

Economic evaluations of educational, physical, and psychological treatments for fibromyalgia: a systematic review with meta-analysis

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Abstract

Nonpharmacological interventions are recommended for the treatment of fibromyalgia, but there is a lack of knowledge about the cost-effectiveness of these interventions. The aim of this study was to systematically review economic evaluations of educational, physical, and psychological interventions for the treatment of fibromyalgia. The search was performed in PUBMED, EMBASE, CINAHL, Cochrane Library, Physiotherapy Evidence Database, PsycINFO, EconLit, National Health Service Economic Evaluation Database, and Health Technology Assessment. Economic evaluations of educational, physical, and psychological interventions for adult patients with fibromyalgia were included. Primary outcomes were healthcare and societal costs, and quality-adjusted life-years, and secondary outcomes were any disease-specific clinical outcome. Costs and effects were pooled in a meta-analysis, when possible. Eleven studies were included, of which 7 compared a psychological intervention with another intervention or usual care/control. Over a 6-month time horizon, healthcare and societal costs of the psychological intervention were significantly lower than usual care (mean difference: \$-2087, 95% confidence interval [CI]: -3061 to -1112; mean difference: \$-2411, 95% CI: -3582 to -1240, respectively), and healthcare costs were significantly lower for the psychological intervention compared with a pharmacological intervention (mean difference: \$-1443, 95% CI: -2165 to -721). Over a 12-month time horizon, healthcare costs for the psychological intervention were significantly lower than for usual care (mean difference: \$-538, 95% CI: -917 to -158). Incremental cost-effectiveness ratios for quality-adjusted life-years and impact of fibromyalgia showed that the psychological intervention was cost-effective compared with other interventions and control conditions. There is a need of more economic evaluations conducted alongside randomized controlled trials with interventions recommended for the treatment of fibromyalgia, such as physical exercise.

Keywords: Fibromyalgia, Systematic review, Economic evaluation, Nonpharmacological intervention

1. Introduction

Fibromyalgia is a chronic widespread pain, often accompanied by physical exhaustion, and sleep and cognitive disturbances.¹² Patients with fibromyalgia report a wide range of comorbid conditions, such as functional somatic syndromes, anxiety and depressive symptoms, and rheumatic diseases.¹² The overall prevalence of fibromyalgia in the general population ranges between 1.8%¹⁵ and 2.7%.³⁹ Treatment should focus first on

nonpharmacological modalities, such as exercise therapy and psychological and multicomponent therapies, including education.^{12,29,42} Pharmacological therapy is recommended only if there is a lack of effect of nonpharmacological treatments²⁹ because pharmacological interventions have several potential adverse effects and unsustainable effects.^{5,12}

Fibromyalgia carries a significant economic burden for patients and society.²³ Costs related to fibromyalgia are substantial, with a large share resulting from lost productivity costs.²⁰ Moreover, healthcare and lost productivity costs of patients with fibromyalgia are higher than those of matched peers and similar to patients with other chronic diseases, such as rheumatoid arthritis.¹² Considering the scarcity of resources available for health care worldwide, policy makers need to make choices about which treatments to reimburse and which ones not, to ensure that treatments provide value for money for patients and society.¹² Such decisions are often made using information from economic evaluations. Economic evaluations compare the differences in costs and effects of 2 or more interventions.⁴⁷ Within the field of musculoskeletal and painful disorders, cost-effectiveness (effects are expressed as disease-specific outcomes) and cost-utility (effects are expressed as quality-adjusted life-years [QALYs]), studies are the most commonly encountered types of economic evaluations.^{30,46}

There is a lack of knowledge about the cost-effectiveness of educational, physical, and psychological interventions for patients

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with fibromyalgia,⁴³ and doubts exist about the methodological quality of existing studies. Recently, a systematic review⁵³ on the cost-effectiveness of interventions for functional somatic syndromes including fibromyalgia was published. However, only the available information in the included studies was presented without performing a meta-analysis, and no effort was made to calculate incremental cost-effectiveness ratios (ICERs) for studies that did not present ICERs. However, more complete reporting of costs, effects, and ICERs will result in important information for patients, clinicians, and decision makers. Therefore, the aim of this study was to systematically review economic evaluations of educational, physical, and psychological interventions in the treatment of patients with fibromyalgia, while also assessing the quality of the studies and performing a meta-analysis of the results when possible.

2. Methods

2.1. Study design and registration

The protocol of this systematic review was prospectively registered in the International Prospective Register of Systematic Reviews—PROSPERO (CRD42019119972).

2.2. Inclusion criteria

We included economic evaluations conducted alongside randomized controlled trials or performed using modelling methods that evaluated educational, physical, and psychological interventions for patients with fibromyalgia. Studies conducted in adult patients (aged 18 years or older) were included. Diagnosis should be based on published classification and diagnostic criteria for fibromyalgia of the American College of Rheumatology (1990 and/or 2010/2011 and/or 2016 criteria⁵¹) or on rheumatologist diagnosis. All nonpharmacological interventions to manage fibromyalgia delivered in any setting (inpatient, outpatient, community, or home-based²) were included, such as exercise therapy, behavioural therapy, educational intervention, manual therapy, and acupuncture, among others. The comparator was no treatment, usual care, and other types of nonpharmacological or pharmacological interventions.

2.3. Outcomes

The primary outcomes were healthcare and societal costs, and QALYs. Healthcare costs included use of all medical care services, comprising the study intervention, any other services received for health problems, and follow-up care to the intervention or the underlying condition. Societal costs considered, in addition to healthcare costs, the care provided by family or friends, costs paid by patients and their family themselves, and productivity losses.³⁸ A QALY is a measure of health that combines both length of life and health-related quality of life.^{38,47} The secondary outcome was any important clinical outcome, eg, impact of fibromyalgia and pain intensity, among others.

2.4. Literature search

The search was performed in the following databases: PUBMED, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, Physiotherapy Evidence Database (PEDro), PsycINFO, EconLit, National Health Service Economic Evaluation Database, and Health Technology Assessment Database. The search terms were based on search strategies used in previously conducted systematic reviews regarding fibromyalgia^{6,19} and economic evaluations.^{31,53} The complete search strategy is presented in

Appendix 1 (available as supplemental digital content at <http://links.lww.com/PAIN/B305>). All databases were searched from the inception to April 1, 2020, except the National Health Service Economic Evaluation Database (updated until March 31, 2015) and Health Technology Assessment Database (updated until March 31, 2018). In addition, clinical trial databases from the US National Library of Medicine⁴⁵ and from the World Health Organization International Clinical Trials Registry Platform⁵² were searched for study protocols. Reference lists of included studies and relevant systematic reviews were hand searched to identify additional studies. There were no language restrictions, and only full-text articles were included.

2.5. Data collection and extraction

Two independent reviewers (C.M.N.C. and G.C.M.) selected eligible studies, first based on the title and abstract, and then the full-text article. Disagreements between reviewers were solved first by discussion and then by arbitration of a third reviewer (J.E.B.), if disagreement persisted. All publications related to the eligible studies, such as published protocols or clinical studies, were used for data extraction. Two independent reviewers (C.M.N.C. and G.C.M.) extracted data using a customized data extraction sheet on bibliometric properties (authors, year of publication, and language), demographic and clinical characteristics of the participants (eg, age, sex, sample size, diagnostic criteria, and pain duration), the content of the interventions according to the Template for Intervention Description and Replication guide,¹⁷ design aspects of the economic evaluation (country, currency, type and perspective of the economic evaluation, time horizon, willingness to pay threshold, reference year, and discounting), outcome measurement (clinical outcomes, instruments/questionnaires, duration of follow-ups, and type of healthcare and societal costs), and study results (costs and effects stratified by the group).³¹ Disagreements between the reviewers during data extraction were also solved first by discussion and then by arbitration of a third reviewer (J.E.B.), if disagreement persisted.

2.6. Quality assessment

Two independent reviewers (C.M.N.C. and G.C.M.) assessed the risk of bias of the eligible studies. Disagreements between the reviewers were solved first by discussion and then by arbitration of a third reviewer (J.E.B.), if disagreement persisted. The reporting quality of the economic evaluations was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement,¹⁸ which provides recommendations to improve the reporting of health economic evaluations. The CHEERS checklist has 24 items, and each item was scored as *yes*, *no*, or *not applicable*. Items 4 (target population and subgroups), 7 (comparators), 8 (time horizon), and 11 (measurement of effectiveness) were scored as *yes* even if the rationale for the choice of participants or comparators, the appropriateness of the time horizon, and the use of a single study as a sufficient source of clinical effectiveness was not presented.³¹ Item 9 (discount rate) was scored as *yes* if the authors clearly stated the discount rate in the study and *not applicable* if the authors did not state the time horizon but used a time horizon of 12 months or less. Modelling studies with *yes* for at least 17 of 24 items (71%), and randomized controlled trials with *yes* for at least 14 of 21 (67%) possible items (items 15, 16, and 18 are specific for modelling studies³¹) were considered as having sufficient quality.

The risk of bias of the randomized controlled trials was assessed using the Cochrane risk-of-bias tool (RoB 2).¹⁶ The RoB 2 is

structured in 5 domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. For each domain, the RoB 2 comprises a series of signalling questions and a judgement about the risk of bias of the domain facilitated by an algorithm. The criterion to reach an overall risk of bias judgement for a specific outcome is the following: *low risk of bias* if the trial is judged to be at low risk of bias for all domains, *some concerns* if the trial is judged to raise some concerns for at least one domain, but not to be at high risk of bias for any domain, and *high risk of bias* if the trial is judged to be at high risk of bias in at least one domain or the trial is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result. Although the RoB 2 should be assessed for each outcome separately, we reported this for the randomized controlled trial on the whole because there were no differences in the RoB 2 assessment between self-reported outcomes.

2.7. Data synthesis

Costs were converted to American Dollars (\$) and Euros (€), using values from the 19 countries of the Euro area) using the purchasing power parity for the reference year of the study.³³ Subsequently, costs were inflated to 2019 prices using the consumer price indices for American Dollars⁴⁴ and Euros.⁴¹ If the index year of the study was not reported in the included study, the year of publication was used. Mean differences between costs and effects and 95% confidence intervals (CIs) of a study were calculated, when not presented by the study itself, using the Review Manager 5.3 based on the means and standard deviations stratified by groups if available. If only the mean values of each group were available, the mean difference was calculated by subtracting the mean in the intervention group from the mean in the comparator group. The ICERs for all eligible studies were recalculated to reflect 2019 Dollars and Euros by dividing the difference in costs by the difference in effects. An intervention was considered dominant over the comparator when it was more effective and less costly than the comparator treatment, and dominated by the comparator if it was less effective and more costly than the comparator treatment.⁹ If an intervention was more expensive and more effective than the comparator treatment, the intervention was deemed cost-effective in comparison with the comparator treatment if the incremental cost-utility ratio was below the defined willingness to pay threshold. The threshold we used was equal to the one used by the United Kingdom's National Institute for Health and Clinical Excellence (NICE) of £20,000 per QALY gained (ie, \$29,412 or €20,765).^{3,4} For clinical outcomes other than QALYs, no formal willingness to pay thresholds exist.

Costs and effects were pooled in a meta-analysis for studies in which interventions and comparators, time horizon and perspective of the economic evaluation were similar. Assuming that the intervention effects across the studies were not identical, we used a random-effects model and assessed heterogeneity based on the I^2 statistics.¹⁶ When substantial heterogeneity was present ($I^2 > 50\%$), we scrutinised the studies for differences in sample characteristics, details of the economic evaluation, instruments used for outcome data collection and risk of bias. After that, if we could not find an explanation for the heterogeneity, we performed meta-analysis and presented the results with caution.

3. Results

Our search strategy identified 2899 studies, of which 703 were duplicates. After screening of titles and abstracts, the full-text of 77

studies were checked, and 11 studies were included. No study was found in protocol registration databases and through hand searching. The main reasons of exclusion were not full article but, for example, conference abstracts, and not economic evaluations (Appendix 2, available as supplemental digital content at <http://links.lww.com/PAIN/B305>). A flow diagram of the study selection is presented in **Figure 1**.

3.1. Overview of the included studies

The main characteristics of the included studies are presented in **Table 1**. The most recent study was published in 2020,⁸ and the oldest study was published in 1996.¹⁰ Most studies were conducted in Europe^{8,10,11,14,25,26,28,35,49,55}; only 1 study was conducted in the United States.³⁴ The studies included 2028 participants in total, varying from 33¹¹ to 600 participants³⁴ per study. All studies were randomized controlled trials.^{8,10,11,14,25,26,28,34,35,49,55} Most studies were performed from both the healthcare and societal perspectives; 11,14,25,26,28,35,49 2 were performed only from the healthcare perspective^{8,34} and 2 only from the societal perspective.^{10,55} The time horizon was shorter than 9 months in 5 studies,^{8,11,14,26,28} 12 months in 5 studies,^{10,25,34,35,55} and 24 months in 1 study.⁴⁹ Two studies conducted only a cost-effectiveness analysis,^{34,49} 6 studies conducted only a cost-utility analysis,^{10,11,25,26,35,55} and 3 studies conducted both analyses.^{8,14,28} Nine studies measured utilities to calculate QALYs: 7 studies using the EuroQoL-5 Dimension (EQ-5D),^{8,11,14,25,26,28,35} 1 study using the Short-Form 6 Dimension (SF-6D),⁵⁵ and 1 study using the Maastricht Utility Measurement Questionnaire.¹⁰ The other clinical outcome measured was the impact of fibromyalgia, assessed in 5 studies using the Fibromyalgia Impact Questionnaire.^{8,14,28,34,49} Healthcare costs were assessed in all studies,^{8,10,11,14,25,26,28,34,35,49,55} patient and family costs were assessed in 6 studies,^{10,11,14,25,49,55} and lost productivity costs were also assessed in 6 studies.^{10,14,26,28,35,55}

The included studies compared a psychological intervention with an educational discussion group,¹⁰ pharmacological treatment,^{26,28} mindfulness-based stress reduction,³⁵ another psychological intervention,⁸ waiting list,^{10,14} and usual care.^{25,26,28,35} Two studies compared aquatic program¹¹ or spa treatment⁵⁵ to usual care, one study compared aerobic exercise with multidisciplinary intervention and usual care,⁴⁹ and the last study compared social support to social support plus education and the control group (CG).³⁴ A detailed description of the interventions evaluated in each study can be found in Appendix 3 (available as supplemental digital content at <http://links.lww.com/PAIN/B305>).

3.2. Quality assessment

Based on the CHEERS statement, most of the economic evaluations^{8,11,14,25,26,28,35,49,55} was considered to be of sufficient quality (**Table 2**). Items referring to title, target population and subgroups, setting and location, comparators, time horizon, choice of health outcomes, measurement of effectiveness, estimating resources and costs, and source of funding were scored as yes in all included studies.^{8,10,11,14,25,26,28,34,35,49,55} The item referring to abstract was scored as yes in only 2 studies,^{8,26} and the item referring to study findings, limitations, generalizability, and current knowledge was scored as yes in 6 included studies.^{8,11,14,35,49,55} Finally, the item referring to the discount

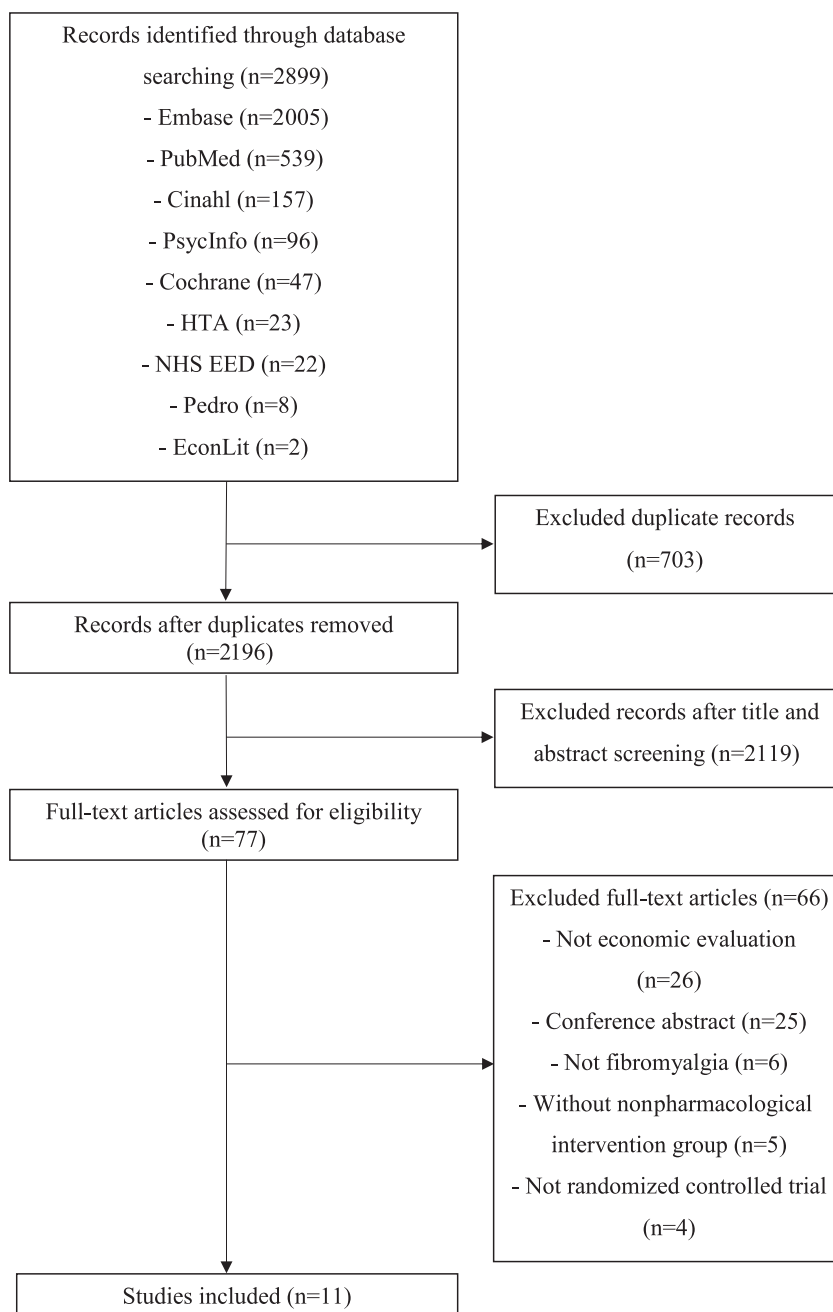


Figure 1. Flow diagram of the study selection. HTA, Health Technology Assessment; NHS EED, National Health Service Economic Evaluation Database.

rate was scored as *not applicable* in 4 studies^{10,14,34,55} because the time horizon was 12 months or less.

All included studies were considered to have a *high overall risk of bias* (Table 3). The domain regarding bias in measurement of the outcome was classified as having *high risk of bias* in all studies because QALYs and impact of fibromyalgia are participant-reported outcomes, and blinding is not possible, while the domain regarding bias in selection of the reported result was classified as having a *low risk of bias* in all studies.^{8,10,11,14,25,26,28,34,35,49,55} Bias arising from the randomization process mostly arose because of the absence of concealed allocation.^{10,11,25,34,35} Bias due to deviations from the intended interventions mostly arose because participants and carers were aware of participants' assigned intervention.^{8,10,11,14,25,26,28,34,35,49,55} Finally, bias due to

missing outcome data mostly arose because data were not available for nearly all participants randomized.^{10,34,35,49,55}

3.3. Cost-effectiveness of the educational, physical, and psychological treatments

Table 4 presents the costs and effects outcomes, and the ICERs for the included studies.

3.3.1. Psychological interventions

Among studies that evaluated a psychological intervention compared with another intervention or usual care/CG,^{8,10,14,25,26,28,35} mean healthcare costs in the psychological intervention group ranged between \$961 (€698)⁸ and \$3542

Table 1**Characteristics of the included studies.**

Authors, year, and language of publication	Interventions	Participants' characteristics*	Details of the economic evaluation	Outcomes, costs categories, and follow-ups
Goossens et al., 1996, ¹⁰ English Support paper for data extraction: Vlaeyen et al., 1996 ⁵⁰	Educational cognitive group (ECO): received education and cognitive treatment (psychological intervention) Educational discussion group (EDI): received education and participated in a group discussion program Waiting list condition group (WLC): not described in the study	Age: ECO 44.6 years (9.3), EDI 44.6 years (9.6), WLC 42.8 years (9.6) Female: ECO 93%, EDI 87%, and WLC 82% Diagnostic criteria: ACR 1990 Pain duration: ECO 10.4 years (7.7), EDI 10.2 years (8.8), WLC 9.9 years (7.9) Total sample size: 131	Country: Netherlands Currency: US Dollars Time horizon: 12 months Perspective: societal Type of economic evaluation: cost-utility analysis Willingness to pay: NR Reference year: 1993 Discounting: NA	QALY (Maastricht Utility Measurement Questionnaire, 0-1) Healthcare costs, patient and family costs, and lost productivity costs Follow-up at 12 months
Oliver et al., 2001, ³⁴ English	Social support group (SS): received an intervention based on promoting empathy and sharing of coping techniques between group members Social support and education group (SSE): received social support and education Control group (CG): received no treatment	Age: SS 53.7 years (11.6), SSE 55.1 years (11), CG 52.9 years (11.7) Female: SS 95.5%, SSE 96.1%, CG 94.3% Diagnostic criteria: ACR 1990 Pain duration: SS 13.6 years (13.2), SSE 14.4 years (14.2), CG 11.7 years (12.1) Total sample size: 600	Country: United States Currency: US Dollars Time horizon: 12 months Perspective: healthcare (assumed) Type of economic evaluation: cost-effectiveness analysis (assumed) Willingness to pay: NR Reference year: 1996 (assumed) Discounting: NA	Impact of fibromyalgia (Fibromyalgia Impact Questionnaire, 0-100) Healthcare costs Follow-up at 12 months
Zijlstra et al., 2007, ⁵⁵ English Support paper for data extraction: Zijlstra et al., 2005 ⁵⁴	Spa treatment group (SPA): received thalassotherapy, exercise, and education programme Control group (CG): received usual care	Age, median (range): SPA 48 years (22-64), CG 47 years (24-64) Female: SPA 95%, CG 96% Diagnostic criteria: ACR 1990 Years since continuous symptoms onset, median (range): SPA 10 (2-35), CG 10 (1-42) Total sample size: 134	Country: Netherlands Currency: Euros Time horizon: 12 months Perspective: societal Type of economic evaluation: cost-utility analysis Willingness to pay: NR Reference year: 2000 Discounting: NA	QALY (SF-6D, 0-1) Healthcare costs, patient and family costs, and lost productivity costs Follow-up at 12 months
Gusi and Tomas-Carus, 2008, ¹¹ English	Exercise group (EG): received usual care and the addition of an aquatic exercise programme Control group (CG): received standard care	Age: EG 50.7 years (10.6), CG: 50.9 years (6.7) Female: 100% in both groups Diagnostic criteria: ACR 1990 Duration of symptoms: EG 20.1 years (8), CG 19.4 years (6.9) Total sample size: 33	Country: Spain Currency: Euros Time horizon: 8 months Perspective: healthcare and societal Type of economic evaluation: cost-utility analysis Willingness to pay: €23,153/QALY Reference year: 2005 Discounting: NA	QALY (EQ-5D, 0-1) Healthcare costs and patient and family costs Follow-up at 8 months
Luciano et al., 2013, ²⁵ English Support paper for data extraction: Luciano et al., 2011 ²⁴	Intervention group (IG): received a psychoeducative program added to usual care (psychological intervention) Control group (CG): received usual care	Age: IG 55.2 years (8.6), CG 55.4 years (8.7) Female: IG 97.2%, CG 98.1% Diagnostic criteria: ACR 1990 Years of diagnosis: IG 15.2 (11.7), CG 14.3 (10.6) Total sample size: 216	Country: Spain Currency: Euros Time horizon: 12 months Perspective: healthcare and societal Type of economic evaluation: cost-utility analysis Willingness to pay: NR Reference year: 2008 Discounting: NA	QALY (EQ-5D, 0-1) Healthcare costs and patient and family costs Follow-up at 12 months
Luciano et al., 2014, ²⁶ English Support paper for data extraction: Alda et al., 2011 ¹	Cognitive behavioural therapy group (CBT): received cognitive behavioural therapy intervention (psychological intervention) Food and Drug Administration-recommended pharmacological treatment group (RPT): received a pharmacological treatment Treatment-as-usual group (TAU): received standard care	Age: CBT 46.5 years (6.7), RPT: 47.1 (6.5), TAU: 47 (6.5) Female: CBT 94.7%, RPT 92.9%, TAU 96.4% Diagnostic criteria: ACR 1990 Mean years since diagnosis: CBT 12.9 (7.5), RPT: 11.2 (3.9), TAU 11.4 (4) Total sample size: 169	Country: Spain Currency: Euros Time horizon: 6 months Perspective: healthcare and societal Type of economic evaluation: cost-utility analysis Willingness to pay: NR Reference year: 2011 Discounting: NA	QALY (EQ-5D, 0-1) Healthcare costs and lost productivity costs Follow-up at 6 months

(continued on next page)

Table 1 (continued)

Authors, year, and language of publication	Interventions	Participants' characteristics*	Details of the economic evaluation	Outcomes, costs categories, and follow-ups
van Eijk-Hustings et al., 2016, ⁴⁹ English Support paper for data extraction: van Eijk-Hustings et al., 2013 ⁴⁸	Multidisciplinary intervention group (MD): received sociotherapy, physical therapy, psychotherapy, and creative arts therapy Aerobic exercise group (AE): received aerobic exercise Usual care group (UC): received usual care	Age: MD 41.5 years (9.6), AE 41 years (9), UC 42.9 years (11) Female: MD 93.5%, AE 100%, UC 97.9% Diagnostic criteria: ACR 1990 Duration of fibromyalgia related symptoms before diagnosis: MD 6.9 years (6.2), AE 6.9 years (6.1), UC 7.1 years (6.4) Total sample size: 203	Country: Netherlands Currency: Euros Time horizon: 24 months Perspective: healthcare and societal (assumed) Type of economic evaluation: cost-effectiveness analysis (assumed) Willingness to pay: NR Reference year: 2010 Discounting: NR	Impact of fibromyalgia (Fibromyalgia Impact Questionnaire, 0-100) Healthcare costs and patient and family costs Follow-up at 24 months
Luciano et al., 2017, ²⁸ English Support paper for data extraction: Luciano et al., 2014 ²⁷	Acceptance and commitment therapy group (ACT): received acceptance and commitment therapy (psychological intervention) Recommended pharmacological treatment group (RPT): received a pharmacological treatment Waiting list group (WL): received usual care	Age: ACT 48.9 years (6), RPT 47.8 years (5.0), WL 48.3 years (5.7) Female: ACT 96.1%, RPT 98.1%, WL 94.3% Diagnostic criteria: ACR 1990 Years of diagnosis: ACT 14.1 (9), RPT 11.4 (8), WL 13 (8.8) Total sample size: 156	Country: Spain Currency: Euros Time horizon: 6 months Perspective: healthcare and societal Type of economic evaluation: cost-utility and cost-effectiveness (assumed) analyses Willingness to pay: NR Reference year: 2014 Discounting: NA	QALY (EQ-5D, 0-1) Impact of fibromyalgia (Fibromyalgia Impact Questionnaire, 0-100) Healthcare costs and lost productivity costs Follow-up at 6 months
Hedman-Lagerlof et al., 2019, ¹⁴ English Support paper for data extraction: Hedman-Lagerlof et al., 2018 ¹³	Internet-delivery exposure therapy group (iExp): received psychoeducation exposure to fibromyalgia-related and pain-related stimuli, and mindfulness (psychological intervention) Waiting list control group (WLC): received no treatment	Age: iExp 51.8 years (10.7), WLC 49.3 years (10) Female: iExp 97%, WLC 99% Diagnostic criteria: made by a physician Years with diagnosis: iExp 11 (7.3), WLC 9.2 (7.5) Total sample size: 140	Country: Sweden Currency: US Dollars Time horizon: 3 months Perspective: healthcare and societal Type of economic evaluation: cost-utility and cost-effectiveness analyses Willingness to pay: NR Reference year: 2016 Discounting: NR	QALY (EQ-5D, 0-1) Impact of fibromyalgia (Fibromyalgia Impact Questionnaire, 0-100) Healthcare costs, patient and family costs, and lost productivity costs Follow-up at 3 months
Pérez-Aranda et al., 2019, ³⁵ English Support paper for data extraction: Pérez-Aranda et al., 2019 ³⁶	Mindfulness-based stress reduction added to treatment-as-usual group (MBSR): received a transdiagnostic mindfulness-based intervention FibroQoL added to treatment-as-usual group (FibroQoL): received psychoeducation and self-hypnosis (psychological intervention) Treatment-as-usual group (TAU): continued regular pattern of medication	Age: MBSR 52.6 years (8), FibroQoL 54.4 years (7.7), TAU 53.2 years (8.4) Female: MBSR 97.1%, FibroQoL 98.5%, TAU 98.5% Diagnostic criteria: ACR 1990 Years of diagnosis: MBSR 14.5 (9.2), FibroQoL 11.3 (7.2), TAU 13.7 (10) Total sample size: 204	Country: Spain Currency: Euros Time horizon: 12 months Perspective: healthcare and societal Type of economic evaluation: cost-utility analysis Willingness to pay: €25,000/QALY Reference year: 2016 Discounting: NA	QALY (EQ-5D, 0-1) Healthcare costs and lost productivity costs Follow-up at 12 months
D'Amico et al., 2020, ⁸ English Support paper for data extraction: Montero-Marin et al., 2018 ³²	Attachment-based compassion therapy added to treatment-as-usual group (ABCT): received mindfulness and self-compassion Relaxation group (REL): received relaxation (intervention of both groups was considered as psychological)	Age: ABCT 50.8 (8.7), REL 52.2 (6) Female: ABCT 100%, REL 100% Diagnostic criteria: ACR 1990 Years of diagnosis: NR Total sample size: 42	Country: Spain Currency: Euros Time horizon: 3 months Perspective: healthcare Type of economic evaluation: cost-utility and cost-effectiveness (assumed) analyses Willingness to pay: NR Reference year: 2016 Discounting: NA	QALY (EQ-5D, 0-1) Impact of fibromyalgia (Fibromyalgia Impact Questionnaire, 0-100) Healthcare costs Follow-up at 3 months

* Data presented as mean (SD), unless when stated.

ACR, American College of Rheumatology; EQ-5D, EuroQol-5 dimension; NA, not applicable; NR, not reported; QALY, quality-adjusted life-year; SF-6D, Short-Form 6 Dimension.

Table 2**Assessment of the consolidated health economic evaluation reporting standards statement for the included economic evaluations.**

Study	Items																								Overall score (0-24)	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24		
Goossens et al. ¹⁰	Y	N	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	NA	NA	N	NA	N	N	NA	N	Y	N	13 Y, 6 N, 5 NA
Oliver et al. ³⁴	Y	N	Y	Y	Y	N	Y	Y	NA	Y	Y	NA	Y	N	NA	NA	Y	NA	N	N	NA	N	Y	N	11 Y, 7 N, 6 NA	
Zijlstra et al. ⁵⁵	Y	N	N	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	NA	NA	Y	NA	Y	Y	NA	Y	Y	Y	17 Y, 2 N, 5 NA	
Gusi and Tomas-Carus ¹¹	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	Y	NA	Y	Y	NA	Y	Y	Y	19 Y, 1 N, 4 NA	
Luciano et al. ²⁵	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	Y	NA	Y	Y	NA	N	Y	Y	18 Y, 2 N, 4 NA	
Luciano et al. ²⁶	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	Y	NA	Y	Y	NA	N	Y	Y	19 Y, 1 N, 4 NA	
Van Eijk-Hustings et al. ⁴⁹	Y	N	Y	Y	Y	N	Y	Y	N	Y	Y	NA	Y	Y	NA	NA	Y	NA	N	N	NA	Y	Y	Y	14 Y, 5 N, 5 NA	
Luciano et al. ²⁸	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	Y	NA	Y	Y	NA	N	Y	Y	18 Y, 2 N, 4 NA	
Hedman-Lagerlof et al. ¹⁴	Y	N	Y	Y	Y	Y	Y	Y	NA	Y	Y	N	Y	Y	NA	NA	Y	NA	Y	Y	NA	Y	Y	Y	17 Y, 2 N, 5 NA	
Pérez-Aranda et al. ³⁵	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	Y	NA	Y	Y	NA	Y	Y	Y	19 Y, 1 N, 4 NA	
D'Amico et al. ⁸	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	Y	NA	Y	Y	NA	Y	Y	Y	20Y, 4 NA	

1: title, 2: abstract, 3: background and objective, 4: target population and subgroups, 5: setting and location, 6: study perspective, 7: comparators, 8: time horizon, 9: discount rate, 10: choice of health outcomes, 11: measurement of effectiveness, 12: measurement and valuation of preference-based outcomes, 13: estimating resources and costs, 14: currency, price date, and conversion, 15: choice of model, 16: assumptions, 17: analytic models, 18: study parameters, 19: incremental costs and outcomes, 20: characterizing uncertainty, 21: characterizing heterogeneity, 22: study findings, limitations, generalizability, and current knowledge, 23: source of funding, 24: conflicts of interest.

Y, yes; N, no; NA: not applicable.

(€3013).¹⁰ From the societal perspective, mean costs in the psychological intervention group varied from \$2696 (€2092)²⁶ to \$17,238 (€14,663).¹⁰ Effects also showed high variability, with the incremental QALYs ranging from 0.01^{26,28} to 0.12²⁵ and improvement on the impact of fibromyalgia score ranging from 15.62²⁸ to 21.07.¹⁴ Incremental cost-effectiveness ratios for QALYs showed that the psychological intervention was dominant (ie, less expensive and more effective) over the comparator treatment from both the healthcare and societal perspectives in 4 studies^{25,26,28,35} and from the societal perspective in one study.¹⁴ In one study,¹⁰ the psychological intervention was not cost-effective compared with the control intervention from both perspectives using the NICE willingness to pay threshold. In another study,¹⁴ the psychological intervention was cost-effective compared with control from the healthcare perspective using the NICE willingness to pay threshold. Incremental cost-effectiveness ratios for impact of fibromyalgia showed that the psychological intervention was also dominant compared with the comparator treatment from the societal perspective in one study¹⁴ and from both perspectives in another study.²⁸ Finally, the most recent study⁸ compared 2 psychological interventions, and ICERs for QALYs and impact of fibromyalgia indicated that attachment-based compassion therapy was dominant over the active CG (relaxation) from the healthcare perspective.

Meta-analyses were conducted for incremental QALYs and incremental costs. The first meta-analysis included 2 studies with a total of 217 participants over a 6-month time horizon^{26,28} (Fig. 2) and showed that the difference in QALYs between psychological treatment and usual care was not statistically significant different, whereas healthcare and societal costs were statistically significantly lower in the psychological intervention group compared with usual care (mean difference: \$-2087, 95% CI: -3061 to -1112; mean difference: \$-2411, 95% CI: -3582 to -1,240, respectively). Heterogeneity for QALYs was high in this meta-analysis. The second meta-analysis included 2 studies with a total of 216 participants and compared psychological treatment with recommended pharmacological intervention over a 6-month time horizon^{26,28} (Fig. 3). In this analysis, there was only a

statistically significant difference in healthcare costs, which were lower in the psychological intervention group than in the recommended pharmacological intervention group (mean difference: \$-1443, 95% CI: -2165 to -721). The same was not found for QALYs and societal costs. For societal costs, heterogeneity was high in this meta-analysis. The third meta-analysis included 2 studies and a total of 352 participants over a 12-month time horizon^{25,35} (Fig. 4), and showed that healthcare costs in the psychological intervention group were significantly lower than in the usual care (mean difference: \$-538, 95% CI: -917 to -158). The same was not found for societal costs.

3.3.2. Physical interventions

Two studies compared exercise therapy with usual care. In the comparison between aquatic exercise with usual care,¹¹ healthcare and societal costs were higher in the aquatic exercise group (EG) compared with usual care, but no measure of uncertainty was presented. The aquatic EG gained 0.131 QALYs compared with the usual care group, which was a statistically significant difference.¹¹ Both from the healthcare and societal perspectives, the ICERs were lower than the NICE willingness to pay threshold, indicating that aquatic exercise was cost-effective compared with usual care. In the comparison between aerobic exercise, multidisciplinary intervention, and usual care,⁴⁹ costs varied depending on the perspective. The multidisciplinary intervention was associated with the lowest costs from the healthcare perspective and the highest costs from the societal perspective, although not statistically significantly so. In addition, the multidisciplinary intervention resulted in statistically significantly larger effects than aerobic exercise and usual care. Aerobic exercise was dominated by the multidisciplinary intervention and was dominant compared with usual care from the healthcare perspective for the impact of fibromyalgia. From the societal perspective, the ICER for the comparison between aerobic exercise and multidisciplinary intervention showed that to lose 1 point of improvement in impact of fibromyalgia, \$564 (€442) is saved in the aerobic EG

Table 3**Risk of bias assessment of the randomized controlled trials.**

Study	Domain					
	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias judgement
Goossens et al. ¹⁰	High	High	High	High	Low	High
Oliver et al. ³⁴	High	High	High	High	Low	High
Zijlstra et al. ⁵⁵	Low	High	High	High	Low	High
Gusi and Tomas-Carus ¹¹	High	Some concerns	Low	High	Low	High
Luciano et al. ²⁵	High	Some concerns	Low	High	Low	High
Luciano et al. ²⁶	Low	Some concerns	Low	High	Low	High
Van Eijk-Hustings et al. ⁴⁹	Low	Some concerns	High	High	Low	High
Luciano et al. ²⁸	Low	Some concerns	Low	High	Low	High
Hedman-Lagerlof et al. ¹⁴	Low	Some concerns	Low	High	Low	High
Pérez-Aranda et al. ³⁵	High	Some concerns	High	High	Low	High
D'Amico et al. ⁸	Low	Some concerns	Low	High	Low	High

compared with the multidisciplinary group. For the comparison between aerobic exercise and usual care from the societal perspective, the ICER showed that to gain 1 point of improvement in impact of fibromyalgia, \$24 (€19) should be invested in the aerobic EG compared with the usual care group.

3.3.3. Other interventions

In 2 studies^{34,55} evaluating other interventions than psychological interventions, it was not possible to recalculate the ICERs. In the first study,³⁴ incremental healthcare costs and effects were in favour of the comparison intervention (social support group), although differences were not statistically significant. In the second study,⁵⁵ healthcare and societal costs in the spa treatment group were nonsignificantly higher than in the CG, and no significant differences in QALYs were observed.

4. Discussion

The aim of this study was to perform a systematic review of economic evaluations of educational, physical, and psychological interventions in the treatment of patients with fibromyalgia. Psychological interventions^{14,25,26,28,35} can be considered cost-effective compared with different comparator treatments. Meta-analyses showed that healthcare costs in the psychological intervention group were statistically significantly lower than in usual care and pharmacological intervention group after 6 months, and than usual care after 12 months. Finally, for QALYs, aquatic exercise was cost-effective compared with usual care, and for impact of fibromyalgia, whether aerobic exercise is considered cost-effective compared with usual care depends on the willingness to pay of decision makers.

Some strengths of this systematic review can be highlighted. We used a search strategy including broad terms for fibromyalgia and economic evaluations, without searching for specific treatments.⁷ All types of economic evaluations were included in this review, although we only identified cost-

effectiveness and cost-utility analyses conducted alongside randomized controlled trials. Finally, by calculating ICERs for impact of fibromyalgia in 3 studies^{8,14,28} and in a study that only reported costs and effects,⁴⁹ results of this review are of interest and use for patients, clinicians, and decision makers alike. On the other hand, the adoption of different interventions and time horizons in the economic evaluations limited our possibility to pool data, which was performed only for 2 studies per meta-analysis. This is not a specific limitation of our systematic review but of the research in the field of economic evaluations on interventions for fibromyalgia. Data of costs and outcomes stratified by the group were missing in some studies, which also limited our meta-analyses. Efforts were made to obtain complementary data from 2 studies,^{10,25} but no response was acquired from one study,¹⁰ and the sample size was different for QALYs and costs from another study.²⁵

Despite the economic burden of fibromyalgia,²³ the evidence base on cost-effective treatments is limited. A recent systematic review⁵³ on the cost-effectiveness of interventions for functional somatic syndromes including fibromyalgia showed similar results to ours. However, our search has been conducted more recently resulting in the addition of 3 recently published studies.^{8,14,35} Moreover, we presented novel findings on costs and effects in 4 studies^{8,14,28,49} that we used to calculate ICERs for impact of fibromyalgia, which are important to allow the comparison of ICERs for the same health condition³⁰ and more meaningful for decision makers.⁴⁷ Impact of fibromyalgia is an umbrella term that encompasses outcomes, such as health-related quality of life, pain, fatigue, stiffness, and physical function, and is commonly assessed in randomized controlled trials with intervention for fibromyalgia.^{6,12,19} Therefore, we considered it important to include this outcome in our systematic review, whereas the previous review⁵³ did not. Finally, we could perform 3 meta-analyses, to improve precision with bigger sample sizes and to answer different questions,¹⁶ especially related to which intervention presented lower healthcare and societal costs.

Two other systematic reviews also assessed the cost-effectiveness of interventions for patients with chronic

Table 4**Results of the included studies.**

Study	Intervention (sample size)	Costs, mean (SD), incremental costs (95% CI)		Effects, mean (SD)*, incremental effects (95% CI)	ICER
		Healthcare perspective	Societal perspective		
Goossens et al. ¹⁰	Educational cognitive group (ECO), n = 49 Educational discussion group (EDI), n = 39	Costs ECO† \$3542 (NR)/€3013 (NR) Costs EDI \$2395 (NR)/€2037 (NR) Incremental costs‡ \$1147/€976	Costs ECO† \$17,238 (NR)/€14,663 (NR) Costs EDI \$13,698 (NR)/€11,651 (NR) Incremental costs‡ \$3540/€3011	QALY effects ECO: NR EDI: NR Incremental QALY effects: 0.027 (NR)	Healthcare \$42,487 or €36,140/QALY Societal \$131,122 or €111,532/QALY
Oliver et al. ³⁴	Social support group (SS), n = 200 Social support and education group (SSE), n = 207 Control group (CG), n = 193	Costs SS \$6763 (6578)/€5753 (5596) Costs SSE \$7126 (9061)/€6061 (7707) Costs CG \$6849 (12,959) €5826 (11,023) Incremental costs SS vs SSE \$-363 (-1897 to 1172) €-309 (-1614 to 997) Incremental costs SS vs CG \$-86 (-2129 to 1957) €-73 (-1811 to 1665) Incremental costs SSE vs CG \$277 (-1929 to 2483) €236 (-1641 to 2112)	Not collected	IF effects SS: 54.70 (18.00) SSE: 56.00 (16.50) CG: 58.30 (17.30) Incremental IF effects SS vs SSE: -1.30 (-4.66 to 2.06) SS vs CG: -3.60 (-7.09 to -0.11) SSE vs CG: -2.30 (-5.62 to 1.02)	Not calculated because the sample size for costs and effects is different. ICER was also not presented in the study.
Zijlstra et al. ⁵⁵	Spa treatment group (SPA), n = 58 Control group (CG), n = 76	Costs SPA \$5733 (2902)/€4738 (2399) Costs CG \$3457 (5113)/€2857 (4226) Incremental costs \$2276 (-60 to 4090) €1881 (-50 to 3380)	Costs SPA \$12,600 (NR)/€10,414 (NR) Costs CG \$10,511 (NR)/€8687 (NR) Incremental costs Societal‡: \$2090/ €1727	QALY effects SPA: 0.610 (0.080) CG: 0.610 (0.070) Incremental QALY effects : 0.000 (-0.030 to 0.030)	Not calculated because the incremental QALY is 0
Gusi and Tomas-Carus ¹¹	Exercise group (EG), n = 17 Control group (CG), n = 16	Costs EG: NR Costs CG: NR Incremental costs: \$791 (NR)/€647 (NR)	Costs EG: NR Costs CG: NR Incremental costs: \$1580 (NR)/€1291 (NR)	QALY effects EG: 0.133 (NR) CG: 0.002 (NR) Incremental QALY effects: 0.131 (0.011 to 0.290)	Healthcare \$6041 or €4936/QALY Societal \$12,061 or €9853/QALY
Luciano et al. ²⁵	Intervention group (IG), n = 108 Control group (CG), n = 108	Costs IG \$2073 (1910)/€1624 (1496) Costs CG \$2717 (2140)/€2128 (1676) Incremental costs \$-327 (-933 to 437) €-256 (-731 to 342)	Costs IG \$2789 (3124)/€2184 (2447) Costs CG \$3339 (3082)/€2615 (2414) Incremental costs \$-299 (-1191 to 600) €-234 (-933 to 470)	QALY effects IG: NR CG: NR Incremental QALY effects: 0.120 (0.060 to 0.190)	Healthcare: IG dominant Societal: IG dominant

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Table 4 (continued)

Study	Intervention (sample size)	Costs, mean (SD), incremental costs (95% CI)		Effects, mean (SD)*, incremental effects (95% CI)	ICER
		Healthcare perspective	Societal perspective		
Luciano et al. ²⁶	Cognitive behavioural therapy group (CBT), n = 57 Food and Drug Administration–recommended pharmacological treatment group (RPT), n = 56 Treatment-as-usual group (TAU), n = 56	Costs CBT	Costs CBT	QALY effects	CBT vs RPT
		\$2000 (3998)/€1552 (3102)	\$2696 (4296)/€2092 (3333)	CBT: 0.250 (0.120)	Healthcare: CBT dominant
		Costs RPT	Costs RPT	RPT: 0.230 (0.130)	Societal: CBT dominant
		\$4176 (6075)/€3240 (4713)	\$5349 (6627)/€4150 (5141)	TAU: 0.240 (0.130)	CBT vs TAU
		Costs TAU	Costs TAU	Incremental QALY effects	Healthcare: CBT dominant
		\$3464 (5212)/€2688 (4044)	\$4560 (5770)/€3538 (4477)	CBT vs RPT: 0.010 (0.000 to 0.030)	Societal: CBT dominant
		Incremental costs CBT vs RPT	Incremental costs CBT vs RPT	CBT vs TAU: 0.020 (0.000 to 0.030)	RPT vs TAU¶
		\$–2634 (–4068 to –1199)	\$–3365 (–4856 to –1873)	RPT vs TAU: 0.000 (0.010 to 0.020)	Healthcare
		€–2043 (–3156 to –930)	€–2610 (–3768 to –1453)		\$143,701 or €111,488/QALY
		Incremental costs CBT vs TAU	Incremental costs CBT vs TAU		Societal
		\$–2383 (–4007 to –760)	\$–3152 (–4901 to –1402)		\$115,434 or €89,557/QALY
		€–1849 (–3109 to –590)	€–2445 (–3802 to –1088)		
		Incremental costs RPT vs TAU	Incremental costs RPT vs TAU		
		\$250 (–1514 to 2015)	\$213 (–1680 to 2106)		
		€194 (–1175 to 1563)	€166 (–1303 to 1634)		
Van Eijk-Hustings et al. ⁴⁹	Multidisciplinary intervention group (MD), n = 108 Aerobic exercise group (AE), n = 47 Usual care group (UC), n = 48	Costs MD	Costs MD	IF effects	MD vs AE
		\$5196 (NR)/€4068 (NR)	\$7017 (NR)/€5494 (NR)	MD: 50.90 (2.00)	Healthcare: MD dominant
		Costs AE	Costs AE	AE: 52.00 (3.20)	Societal
		\$5320 (NR)/€4166 (NR)	\$6397 (NR)/€5008 (NR)	UC: 56.20 (2.90)	\$–564 or €–442/IF
		Costs UC	Costs UC	Incremental IF effects	MD vs UC
		\$5625 (NR)/€4405 (NR)	\$6295 (NR)/€4928 (NR)	MD vs AE: –1.10 (–2.09 to –0.11)	Healthcare: MD dominant
		Incremental costs MD vs AE	Incremental costs MD vs AE	MD vs UC: –5.30 (–6.20 to –4.40)	Societal
		\$–124 (–1266 to 1321)	\$620 (–2028 to 709)	AE vs UC: –4.20 (–5.43 to –2.97)	\$–136 or €–107/IF
		€–97 (–991 to 1034)	€486 (–1588 to 555)		Healthcare: AE dominant
		Incremental costs MD vs UC	Incremental costs MD vs UC		Societal
		\$–429 (–1679 to 896)	\$722 (–619 to 2158)		\$–24 or €–19/IF§
		€–336 (–1314 to 701)	€566 (–485 to 1690)		
		Incremental costs AE vs UC	Incremental costs AE vs UC		
		\$–305 (–1787 to 1193)	\$102 (–1517 to 1779)		
		€–239 (–1399 to 934)	€80 (–1188 to 1393)		

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Table 4 (continued)

Study	Intervention (sample size)	Costs, mean (SD), incremental costs (95% CI)		Effects, mean (SD)*, incremental effects (95% CI)	ICER
		Healthcare perspective	Societal perspective		
Luciano et al. ²⁸	Acceptance and commitment therapy group (ACT), n = 51 Recommended pharmacological treatment group (RPT), n = 52 Waiting list group (WL), n = 53	Costs ACT	Costs ACT	QALY effects	ACT vs RPT
		\$1200 (1547)/€880 (1135)	\$3300 (2596)/€2422 (1905)	ACT: 0.340 (0.060)	Healthcare
		Costs RPT	Costs RPT	RPT: 0.330 (0.060)	QALY: ACT dominant
		\$2519 (2411)/€1848 (1770)	\$3863 (3037)/€2835 (2229)	WL: 0.280 (0.070)	IF: ACT dominant\$
		Costs WL	Costs WL	Incremental QALY effects	Societal
		\$3584 (4107)/€2630 (3014)	\$6059 (4892)/€4447 (3590)	ACT vs RPT: 0.010 (0.000 to 0.030)	QALY: ACT dominant
		Incremental costs ACT vs RPT	Incremental costs ACT vs RPT	ACT vs WL: 0.050 (0.040 to 0.070)	IF: ACT dominant\$
		\$-1294 (-2248 to -339)	\$-567 (-1769 to 635)	RPT vs WL: 0.040 (0.020 to 0.050)	ACT vs WL
		€-949 (-1650 to -249)	€-416 (-1298 to 466)	IF effects	Healthcare
		Incremental costs ACT vs WL	Incremental costs ACT vs WL	ACT: 49.49 (8.77)	QALY: ACT dominant
		\$-2368 (-3653 to -1083)	\$-2704 (-4225 to -1182)	RPT: 65.11 (8.87)	IF: ACT dominant\$
		€-1738 (-2681 to -795)	€-1984 (-3101 to -867)	WL: 67.45 (9.15)	RPT vs WL
		Incremental costs RPT vs WL	Incremental costs RPT vs WL	Incremental IF effects	Healthcare
		\$-1074 (-2525 to 377)	\$-2137 (-3786 to -487)	ACT vs RPT: -15.62 (-19.03 to -12.21)	QALY: RPT dominant
		€-788 (-1853 to 276)	€-1568 (-2779 to -358)	ACT vs WL: -17.96 (-21.40 to -14.52)	IF: RPT dominant\$
				RPT vs WL: -2.34 (-5.79 to 1.11)	Societal
					QALY: RPT dominant
Hedman-Lagerlof et al. ¹⁴	Internet-delivery exposure therapy group (iExp), n = 70 Waiting list control group (WLC), n = 70	Costs iExp	Costs iExp	QALY effects iExp: 0.600 (0.300)	Healthcare
		\$3030 (3969)/€2199 (2881)	\$9476 (8646)/€6878 (6275)	WLC: 0.440 (0.320)	QALY
		Costs WLC	Costs WLC	Incremental QALY effects: 0.070 (NR)	\$11,039 or €8012
		\$2858 (3550)/€2074 (2576)	\$12,709 (12,595)/€9224 (9141)	IF effects iExp: 36.44 (25.56)	IF: \$-37 or €-27
		Incremental costs	Incremental costs	WLC: 57.71 (21.62)	Societal
Pérez-Aranda et al. ³⁵	Mindfulness-based stress reduction added to treatment-as-usual group (MBSR), n = 68 FibroQoL added to treatment-as-usual group, n = 68 Treatment-as-usual group (TAU), n = 68	Costs MBSR	Costs MBSR	Incremental IF effects : -21.07 (-28.91 to -13.23)	QALY: iExp dominant
		\$1686 (1368)/€1224 (993)	\$2271 (2372)/€1648 (1722)		
		Costs FibroQoL	Costs FibroQoL		
		\$1896 (1272)/€1376 (923)	\$2938 (3094)/€2133 (2246)		
		Costs TAU	Costs TAU		
		\$2331 (1845)/€1692 (1339)	\$3687 (4399)/€2676 (3193)		
		Incremental costs MBSR vs FibroQoL	Incremental costs MBSR vs FibroQoL		
		\$-344 (-805 to 116)	\$-787 (-1771 to 197)		
		€-250 (-584 to 84)	€-571 (-1285 to 143)		
		Incremental costs MBSR vs TAU	Incremental costs MBSR vs TAU		
		\$-664 (-1319 to -7)	\$-1207 (-2478 to 63)		
		€-482 (-957 to -5)	€-876 (-1798 to 46)		
		Incremental costs FibroQoL vs TAU	Incremental costs FibroQoL vs TAU		
		\$-320 (-957 to 318)	\$-420 (-1907 to 1064)		
		€-232 (-695 to 231)	€-305 (-1384 to 774)		

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Table 4 (continued)

Study	Intervention (sample size)	Costs, mean (SD), incremental costs (95% CI)		Effects, mean (SD)*, incremental effects (95% CI)	ICER
		Healthcare perspective	Societal perspective		
D'Amico et al. ⁸	Attachment-based compassion therapy added to treatment-as-usual group (ABCT), n = 23 Relaxation group (REL), n = 19	Costs ABCT \$961 (240)/€698 (174) Costs REL \$1358 (317)/€986 (230) Incremental costs \$-374 (-652 to -95) €-271 (-473 to -69)	Not collected	QALY effects ABCT: 0.17 (0.04) REL: 0.13 (0.06) Incremental QALY effects: 0.021 (0.009 to 0.033) IF effects ABCT: 49.13 (15.07) REL: 67.82 (17.77) Incremental IF effects : -18.69 (-28.78 to -8.60)	Healthcare QALY: dominant IF: dominant§

CI, confidence interval; ICER, incremental cost effectiveness ratio; IF, impact of fibromyalgia; NR, not reported; QALY, quality-adjusted life-year.

* Higher scores for QALY and lower scores for impact of fibromyalgia indicate a better condition.

† The year considered for conversion was 1996 because data from 1993 (reference year of the paper) were not available in one conversion database.⁴¹

‡ Incremental costs were calculated as described in Methods.

§ ICERs were calculated as described in Methods.

|| Calculated using Review Manager version 5.3.

¶ ICER was converted using the values presented in the article because it was not possible to recalculate as incremental QALY was 0.

nonmalignant pain⁴³ and medically unexplained symptoms,²¹ which are health conditions that typically include fibromyalgia. Because of different inclusion criteria, these systematic reviews included only one study¹⁰ also included in our systematic review and presented general results for chronic nonmalignant pain⁴³ and medically unexplained symptoms.²¹ These differences prevented a detailed comparison between our results and the results of these systematic reviews.

The reporting quality of the economic evaluations according to the CHEERS statement was sufficient. Information, such as target population and comparators, was rarely complete in the economic evaluation study, because reporting all important details requires substantial space. Word limits prevent doing this and are a known challenge for both authors and editors.¹⁸ To overcome this issue, we did not only extract data from the included studies, but also from supporting studies, ie, design

and effectiveness studies.^{1,13,24,27,32,36,48,50,54} On the other hand, the risk of bias of the randomized controlled trial for all included studies was high. The domain judged as having high risk of bias in all studies was bias in measurement of the outcomes, because blinding of outcome assessors is difficult for patient-reported outcomes.¹⁶ In addition, the high overall risk of bias found in the included studies of this systematic review may lead to an overestimation or underestimation of the true effectiveness of the interventions,⁴⁰ which can compromise the validity of the results presented here.

The results of this systematic review show that psychological interventions are dominant over other active interventions and usual care or control groups. Cost-effective psychological interventions mainly consist of psychoeducative program, cognitive behavioural therapy, acceptance and commitment therapy, exposure therapy, and attachment-based

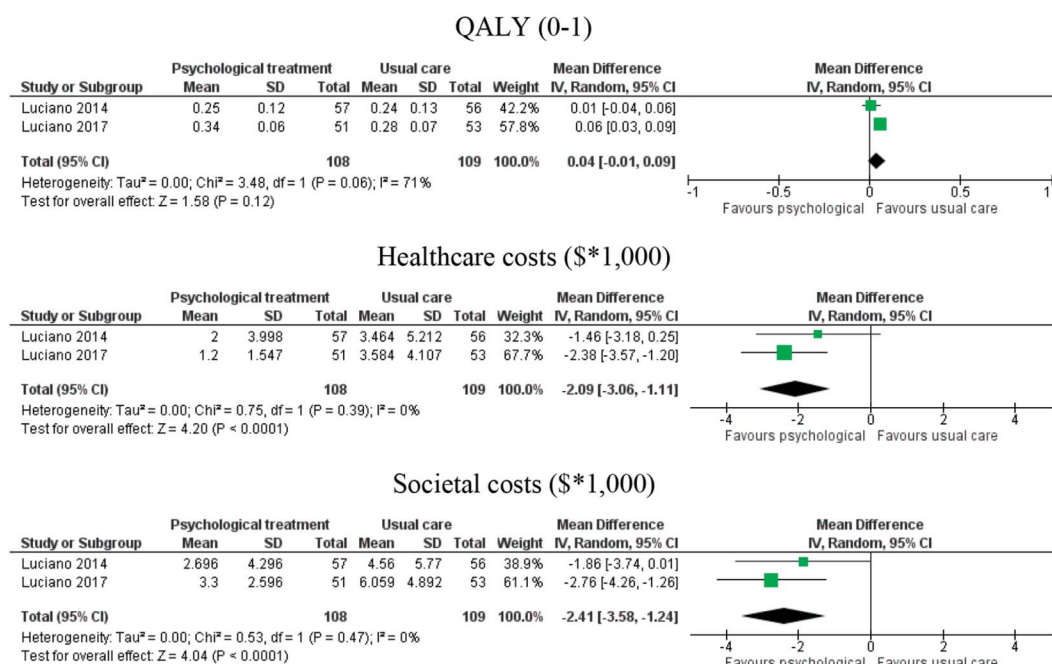


Figure 2. Forest plots of the comparison between psychological treatment vs usual care from a 6-month time horizon. CI, confidence interval; QALY, quality-adjusted life-years.

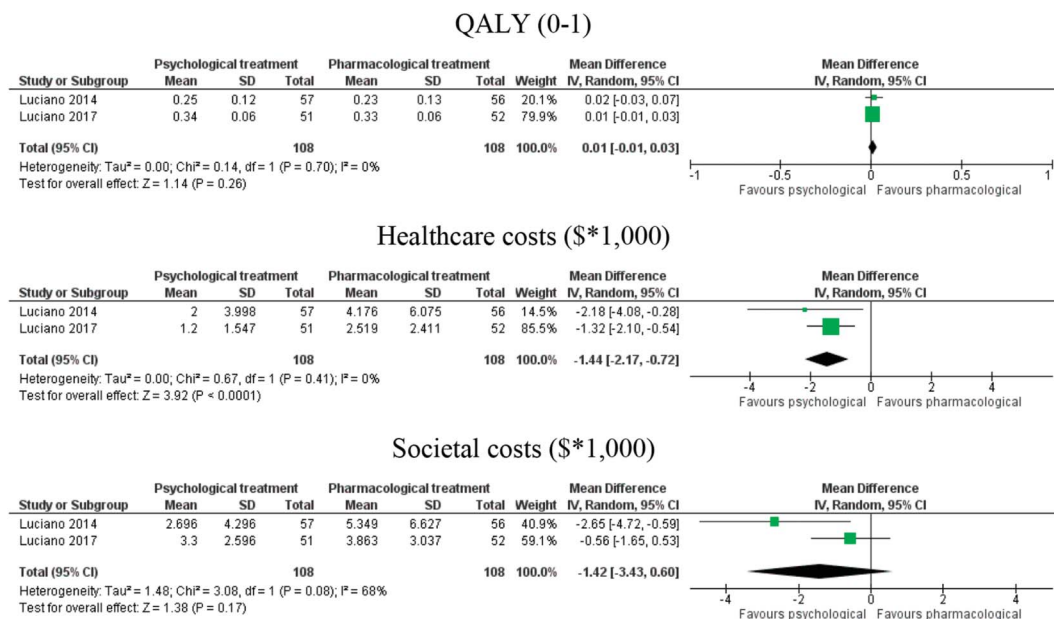


Figure 3. Forest plots of the comparison between psychological treatment vs recommended pharmacological treatment from a 6-month time horizon. CI, confidence interval; QALY, quality-adjusted life-years.

compassion therapy. Future studies should indicate which specific elements of the interventions are effective in fibromyalgia. However, economic evaluations of other interventions recommended for the treatment of fibromyalgia, such as acupuncture, exercises, meditative, and multicomponent therapies,^{5,12,29,42} are missing and need to be performed. We found only 2 economic evaluations on the cost-effectiveness of physical exercise in the treatment of patients with fibromyalgia,^{11,49} and, thus, definitive conclusions cannot be drawn about this type of treatment. The risk of bias of the randomized controlled trials should be reduced, especially concerning bias due to missing outcome data and in measurement of the outcome. Finally, the time horizon was less than 12 months in 5 studies.^{8,11,14,26,28} Considering the chronic nature of fibromyalgia symptoms, future research in this field should consider longer time horizons with a minimum of 12 months, which is comparable with studies on chronic spinal disorders,²² a chronic health condition similar to fibromyalgia. Results from high-quality economic evaluations

can be used to develop health economic decision analytical models. These models synthesize information from multiple sources, including economic evaluations alongside randomized controlled trials, and apply mathematical techniques to estimate cost-effectiveness.³⁷ Using such models allows for indirect comparison of different interventions groups and longer time horizons than feasible in randomized controlled trials. At this time, only economic evaluations alongside randomized controlled trials with educational, physical, and psychological interventions were found.

5. Conclusion

Psychological interventions for the treatment of patients with fibromyalgia are dominant over other interventions and control conditions. No robust conclusions can be drawn on the cost-effectiveness of physical exercise. There is a need for more high-quality economic evaluations conducted alongside randomized controlled trials evaluating interventions recommended by

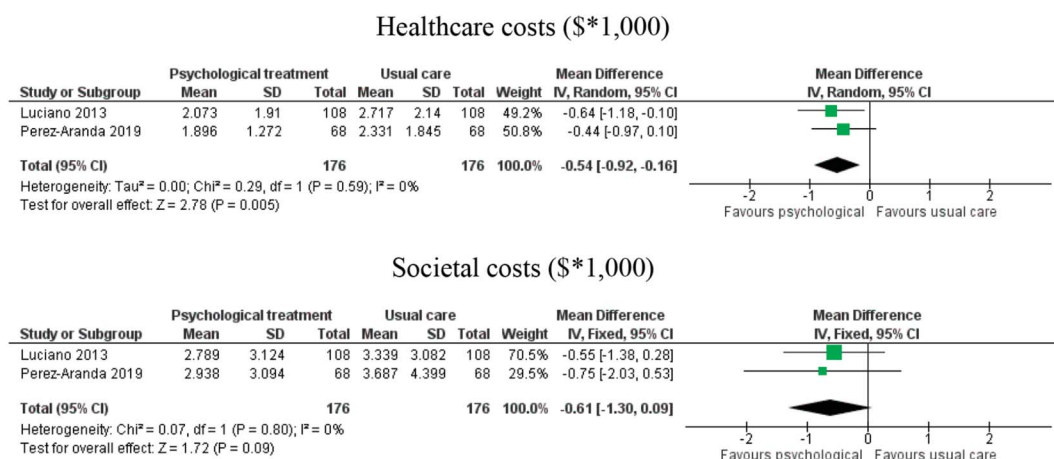


Figure 4. Forest plots of the comparison between psychological treatment vs usual care from a 12-month time horizon. CI, confidence interval.

fibromyalgia guidelines. These studies should include an adequate time horizon and perspective, to allow for the comparison of the results between studies. This will result in a solid evidence based on the cost-effectiveness of treatments for fibromyalgia.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at <http://links.lww.com/PAIN/B305>.

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