gender); civil status; number of children; education level (categorized as 'up to secondary school' and 'higher level'); employment status; age at diagnosis of FM; socioeconomic deprivation index (computed by the Health Research Service of the Basque country from 2011 census of population and housing (Domínguez-Berjón et al., 2008) and divided into quintiles); the Fibromyalgia Impact Questionnaire (FIQ) (Burckhardt et al., 1991); the Brief Pain Inventory-Short Form (BPI-SF) (Tan et al., 2004); the Health Assessment Questionnaire (HAQ) (Fries, 1983); the Hospital Anxiety and Depression Scale (HADS) (Zigmond et al., 2014); the Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995); the WPI (Wolfe et al., 2010); the SS score (Wolfe et al., 2010); the Polysymptomatic Distress Scale (PSD) (Wolfe et al., 2013) and adverse events in response to direct questioning.

The FIQ is composed of 10 items. The first item contains 11 questions related to physical functioning (each question is rated on a 4-point Likert-type scale). Items 2 and 3 ask the patient to mark the number of days they felt well and the number of days they were unable to work because of FM symptoms. Items 4 through 10 are horizontal linear scales marked in 10 increments on which the patient rates work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety and depression. The maximum possible score is 100, with the higher the score, the greater impairment. The BPI-SF is an 11-item scale that assesses the severity or intensity of pain and its impact on functioning or interference, with 4 BPI severity items and 7 BPI interference items (Tan et al., 2004). Higher scores indicate greater severity and interference. The HAQ, developed for the assessment of disability in patients with rheumatoid arthritis, is composed of 20 questions concerning activities of daily living and 14 questions relating to the use of aids and devices. Higher scores mean more severe symptoms. The HADS consists of two subscales, anxiety and depression (7 items for each subscale), with higher scores indicating the most severe symptoms. The PCS consists of 13 items with three subscales (magnification, rumination and helplessness) and scored from 0 to 4, resulting in a total possible score of 52. The higher the score, the more catastrophizing thoughts are present. The WPI quantifies the extent of bodily pain on a 0–19 scale by asking patients if they have had pain or tenderness in 19 different body regions over the past week, with each painful or tender region scoring 1 point. The SS final score is the sum of the fatigue, nonrestorative sleep and cognitive symptom scores in addition to 'other symptoms' score, with a final score ranging between 0 and 12. The sum of the WPI and the SS score constitutes

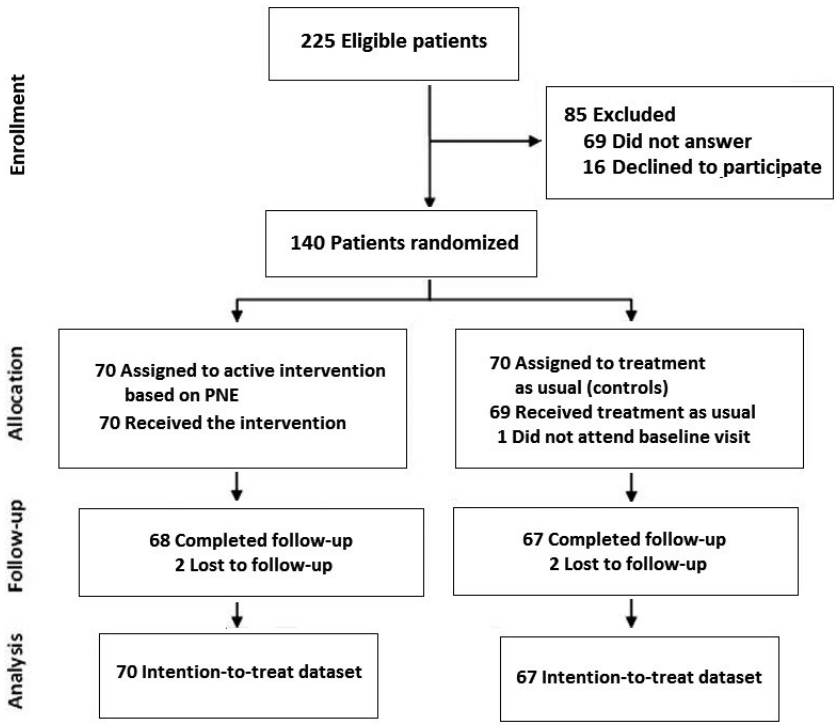

FIGURE 1 Flow diagram of the study population

TABLE 1 Baseline characteristics of the study population

Variable	Intervention group ($n = 70$)	Control group ($n = 69$)	*P* value
Gender (*N* [%])			
Males	2 (2.9)	6 (8.7)	0.139
Females	68 (97.1)	63 (91.3)	
Age, years (mean [*SD*])	52.3 (9.2)	51.4 (10.2)	0.845
Civil status (*N* [%])			
Single	10 (14.3)	12 (17.4)	0.725
Married/with partner	49 (70)	46 (66.7)	
Widowed	1 (1.4)	0	
Separate/ divorced	10 (14.3)	11 (15.9)	
Number of children (*N* [%])			
None	17 (24.3)	16 (23.2)	0.560
1	22 (31.4)	15 (21.7)	
2	26 (37.1)	32 (46.4)	
≥3	5 (7.1)	6 (8.7)	
Education level (*N* [%])			
Up to secondary school	44 (62.9)	46 (66.7)	0.638
Higher	26 (37.1)	23 (33.3)	
Deprivation index (*N* [%])			
1–2	29 (47,5)	21 (31.3)	0.168
3	9 (14.8)	14 (20.9)	
4–5	23 (37.7)	32 (47.8)	
Employment status (*N* [%])			
Retired/ invalidity	10 (14.3)	7 (10.1)	0.868
Unemployed/ sick leave	23 (32.9)	26 (37.7)	
Active	29 (41.4)	28 (40.6)	
Unpaid housework	8 (11.4)	8 (11.6)	
Age at diagnosis of FM, years (*N* [%])			
≤14	7 (10)	5 (7.2)	0.690
15–24	15 (21.4)	16 (23.2)	
25–34	16 (22.9)	18 (26.1)	
35–44	20 (28.6)	22 (31.9)	
45–54	7 (10)	7 (10)	
55–64	2 (2.9)	1 (1.4)	
Patients with Pharmacological treatment, (*N* [%]). See also Figure 2	66 (94.28)	64 (92.75)	0.714
Antidepressants	33 (47.14)	32 (46.38)	0.928
Anticonvulsants	38 (54.28)	37 (53.62)	0.938
Total analgesics	57 (81.43)	58 (84.06)	0.682
Opioid analgesics	23 (32.86)	23 (33.33)	0.952

the fibromyalgianess scale or PSD, a measure of physical and psychological symptom intensity (distress) that can be applied to subjects regardless of disease. The study questionnaires were administered by the therapists at each study visit using the Spanish validated version of the FIQ (Monterde et al., 2004), BPI-SF (Arreola Ornelas et al., 2012), HAQ (Esteve-Vives et al., 1993), HADS (Vallejo et al., 2012) and PCS (García Campayo et al., 2008).

2.6 | Outcomes

The primary outcome was the decrease in FIQ scores at the end of the study as compared with baseline in patients undergoing the intervention versus controls. Secondary outcomes were the decreases in BPI-SF, HAQ, HADS, PCS and PSD as well the percentage of responders and nonresponders in the two study groups according to a ≥20% reduction in the FIQ score from baseline to the end of the study, ≥ 50% reduction in the FIQ score from baseline to the end of the study and number of patients reaching no worse than moderate functional impairment (FIQ score <39) (Luciano et al., 2014).

Losses were defined as participants who did not attend more that 50% of the classes and/or those who failed to attend the follow-up visit at 12 months.

2.7 | Statistical analysis

Based on a medium effect size of 0.52 for functional status of the FIQ reported in a previous meta-analysis of psychological treatments for FM (Glombiewski et al., 2010), a sample size of 70 patients per group was needed to achieve a 5% two-sided significance level and 80% power while accounting for a maximum loss rate of 20%. Categorical variables were compared with the chi-square test or the Fisher's exact test, and continuous variables with the Student's *t* test, the analysis of variance (ANOVA) or the Mann-Whitney *U* test according to the conditions of application. The Bonferroni's correction was used to adjust in multiple pairwise comparisons. Main analyses of effectiveness were performed in the intention-to-treat (ITT) dataset; missing data were handled with imputation. Linear mixed-effect regression models were used to assess differences in the study variables between the

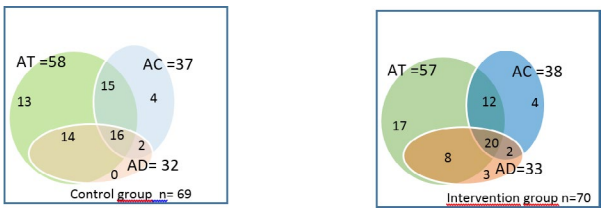

FIGURE 2 Details of pharmacological treatment in the study groups. No pharmacological treatment, intervention group, $n = 4$, control group, $n = 5$ (AT, analgesics total, AC, anticonvulsants, AD, antidepressants)

intervention and control groups (response variable: score of each study questionnaire at follow-up; explanatory variables: baseline score, group, time and interaction between group and time). The effect size was evaluated using Cohen's d ($d = 0.20$ small, $d = 0.50$ medium and $d = 0.80$ large effect sizes respectively). The absolute risk reduction (ARR) with the 95% confidence interval (CI) and number needed to treat (NNT) with the intervention to achieve response for a FIQ score reduction ≥20% and ≥50%, and FIQ total score <39 were also calculated. Statistical significance was set

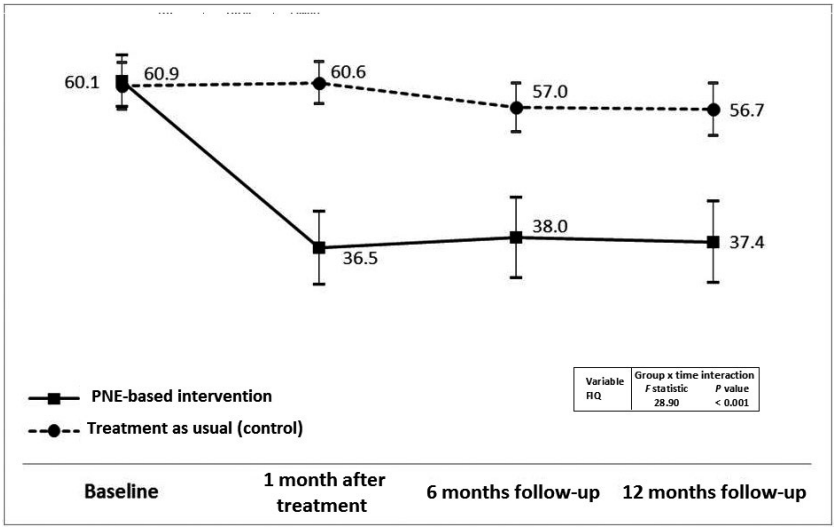

FIGURE 3 Changes of FIQ scores during the study period

TABLE 2 Changes of the Fibromyalgia Impact Questionnaire (FIQ) during the study period

	Baseline			End of therapy (1 month)	
FIQ items	PNE-based intervention mean (*SD*)	Treatment as usual mean (*SD*)	Cohen´s *d* ES (95% CI)	PNE-based intervention mean (*SD*)	Treatment as usual mean (*SD*)
Physical functioning	3.6 (2.4)	3.6 (2.4)	0.00 (−0.001–0.01)	1.4 (1.7)	1.4 (2.4)
Days felt good	8.3 (2.9)	8.3 (2.4)	0.07 (−0.01–0.19)	4.5 (3.7)	8.7 (2.2)
Pain influencing work	6.1 (2.0)	5.9 (2.2)	0.09 (−0.002–0.21)	3.3 (3.5)	6.9 (2.3)
Pain	7.3 (2.3)	7.2 (2.0)	0.04 (−0.02–0.11)	5.0 (2.8)	7.6 (1.7)
Fatigue	8.2 (1.9)	8.1 (1.9)	0.05 (−0.02–0.14)	5.1 (3.1)	8.1 (1.8)
Morning tiredness	7.9 (2.2)	7.8 (2.5)	0.04 (−0.02–0.12)	5.0 (3.5)	8.0 (2.0)
Stiffness	7.4 (2.8)	7.2 (2.7)	0.07 (−0.01–0.18)	4.0 (3.2)	6.9 (3.0)
Anxiety	7.0 (2.6)	7.3 (2.4)	0.12 (0.01–0.26)	4.7 (3.3)	6.9 (3.0)
Depression	6.7 (3.0)	6.7 (3.0)	0.00 (−0.001–0.01)	3.5 (3.4)	6.5 (3.0)
FIQ total score	60.9 (15.3)	60.1 (13.8)	0.05 (−0.02–0.14)	36.5 (21.8)	60.6 (12.8)

Note: PNE, pain Neurobiology Education; *SD*, standard deviation; ES, effect size; CI, confidence interval.

at $p < .05$. SPSS version 23.0 and SAS version 9.3 (SAS Institute) were used for statistical analysis.

3 | RESULTS

From a total of 225 eligible patients diagnosed with FM, 156 (69.3%) were contacted by phone and 140 (89%) of them agreed to participate in the study. The remaining 16 patients refused for several reasons including working, maternity, surgical procedure or hospital admission. As shown in the flow diagram of the study population (Figure 1), of the 140 patients randomized, 70 were assigned to the intervention group and 70 to the control group. One patient in the control group did not attend the baseline visit. At follow-up, two patients from each group were lost (did not attend at least 50% of classes and/or the 12-month follow-up). The ITT dataset included 70 patients in the intervention group (97.1%, $n = 68$, completed the study) and 69 in the control group (95.7%, $n = 67$, completed the study). More than 90% of patients were women with a mean age of 51.9 years. As shown in Table 1, significant differences in baseline characteristics of patients between the two study groups were not found. Differences in the use of pharmacological medications were not found. Details of pharmacological treatment regarding the number of patients treated with total analgesics, anticonvulsants and antidepressants are shown in Figure 2.

3.1 | Primary outcome

As shown in Figure 3, the intervention was significantly more effective than treatment as usual for improving mean total score of the FIQ ($p < .001$). The comparison of results in the different items of the FIQ instrument between the intervention and the control groups showed large effect sizes in all dimensions and in the total score, except for a medium effect size for anxiety (Table 2). At 12 months, the effect sizes of the differences between the intervention and the control groups were large for pain, fatigue, morning tiredness, anxiety and FIQ total score, and medium for the remaining dimensions.

3.2 | Secondary outcomes

The intervention was also more effective than treatment as usual with differences in BPI (severity and interference), HAD (anxiety and depression), HAQ, PCS and PSD (Figure 4). As shown in Table 3, the effect size of the intervention after 1 month of treatment was large in all questionnaires, except for the HAD subscale depression in which the effect size was medium. At the end of the study, after 12 months, the effect size of the intervention was large in all questionnaires, except for medium effect sizes in HAD subscale anxiety and HAQ.

	Follow-up (6 months)			Follow-up (12 months)		
Cohen´s *d* ES (95% CI)	**PNE-based intervention mean (*SD*)**	**Treatment as usual mean (*SD*)**	**Cohen´s *d* ES (95% CI)**	**PNE-based intervention mean (*SD*)**	**Treatment as usual mean (*SD*)**	**Cohen´s *d* ES (95% CI)**
0.96 (0.59–1.55)	1.5 (1.8)	3.4 (2.4)	0.89 (0.54–1.45)	1.6 (1.9)	3.2 (2.4)	0.74 (0.43–1.22)
1.38 (0.89–2.18)	5.0 (4.0)	8.5 (2.5)	1.05 (0.66–1.69)	5.3 (3.9)	8.0 (2.9)	0.78 (0.46–1.29)
1.21 (0.78–1.94)	3.0 (3.2)	5.8 (2.6)	0.96 (0.59–1.55)	3.4 (3.2)	5.4 (2.6)	0.68 (0.39–1.39)
1.22 (0.71–1.79)	5.1 (2.9)	6.6 (2.3)	0.57 (0.31–0.97)	4.9 (2.8)	7.3 (2.0)	0.98 (0.61–1.59)
1.18 (0.75–1.89)	5.2 (3.4)	7.6 (1.8)	0.88 (0.53–1.43)	5.1 (3.3)	7.4 (1.9)	0.85 (0.51–1.39)
1.05 (0.66–1.69)	5.0 (3.6)	7.4 (2.5)	0.77 (0.45–1.27)	4.7 (3.2)	7.0 (2.5)	0.80 (0.47–1.31)
0.93 (0.57–1.51)	4.8 (3.4)	6.5 (2.7)	0.65 (0.37–1.09)	4.3 (3.4)	6.4 (2.7)	0.68 (0.39–1.13)
0.69 (0.39–1.16)	4.5 (3.4)	6.7 (2.6)	0.73 (0.42–1.20)	4.5 (3.5)	7.0 (2.5)	0.82 (0.49–1.34)
0.93 (0.57–1.51)	3.7 (3.6)	6.4 (2.9)	0.82 (0.49–1.35)	3.9 (3.6)	6.1 (3.1)	0.65 (0.37–1.09)
1.35 (0.88–2.14)	38.0 (24.2)	57.0 (14.3)	0.95 (0.59–1.55)	37.4 (24.1)	56.7 (15.6)	0.95 (0.58–1.54)

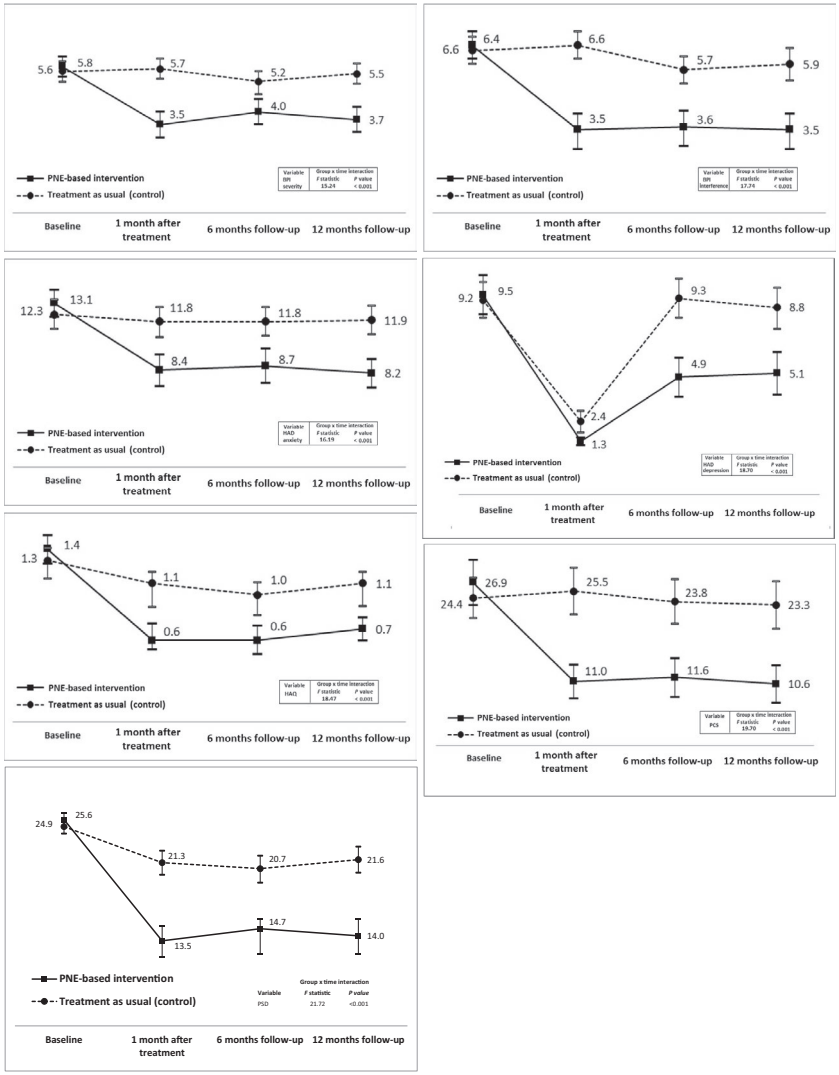

FIGURE 4 Changes of scores in the BPI-SF severity and interference, HAD anxiety and depression, HAQ, PCS and PSD scales during the study period

TABLE 3 Changes of the Brief Pain Inventory-Short Form (BPI-SF), the Health Assessment Questionnaire (HAQ), the Hospital Anxiety and Depression Scale (HADS), the Pain Catastrophizing Scale (PCS), the Widespread Pain Index (WPI), the Symptom Severity (SS) and the Polysymptomatic Distress Scale (PSD) during the study period

	Baseline			End of therapy (1 month)		
Questionnaires	PNE-based intervention mean (*SD*)	Treatment as usual mean (*SD*)	Cohen´s *d* ES (95% CI)	PNE-based intervention mean (*SD*)	Treatment as usual mean (*SD*)	Cohen´s *d* ES (95% CI)
BPI severity	5.8 (1.7)	5.6 (1.7)	0.12 (−0.02–0.11)	3.5 (1.9)	5.7 (1.7)	1.22 (0.78–1.94)
BPI interference	6.6 (2.2)	6.4 (2.2)	0.09 (−0.004–0.21)	3.5 (2.7)	6.6 (2.2)	1.25 (0.81–2.00)
HDA anxiety	13.1 (3.9)	12.3 (4.2)	0.19 (0.05–0.38)	8.4 (4.6)	11.8 (4.3)	0.76 (0.45–1.25)
HDA depression	9.5 (4.4)	9.2 (4.0)	0.07 (−0.01–0.17)	1.3 (0.9)	2.4 (2.4)	0.60 (0.33–1.01)
HAQ	1.4 (0.5)	1.3 (0.6)	0.18 (0.04–0.36)	0.6 (0.5)	1.1 (0.6)	0.90 (0.55–1.47)
PCS	26.9 (14.6)	24.4 (13.0)	0.18 (0.04–0.3)	11.0 (11.3)	25.5 (15.7)	1.06 (0.66–1.70)
PSD	25.6 (2.8)	24.9 (3.1)	0.23 (0.07–0.4)	13.5 (6.4)	21.3 (5.1)	1.34 (0.9–2.1)
WPI	17.3 (2.2)	16.6 (2.5)	0.30 (0.1–0.5)	8.3 (4.5)	13.4 (3.9)	0.21 (0.06–0.4)
SS	8.3 (1.0)	8.3 (1.0)	0	5.2 (2.5)	7.9 (1.9)	1.22 (0.8–1.9)

Note: PNE: pain neurobiology education; *SD*: standard deviation; ES: effect size; CI: confidence interval.

The number of responders with a reduction in the total FIQ score ≥20% and ≥50%, and FIQ score <39 points was significantly higher ($p < .001$) in the intervention group as compared with controls at each time point of the study (Table 4). Also, the intervention was associated with ARR of 49.7% (95% CI 37.3–65.9) and NNT of 2.01 (95% CI 1.99–2.03) for a ≥20% reduction in the total FIQ score, ARR of 35.2% (95% CI 34.8–35.6) and NNT of 2.83 (95% CI 2.80–2.87) for a ≥50% reduction in total FIQ score, and ARR of 39.5% (95% CI 39–39.9) and NNT of 2.53 (95% CI 2.50–2.56) for a total FIQ score <39.

4 | DISCUSSION

This randomized controlled trial shows that a structured group intervention based on PNE was effective in reducing the impact of FM on pain, anxiety and catastrophizing thoughts as compared with treatment as usual only. Significant improvements were already seen after 1 month of treatment and were sustained over the 6-month and 12-month follow-up periods.

The effect sizes for the difference between the intervention control groups were large/medium for almost of components of the study questionnaires, particularly pain, fatigue and morning tiredness of the FIQ, pain severity and interference of the BPI-SF, anxiety of the HAD and catastrophism of the PCS. These findings are clinically relevant and confirm data of a before-and-after study carried out in 85 patients with FM and previously reported by our group (Barrenengoa-Cuadra et al., 2021). In a randomized controlled trial, a similar primary care-based group educational intervention adapted to migraine compared to the routine medical care was effective in preventing migraine attacks and cost-effective in reducing the need for pharmacological treatment (Aguirrezabal et al., 2019).

In a cost-effectiveness analysis of pharmacological treatment options in FM, the use of pregabalin was associated with a reduction in FIQ total score ≥30% in 31.6% of the cases (Arreola Ornelas et al., 2012), whereas in our study, a reduction of ≥50% was achieved in 39.7% of the patients. On the other hand, an in-depth review of pharmacological therapies in fibromyalgia syndrome showed that the majority of drug medications have a modest effect, with substantial benefit in only a minority of patients (Häuser et al., 2014). Also, most patients will discontinue therapy because of either a lack of efficacy or tolerability problems. The promising results of the present study are consistent with recommendations that the initial management of FM should involve patient education proposed in the European League Against Rheumatism (EULAR) revised guidelines for managing FM (Macfarlane et al., 2017).

In a 6-month randomized controlled trial of group acceptance and commitment therapy (EFFIGACT study) (Luciano et al., 2014), the NNT for 50% improvement in the FIQ total score was 46 and for achieving a status of no worse than mild impaired function (FIQ total score <39) also 46. These data are notably more unfavourable that NNT of 2.8 and 2.5 obtained in our study for FIQ ≥50% and FIQ <39, respectively.

Results of a systematic review of randomized controlled trials of PNE in patients with musculoskeletal disorders, support the use of PNE in reducing pain and improving patient knowledge of pain, improving function and lowering disability, reducing psychosocial factors, enhancing movement

Follow-up (6 months)			Follow-up (12 months)		
PNE-based intervention mean (*SD*)	**Treatment as usual mean (*SD*)**	**Cohen´s *d* ES (95% CI)**	**PNE-based intervention mean (*SD*)**	**Treatment as usual mean (*SD*)**	**Cohen´s *d* ES (95% CI)**
4.0 (2.2)	5.2 (1.9)	0.58 (0.32–0.98)	3.7 (2.2)	5.5 (1.8)	0.89 (0.54–1.45)
3.6 (2.7)	5.7 (2.2)	0.85 (0.51–1.39)	3.5 (2.7)	5.9 (2.3)	0.95 (0.59–1.55)
8.7 (4.9)	11.8 (4.1)	0.68 (0.39–1.39)	8.2 (4.2)	11.9 (4.1)	0.89 (0.54–1.45)
4.9 (4.5)	9.3 (4.5)	0.98 (0.60–1.58)	5.1 (4.9)	8.8 (4.7)	0.77 (0.45–1.26)
0.6 (0.5)	1.0 (0.6)	0.72 (0.42–1.19)	0.7 (0.5)	1.1 (0.6)	0.54 (0.29–0.92)
11.6 (12.8)	23.8 (14.2)	0.90 (0.54–1.46)	10.6 (12.3)	23.3 (15.5)	0.91 (0.55–1.47)
14.7 (7.4)	20.7 (5.7)	0.90 (0.5–1.4)	14.0 (7.4)	21.6 (5.5)	1.16 (0.7–1.8)
9.4 (5.0)	13.1 (4.5)	0.78 (0.5–1.3)	8.9 (5.1)	13.6 (4.0)	1.02 (0.6–1.6)
5.3 (2.9)	7.9 (1.9)	1.06 (0.7–1.7)	5.1 (2.9)	8.0 (2.0)	1.16 (0.8–1.8)

TABLE 4 Number of responders according to four cut-off criteria

Cutoff criteria	End of therapy (1 month)			Follow-up (6 months)			Follow-up (12 months)		
	PNE-based intervention no. (%)	Treatment as usual no. (%)	*P* value	PNE-based intervention no. (%)	Treatment as usual no. (%)	*P* value	PNE-based intervention no. (%)	Treatment as usual no. (%)	*P*value
FIQ total score reduction ≥20%	48 (70.6)	6 (9.0)	<0.0001	41 (60.3)	11 (16.4)	<0.0001	48 (70.6)	14 (20.9)	<0.0001
FIQ total score reduction ≥50%	27 (39.7)	2 (3.0)	<0.0001	29 (42.6)	1 (1.5)	< 0.0001	27 (39.7)	3 (4.5)	<0.0001
FIQ total score <39 points	36 (52.9)	4 (6.0)	<0.0001	34 (50.0)	8 (11.9)	<0.0001	36 (52.9)	9 (13.4)	<0.0001

Note: ACR, American College of Rheumatology.

and minimizing health care utilization (Louw et al., 2016). Evidence of the use of PNE in patients with FM is scarce. In a double-blind randomized controlled trial, intensive pain physiology education versus pacing self-management education was associated with significant differences in improvements in physical functioning, vitality, mental health, general health perceptions and lower pain scores (Van Oosterwijck et al., 2013). In another 6-month randomized double-blind multicentre study, written pain neuroscience education compared to written relaxation training, did not change the impact of FM on daily life, catastrophizing or perceived symptoms of patients with FM (Van Ittersum et al., 2014). The study concluded that face-to-face sessions of pain neuroscience education are required to change inappropriate cognitions and perceived health in patients with FM (Van Ittersum et al., 2014). In a single-blind randomized trial of 77 patients with FM, PNE leads to improvements in pain intensity and this improvement was correlated with the duration of the PNE received (6 weekly, 45-min group sessions) (Amer-Cuenca et al., 2019). However, the intervention of our study has a longer duration than "high doses of PNE" described by the authors (Amer-Cuenca et al., 2019), which could be relevant when interpreting better results obtained in the present study.

Our intervention programme, as well as containing information about the neurobiology of pain in common with other published interventions based on PNE (Amer-Cuenca et al., 2019; Van Oosterwijck et al., 2013), adds the concept of cerebral-acquired evaluation error (Goicoechea & Echávarri, 2009; Goicoechea & Goicoechea, 2019). This novel approach incorporates as a sensitizing factor with unconscious nociceptive lifelong learning involved in the etiopathogenetic mechanisms of FM. The symptoms would arise because of an erroneous assessment of danger by the neuronal network. Such an error would be arrived at by multiple and complex mechanisms that define biological learning. We maintain that the alarmist culture, the opinion of experts, the copying of models and erroneous beliefs about one's own organism are major components of this erroneous evaluation process. We consider that the modification of PNE with this concept makes for the great relevance of the results obtained because education in neuroscience leads to new, conscious learning, which can change the previous evaluative errors and enable the patients to modify the confrontation of their symptoms and engage in the gradual re-exposure to activity.

The present findings should be interpreted taking into account some limitations, particularly the open-label design, the absence of an active control group and the lack of control of the pharmacologic treatment. The intervention was known by both evaluators and patients, so that a detection bias in favour of the intervention group cannot be excluded given the subjective component of responses to the questionnaires; data managers and the statistical team were blinded regarding group allocation. On the other hand, the

absence of an active control group receiving an intervention of similar characteristics (structure and duration) does not allow assessing whether or not part of the effect of the intervention was nonspecific related to the care provided by the team of therapists, regardless of the content of the intervention itself. This uncertainty is frequent in clinical trials especially in pragmatic trials, in which nonpharmacological therapies are evaluated in clinical settings in which the usual care does not include similar interventions (as in this study) and nonactive control groups are used (treatment as usual, usual care or waiting list) (Bernardy et al., 2018; Glombiewski et al., 2010; Häuser et al., 2009). This approach, however, increases the external validity of the study and facilitates the clinical applicability of results in other settings (Freedland et al., 2011). A further limitation is the lack of control of the pharmacological treatment. This could be considered a critical methodological problem present in the majority of clinical trials evaluating nonpharmacological interventions in FM (Bernardy et al., 2018; Häuser et al., 2009). Also, ethical considerations are added to the practical difficulties regarding the control of medication mainly due to the presence of frequent comorbidities increasing the risk of overlapping medication. In this respect, the possibility of limiting treatment adjustments could have a negative impact on the patients' health and functionality. In the present study, attending physicians responsible for the patients' pharmacological treatment were unrelated to the intervention and, therefore, it is unlikely that assignment of patients to either of the two arms would have had an influence on medication adjustments. However, the impact of medication adjustments on differences between both study groups cannot be excluded.

It is important to consider that the moderate to high effect sizes observed in the intervention group were also due to the fact that there was no change from baseline to the end of the study in the treatment as usual group, with the large width of most 95% CI influencing on the precision of the results. Accordingly, in the worst case scenario, the effect sizes would have been small to moderate. However, the magnitude of the effect of the intervention in real-world conditions should be assessed in further trials with better designs.

It is unknown whether or not patients in both study groups followed recommendations of physiotherapy and physical exercise (or other complementary therapies) and how involvement in these activities by the patient's own decision could have exerted an influence on the outcomes of the study. However, this situation occurs frequently in other similar studies (Alda et al., 2011; Galan-martin et al., 2020; Glombiewski et al., 2010). The influence of the format of delivery (group only) was not assessed, although results of naturalistic study showed the outcome equivalence of group and individual therapy (Burlingame et al., 2016). On the other hand, the influence of treatment expectations and satisfaction on outcomes was not evaluated, but this interesting aspect may be considered in future studies.

5 | CONCLUSIONS

Although results should be interpreted with an understanding of the study limitations, the improvement in quality of life and control of symptoms obtained by adding a PNE intervention in this patients' sample was significant, equalling or surpassing previously reported outcomes.

CONFLICT OF INTEREST STATEMENT

None to be declared.

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AUTHORSHIP

All the authors have taken part in the acquisition of data and drawing the article. They all discussed the results and commented on the manuscript. In addition of this: MJ. Barrenengoa heads FIMIDOC group, she developed and designed both the educational intervention (Barrenengoa et al., 2020) and the clinical trial, and she carried out the instruction of FIMIDOC group. Rafa Gracia supported the design and development of the intervention. A. Romón did the telephone contacts and first visits of all the patients. LA. Angón collected the data from the questionnaires. E. Arana-Arri and G. Larrinaga did the revision of statistical analyses and results. M. Muñoa-Capron-Manieux and M. Fernández-Luco carried out the redaction of the article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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