

## **Therapeutic interventions associated with improvements in the quality of life of patients with fibromyalgia: a systematic review**

**Intervenções terapêuticas associadas à melhora na qualidade de vida de pacientes com fibromialgia: uma revisão sistemática**

**Intervenciones terapéuticas asociadas con la mejora de la calidad de vida de los pacientes con fibromialgia: una revisión sistemática**

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### **Abstract**

Fibromyalgia is a syndrome characterized by multifaceted symptoms that negatively impact the quality of life. With greater prevalence in women, the syndrome is manifested through widespread pain, fatigue, anxiety, and depression. While different interventions and guidelines for clinical management and diagnosis have been proposed, these are fraught with limiting factors due to the heterogeneity of associated symptoms, chronicity, and therapies with significant side effects. Based on the above, the objective of this study aims to evaluate the therapeutic interventions that improve the different domains of quality of life in patients with fibromyalgia. The research was conducted through systematic searches in the PUBMED, SCOPUS, LILACS and Web of Science databases between March 1, 2020, and May 08, 2021. Articles in Portuguese, English or Spanish were considered for analysis. To verify the risk of bias in each study, the levels of evidence were judged by two independent reviewers using the Cochrane collaboration tool. Articles in Portuguese, English or Spanish were considered for analysis. The scope of this review consisted of thirteen randomized clinical trials that met the pre-established inclusion criteria. The studies reviewed included 3,339 patients with a pre-established diagnosis of fibromyalgia, 92.2% of whom were female. Overall, fifteen interventions were observed that showed results for overall QOL and its physical and mental domains. The results showed high-quality evidence with positive findings for pain, physical functioning, anxiety, and depression with pharmacological and behavioral interventions. There is high-quality evidence supporting pregabalin for overall quality of life and the physical domain (pain and function), cognitive behavior therapy, and milnacipran for the physical domain of quality of life (pain and function), and moderate-quality evidence supporting cognitive behavioral therapy for the domain psychological (anxiety and depression).

**Keywords:** Fibromyalgia; Intervention; Patient; Quality of life.

### **Resumo**

Fibromialgia é uma síndrome caracterizada por sintomas multifacetados que impactam negativamente a qualidade de vida. Com maior prevalência nas mulheres, a síndrome se manifesta através de dor generalizada, fadiga, ansiedade e depressão. Embora tenham sido propostas diferentes intervenções e diretrizes para o manejo clínico e o diagnóstico, estas estão repletas de fatores limitantes devido à heterogeneidade dos sintomas associados, à cronicidade e às terapias com efeitos colaterais significativos. Com base no exposto, o objetivo deste estudo visa avaliar as intervenções terapêuticas que melhoram os diferentes domínios de qualidade de vida em pacientes com fibromialgia. A pesquisa foi realizada por meio de pesquisas sistemáticas nos bancos de dados PUBMED, SCOPUS, LILACS e Web of Science entre 1º de março de 2020 e 08 de maio de 2021. Foram considerados para análise artigos em português, inglês ou espanhol. Para verificar o risco de viés em cada estudo, os níveis de evidência foram julgados por dois revisores independentes usando a ferramenta de colaboração Cochrane. Foram considerados para análise artigos em português,

inglês ou espanhol. O escopo desta revisão consistiu em treze ensaios clínicos randomizados que atenderam aos critérios de inclusão pré-estabelecidos. Os estudos revisados incluíram 3.339 pacientes com diagnóstico pré-estabelecido de fibromialgia, sendo 92,2% do sexo feminino. Ao todo, foram observadas quinze intervenções que apresentaram resultados para qualidade de vida geral e seus domínios físicos e mentais. Os resultados mostraram evidências de alta qualidade com achados positivos para dor, funcionamento físico, ansiedade e depressão com intervenções farmacológicas e comportamentais. Há evidências de alta qualidade que suportam pregabalina para qualidade de vida geral e domínio físico (dor e função), terapia cognitiva comportamental e milnacipran para o domínio físico da qualidade de vida (dor e função), e evidências de qualidade moderada que apoiam a terapia cognitiva comportamental para o domínio psicológico (ansiedade e depressão).

**Palavras-chave:** Fibromialgia; Intervenção; Paciente; Qualidade de vida.

### Resumen

La fibromialgia es un síndrome caracterizado por síntomas multifacéticos que afectan negativamente la calidad de vida. Con mayor prevalencia en las mujeres, el síndrome se manifiesta a través del dolor generalizado, la fatiga, la ansiedad y la depresión. Si bien se han propuesto diferentes intervenciones y guías para el manejo clínico y el diagnóstico, estas están plagadas de factores limitantes debido a la heterogeneidad de los síntomas asociados, la cronicidad y las terapias con efectos secundarios significativos. En base a lo anterior, el objetivo de este estudio es evaluar las intervenciones terapéuticas que mejoran los diferentes dominios de la calidad de vida en pacientes con fibromialgia. La investigación se realizó a través de búsquedas sistemáticas en las bases de datos PUBMED, SCOPUS, LILACS y Web of Science entre el 1 de marzo de 2020 y el 8 de mayo de 2021. Los artículos en portugués, inglés o español fueron considerados para el análisis. Para verificar el riesgo de sesgo en cada estudio, los niveles de evidencia fueron evaluados por dos revisores independientes mediante la herramienta de colaboración Cochrane. Los artículos en portugués, inglés o español fueron considerados para el análisis. El alcance de esta revisión consistió en trece ensayos clínicos aleatorizados que cumplieron con los criterios de inclusión preestablecidos. Los estudios revisados incluyeron a 3.339 pacientes con un diagnóstico preestablecido de fibromialgia, el 92,2% de los cuales eran mujeres. En general, se observaron quince intervenciones que mostraron resultados para la CV general y sus dominios físicos y mentales. Los resultados mostraron evidencia de alta calidad con hallazgos positivos para el dolor, el funcionamiento físico, la ansiedad y la depresión con intervenciones farmacológicas y conductuales. Hay evidencia de alta calidad que apoya la pregabalina para la calidad de vida general y el dominio físico (dolor y función), la terapia cognitivo-conductual y el milnaciprán para el dominio físico de la calidad de vida (dolor y función), y evidencia de calidad moderada que apoya la terapia cognitiva conductual para el dominio psicológico (ansiedad y depresión).

**Palabras clave:** Calidad de vida; Fibromialgia; Intervención; Paciente.

## 1. Introduction

Fibromyalgia (FM) is a disease characterized by chronic musculoskeletal pain. In addition to pain, which is a classic finding in this condition, patients often present reduced physical function, sleep irregularities, cognitive difficulties, fatigue, and even psychological disorders such as depressive symptoms and anxiety (Perrot & Russell, 2014). It is estimated that the prevalence of this condition is around 0.2 to 6.6% of the general population, affecting more women (Marques et al., 2017). The chronicity associated with the difficult management that fibromyalgia syndrome (FMS) presents, makes these symptoms tend to be modulated in intensity and severity during the disease by exacerbating factors (Bennett et al., 2007; Häuser et al., 2015; Williams & Arnold, 2011). Additionally, by exhibiting a heterogeneous clinical picture, different aspects affected by FM generate strong impacts on quality of life (QoL) and economic burdens for health care (Bennett et al., 2007).

The update of diagnostic criteria for FM by the American College of Rheumatology (ACR), emphasizing other symptoms that exceed pain, represented a milestone for identifying the real therapeutic need for this population. Synergistically, it also contributes with scores centered on domains (mainly physical and psychological) that can provide subsidies to assess the quality of life (Wolfe et al., 2010). In fact, FM is a challenging condition due to the absence of specific biomarkers or organic damage. However, the assessment of QoL in this population may, by itself, have a positive impact on targeting therapeutic interventions focused on the spectrum of symptoms with greater clinical relevance. This QoL assessment brings together components such as physical, mental, and social well-being (R. Arnold et al., 2004; Williams & Arnold, 2011). With the progress of research towards the investigation of resources to alleviate FM symptoms, some treatments have emerged and are remarkably encouraging, but these interventions remain a challenge for patients and prescribers, after all, FM is

associated with low levels of therapeutic response (Tzadok & Ablin, 2020).

Currently, guidelines recommend, in addition to pharmacological interventions, complementary and alternative interventions such as psychotherapy, acupuncture, physical exercise and tai chi (Buckhardt et al., 2005; Fitzcharles et al., 2013; Macfarlane et al., 2017). Regarding pharmacological interventions, there are three drugs approved by the Food and Drug Administration (FDA) for the management of FM (pregabalin, duloxetine, and milnacipran), being considered as anchor therapies in the treatment of this disease (Boomershine & Crofford, 2009). Even with a considerable number of therapeutic approaches, progress with reduction of symptoms is limited and does not seem to resolve the manifestations that pose a risk to the QoL of these patients. Long-term drug interventions are hardly well tolerated due to adverse effects, while other therapies appear to have limited effects (Häuser et al., 2015; Tzadok & Ablin, 2020). Accordingly, no intervention produces identical results in different patients, which makes these therapies differ in controlling other symptoms that exceed pain but negatively impact QoL (Boomershine & Crofford, 2009; Häuser et al., 2015). Given the above, the aim of this systematic review is to assess which therapeutic interventions improve the quality of life of patients with fibromyalgia in its different domains.

## **2. Methodology**

The present study consists of a systematic review of the literature and seeks to answer the following research question: “Which therapeutic interventions improve the different domains of quality of life in patients with fibromyalgia?”, which was defined based on the PICOS strategy, an acronym that consists of P: patient, I: intervention, C: comparison, O: outcome and S: study. This review was conducted based on the 'Top Items for Reporting Systematic Reviews and Meta-Analyses' guidelines (PRISMA), which contains relevant instructions for Reporting Systematic Reviews and Meta-Analyses (Page et al., 2021). The review protocol was previously registered in the PROSPERO (CRD42020221309).

### **2.1 Data sources and surveys**

Studies were identified through systematic searches in the following electronic databases: LILACS, PUBMED, SCOPUS, and Web of Science. The survey was conducted between March 2020 and May 2021. The search terms used were according to the Medical Subject Headings (MeSH) and included: fibromyalgia, patient, quality of life, and intervention. To find articles that answered the research question, the following search strategy was used: “Fibromyalgia AND patient AND intervention AND quality of life”. When necessary, each strategy was adapted to the respective database so that potentially eligible studies were not lost.

### **2.2 Inclusion/Exclusion Criteria**

Two reviewers (TCAS and PPM) defined the inclusion and exclusion criteria by consensus and performed a paired search for the studies. Randomized clinical trials were initially evaluated by title and abstract. To be included in the review, articles should be limited to randomized clinical trials with a sample number greater than 100 and written in Portuguese, English, or Spanish. Articles written more than eleven years ago that did not present an association with the proposed theme and presented multidisciplinary interventions were excluded. In addition, studies with incomplete outcomes and a lack of data to be extracted were also excluded.

### **2.3 Selection of Trials**

Titles and abstracts of retrieved studies were analyzed for eligibility criteria by two reviewers (TCAS and PPM). With the preselected articles, the publications obtained were critically evaluated by reading the full text. Additionally, all titles found were imported into a spreadsheet generated in Microsoft Excel; duplicates were removed along with other studies that did not

meet the criteria described or were irrelevant to this review.

## **2.4 Data Extraction and Analysis**

Two independent reviewers (TCAS and PPM) performed the data extraction process to ensure that no relevant data was deleted. When extracted, the information collected was standardized and grouped as follows: authors, date of publication, study site, type of intervention, frequency of intervention and professional involved, type of study, size of the analyzed sample, gender of the patient, and main outcomes observed.

## **2.5 Risk-of-Bias Assessment**

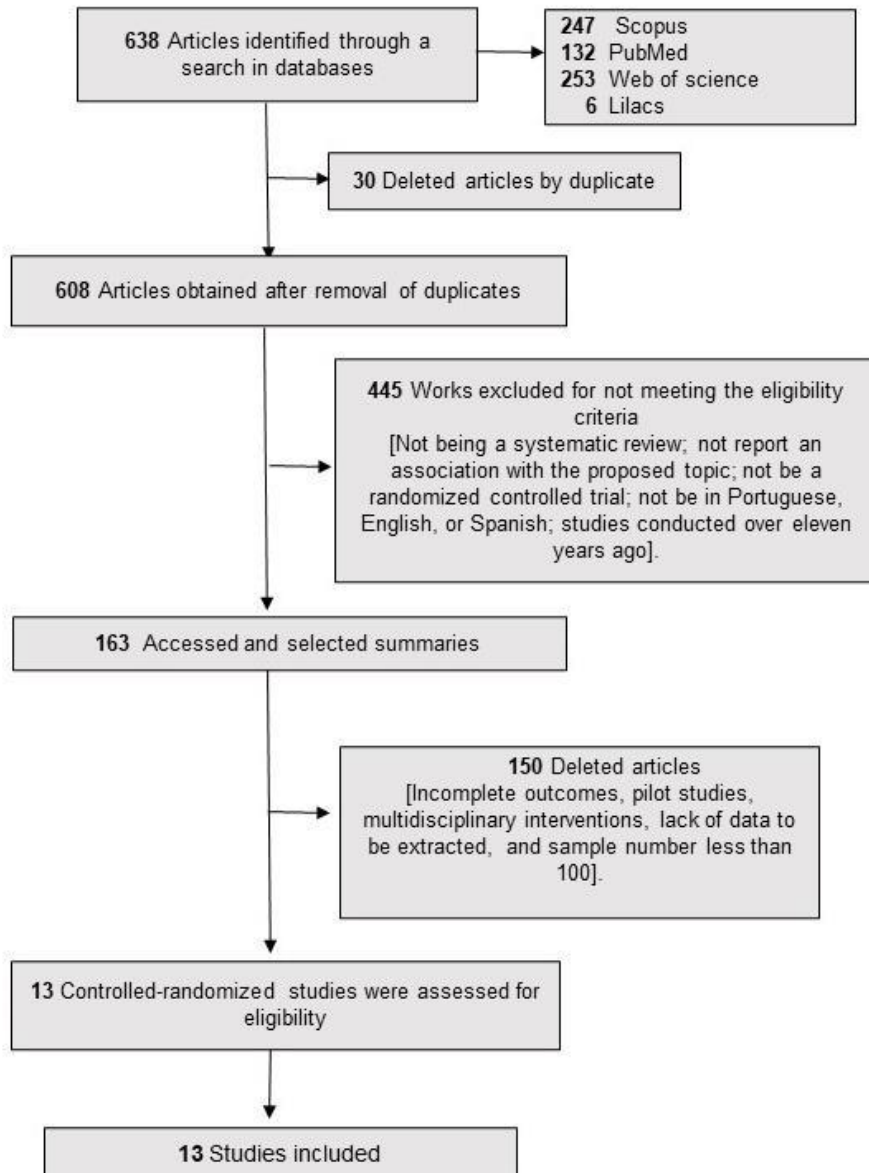
Two independent reviewers (IAG and TCAS) performed the methodological evaluation of the included studies. For the judgment of randomized clinical trials, we used the Cochrane Collaboration Tool included in the Review Manager program (RevMan 5.4), which summarizes domains to be judged regarding possible biases in the studies. Each domain can be classified as low risk of bias, high risk of bias, or unclear risk of bias, according to the support for judgment described by the evaluators (Higgins et al., 2011).

# **3. Results**

## **3.1 Selection of Trials**

Based on the search strategy used, 638 articles published between 2010 and 2021 were retrieved. Of these, 13 studies met the predefined eligibility criteria, and a total of 625 articles were excluded. The entire search flow is summarized in Figure 1.

**Figure 1:** PRISMA Flowchart of the Clinical Trials Selection Process.



Source: Authors.

### 3.2 Study characteristics

A total of 13 randomized controlled trials evaluated 15 interventions and their outcomes for improving the QoL of patients with fibromyalgia are described in Table 1. Therapies consisted of pharmacological, psychological, and exercise interventions or other therapeutic modalities also used as complementary or alternative. The average duration of interventions was 14 weeks. Collectively, an average of 256.8 patients (a total of 3,339) composed the studies. Female participants represented about 92.2% of the study population and all participants had a pre-established diagnosis of fibromyalgia according to the American College of Rheumatology (ACR), and one study used the diagnostic criteria for fibromyalgia proposed by the rheumatologist, like the ACR criteria themselves, as described in Table 2.

**Table 1:** Data extracted from randomized clinical trials included in the review.

Reference	Type of Intervention	Frequency and professional involved	Type of study	Number of Participants	Gender	Main outcomes observed
<b>Exercise type Interventions</b>						
Larsson et al, 2015 Sweden	Resistance exercise compared to an active control group	Twice a week for 15 weeks under the supervision of physiotherapists	RCT	130	Female	The resistance exercise group showed improvements in muscle strength, pain intensity, and quality of life
Wang et al, 2018, USA	Aerobic exercise or one of the four tai chi interventions	Twice a week for 12 or 24 weeks (aerobic exercises or one of the four Tai Chi interventions) under the supervision of instructors and physiologists	RCT	226	Female and male	All groups exhibited improvements in quality of life. At 24 weeks, the tai chi groups showed significant improvements for quality of life and depression, and at 52 weeks, for anxiety, compared to the aerobic exercise group.
<b>Drugs Interventions</b>						
Miki, K et al, 2016, Japan	Mirtazapine 15mg/dl and 30mg/dl compared to placebo	Placebo was used for two weeks, followed by mirtazapine 15mg and after one week, 30mg or matching placebo for 12 weeks	RCT	430	Female and male	Mirtazapine was associated with reduced pain, improvements in QOL, and anxiety compared to placebo
Murakami et al, 2015 Japan	Duloxetine 60 mg compared to placebo	Duloxetine or placebo once daily for 14 weeks	RCT	393	Female and male	Compared to placebo, duloxetine was associated with improvements in pain relief and quality of life.
Ohta e al, 2012, Japan	Pregabalin 300 or 450 mg/day compared to placebo	Pregabalin or placebo for 15 weeks	RCT	443	Female and male	Compared to placebo, pregabalin showed benefits for pain reduction, physical functioning, and quality of life
McIntyre Paisley, Kouassi & Gendron, 2014, Canada	Quetiapine XR 300 mg/day compared to placebo	Quetiapine XR or placebo for 8 weeks	RCT	120	Female and male	Quetiapine XR was associated with positive effects with reduced pain and depression compared to placebo
Branco et al, 2011 France	Milnacipran in doses of 100/150 or 200 mg/day	Milnacipran or placebo prior to 3 months, with a new randomization with milnacipran at different doses (100/150/200 mg/day) for 1 year	RCT	468	Female and male	Milnacipran showed benefits for pain reduction (150/200 mg/day) and improved quality of life (100/150/200 mg/day)
<b>Psychological Interventions</b>						
Lumley et al, 2018, EUA	EAET compared to CBT and the control group (FM education)	8 sessions of 90 minutes, for 6 months, under the supervision of clinical psychologists	RCT	230	Female and male	Improvements were reported in the EAET group to reduce pain, depression, anxiety and improved physical functioning compared to the control. Compared to CBT, EAET was superior only for generalized pain during follow-up

Kashikar-Zuck et al, 2012, EUA	CBT compared to the control group (FM education)	8 weekly sessions of 45 minutes, for 8 weeks, under psychologist supervision	RCT	114	Female and male	CBT showed a reduction in functional disability, pain, and depression. Both CBT and the control group showed improvements in quality of life
Alda et al, 2011, Spain	CBT or RPT compared to TAU	TCC - 10 weekly sessions for 10 or 12 weeks, under the supervision of therapists RPT- 6 months under the supervision of psychiatrists TAU - under the supervision of doctors for 6 months	RCT	169	Female and male	CBT significantly improved pain, anxiety, functional capacity and quality of life compared to RPT or TAU
<b>Other types of interventions</b>						
Vas et al, 2016, Spain	IA compared to SA group	9 acupuncture sessions (real or simulated lasting 20 minutes, once a week, under the supervision of psychiatrists for 6 months)	RCT	164	Female and male	Individualized acupuncture showed positive results for decreasing pain and improving quality of life compared to the simulated acupuncture group
Collazo, Urbano & Ripoll, 2015, Spain	Lidocaine IV, ketamine IV, autohemotherapy with ozone, craniopuncture with electroacupuncture compared to control (usual pharmacotherapy)	Lidocaine- for 60 minutes for 5 days; ketamine- for 60 minutes for 5 days; auto-hemotherapy with ozone 7 sessions in 10 minutes; craniopuncture - twice a week for 5 weeks Both interventions were performed by acupuncturists	RCT	265	Female and male	Positive results were found for pain reduction in the craniopuncture group compared to the other groups
Schmidit et al, 2010 Germany	MBSR, active control or control group (waiting list)	MSBR and active control - 8 weeks, under the supervision of a psychologist	RCT	177	Female	No beneficial effects of MBSR were reported for the analyzed variables

Abbreviations: CBT, Cognitive behavioral therapy; EAET, Emotional Awareness and Expression Therapy; F, Fibromyalgia; FS, Fibromyalgia Syndrome; IA, individualized Acupuncture; IV, intravenous; MBSR, Mindfulness-Based Stress Reduction; NR, Not reported; QOL, Quality of life; RCT, Randomized Clinical Test; AS, Simulated acupuncture; RPT, Recommended pharmacological treatment; TAU, Treatment as usual; XR, Extended Release. Source: Authors.

**Table 2:** Studies using the 1990 and 2010 American College of Rheumatology (ACR) diagnostic criteria

<b>ACR 1990</b>	<b>ACR 2010</b>	<b>Criteria proposed by the rheumatologist</b>
<b>Ohta et al.</b>	Wang et al.	Kashikar Zuck et al.
<b>McIntyre et al.</b>	Murakami et al.	
<b>Alda et al.</b>	Branco et al.	
<b>Schmidt et al.</b>	Lumley et al.	
<b>Larsson et al.</b>	Vas et al.	
<b>Miki et al.</b>	Collazo et al.	

Source: Authors.

### 3.3 Risk-of-Bias Assessment

Of the 13 trials included, 10 studies (76.9%) were classified as high risk of bias, and 7 studies (53.8%) were classified as the uncertain risk of bias (Figures 2 and 3). The main causes for bias were not blinding patients or professionals (6 trials [46.2%]), therapies used simultaneously with the study intervention (3 studies [23%]), and others, such as losses to follow-up and conflicts of interest (2 studies; [7.6%]). A summary of the quality of the evidence found is described in Table 3.



**Figure 2:** Risk of bias for included studies.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Alda et al., 2011	+	+	●	+	+	+	+
Branco et al., 2011	?	?	?	?	+	+	+
Collazo, Urbano & Ripoll, 2015	+	?	●	?	●	+	●
Kashikar-Zuck et al., 2012	+	+	+	+	+	+	●
Larsson, et al., 2015	+	+	+	+	+	+	●
Lumley et al., 2018	+	+	●	?	+	+	+
McIntyre Paisley, Kouassi & Gendron, 2014	?	+	?	?	+	+	●
Miki, K., et al., 2016	+	+	?	+	+	?	+
Murakami., et al., 2015	+	+	+	?	+	+	+
Ohta., e al., 2012	+	+	+	?	+	+	●
Schmidit et al., 2010	+	+	●	+	+	+	+
Vas et al., 2016	+	+	●	+	+	+	+
Wang, et al., 2018	+	+	●	+	+	+	+

Figure generated from Review Manager Version 5.4 program. Source: Authors.

**Figure 3:** Risk of bias graph for included studies. Items that assess the methodological quality of all studies are represented as a percentage.

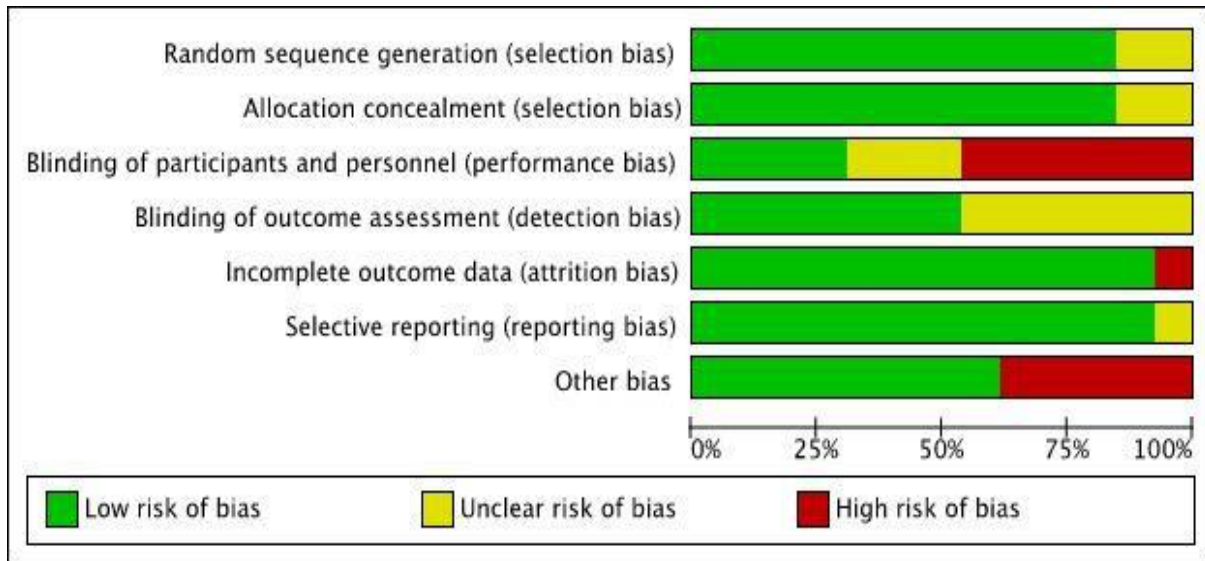


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**Table 3:** Summary of analyzed interventions, observed outcomes and quality of evidence.

Intervention	Outcomes observed	Evidence rating
<b>Exercise-type interventions</b>		
Resistance physical exercise	The resistance exercise group showed positive associations for improvements in pain and quality of life compared to the active control	Low
Tai Chi	Compared to aerobic exercise, the tai chi groups showed significant improvements in quality of life, depression, and anxiety	Low
<b>Drugs interventions</b>		
Mirtazapine	Mirtazapine was associated with reductions in pain, anxiety, and improvements in quality of life compared to placebo	Low
Duloxetine	Compared to placebo, duloxetine was associated with improved quality of life and pain relief.	Low
Pregabalin	Compared to placebo, pregabalin was associated with benefits for pain reduction, improved physical functioning, and quality of life	High to moderate
Quetiapine XR	Quetiapine XR was associated with positive effects on pain and depression reduction compared to placebo	Low
Milnacipran	Milnacipran showed benefits for pain reduction (150/200mg/day) and improved quality of life (100/150/200mg/day)	High
<b>Psychological Interventions</b>		
EAET	EAET was associated with reductions in pain, depression, anxiety, and improvements in physical functioning compared to control. Compared to CBT, EAET was superior only for pain reduction	Low
CBT	CBT was associated with improvements in physical functioning, pain, and depression compared to control. For the quality of life, both groups showed benefits	High to moderate
CBT	CBT showed positive results for pain, anxiety, physical functioning, and quality of life compared to the RPT and TAU groups	High
Individualized Acupuncture	Individualized acupuncture showed positive results for decreasing pain and improving quality of life compared to the simulated acupuncture group	Low
<b>Other types of interventions</b>		
Lidocaine IV, ketamine IV, autohemotherapy with ozone, craniopuncture with electroacupuncture compared	Positive results were found for pain reduction in the craniopuncture group compared to the other groups and to the control	No evidence was found
MBSR	NR	NR

Abbreviations: CBT, Cognitive behavioral therapy; EAET, Emotional Awareness and Expression Therapy; IV, intravenous; MBSR, Mindfulness-Based Stress Reduction; NR, Not reported; RPT, Recommended pharmacological treatment; TAU, Treatment as usual; XR, Extended Release. Source: Authors.

### 3.4 Quality of Life

Two studies evaluated the effect of exercise on quality of life in individuals with FM (Larsson et al., 2015; Wang et al., 2018). Muscle resistance exercises showed significant results in improving QoL compared to the control group. These results were not sustained during the 13- and 18-month follow-up. Supervised aerobic exercise compared to one of four combined tai chi groups also showed benefits in all studies groups. There was no maintenance of these improvements in the 52-week follow-up, only the tai chi group in the most intensive modality sustained these results.

Five studies evaluated associations between drug interventions and QoL (Branco et al., 2011; McIntyre et al., 2014; Miki et al., 2016; Murakami et al., 2015; Ohta et al., 2012). Patients who used mirtazapine 15mg had better QoL scores compared to placebo. Different dosages of Duloxetine (between 60 and 120 mg) have also been shown to produce significant improvements. Another study looked at comparisons between pregabalin and its matching placebo; significant improvements

were observed for QoL in the pregabalin group. Likewise, pharmacological intervention with quetiapine in increasing doses according to the tolerance of each patient demonstrated higher QoL scores compared to the control. Patients using milnacipran in three dose modalities (150/100/200 mg/day) for 1 year showed improvements that extended to the end of the study, at week 52.

Three studies evaluated possible positive associations between psychological interventions and QoL (Alda et al., 2011; Kashikar-Zuck et al., 2012; Lumley et al., 2017; Schmidt et al., 2011). Cognitive-behavioral therapy (CBT) showed greater significant effects compared to active controls in two studies. When compared to recommended pharmacological treatment (RPT) and usual care at the primary care level (TAU), positive results for QoL were found. When compared to education in fibromyalgia, CBT produced greater results for QoL. Treatment effects were maintained until study follow-up at six months. In the study in which mindfulness-based stress reduction (MBSR) was compared to active control, there were no significant results for QoL.

Only one study investigated associations between acupuncture and fibromyalgia symptoms (Vas et al., 2016). Improvements of QoL were observed in the acupuncture group compared to sham acupuncture. Other study, (Collazo et al., 2015) had four different complementary therapies (IV lidocaine, IV ketamine, hairy skull acupuncture with electroacupuncture, and ozone autohemoinfusion) versus a control group were evaluated. Improvements were observed in the craniopuncture group in QoL scores.

### **3.5. Pain and physical ability**

Only one study reported positive associations between endurance exercise, pain, and physical capacity (Larsson et al., 2015). Patients in the exercise group exhibited better results for pain and physical function when compared to the active control group. These results were still maintained at the 18-month follow-up.

Five trials examined fibromyalgia pain and physical functioning against the use of drug therapies (Branco et al., 2011; McIntyre et al., 2014; Miki et al., 2016; Murakami et al., 2015; Ohta et al., 2012). The mirtazapine group was associated with improvements in pain and function, with maintenance of these effects through the end of the intervention and higher response rates compared to placebo (45.5% vs 30.8%). Patients treated with selective serotonin and norepinephrine reuptake inhibitors (SNRIs), duloxetine, and milnacipran (150/200 mg/d) showed associations for a significant reduction in pain when compared to their corresponding placebos, as well as improvements in physical functioning. Similarly, significant reductions in pain and function have been reported with pregabalin when compared to placebo. Reductions in pain measures and improvements in physical function were also observed in patients who used quetiapine XR compared to placebo.

Three studies showed a positive effect of psychological interventions on pain and physical capacity in FM (Alda et al., 2011; Lumley et al., 2017). When the Expression and Emotional Awareness Therapy (EAET) was compared to CBT and active control, reductions in pain intensity and better physical functioning were observed. However, these positive results were like CBT, with no statistically significant differences between these two therapies. Another CBT intervention reported significant findings for pain acceptance and function when compared to pharmacological therapies employed in primary care (RPT and TAU). These improvements were sustained at follow-up only for groups receiving drug therapy. In another trial, both CBT and the control group showed reductions in pain and physical function by the end of the study.

One trial looked at associations between acupuncture and rates of pain and physical ability in FM patients (Vas et al., 2016). Compared to the sham acupuncture group, real acupuncture showed a positive correlation for pain reduction and physical function improvement in these patients. Interestingly, these improvements were still maintained in the follow-up. Another study identified at three and six months of interventions, statistically significant reductions in pain and function in the craniopuncture group when compared to other complementary interventions. In other investigation, the mindfulness-based

stress reduction approach (MBSR) showed no significant reduction in pain reduction compared to control.

### **3.6. Anxiety and Depression**

Just one study evaluated the association between exercise and reduction of depressive and anxiety symptoms (Wang et al., 2018). Patients undergoing tai chi therapy had lower levels of anxiety and depression compared to the aerobic exercise intervention.

Four studies examined the relationship between drug approaches and psychological disorders in FM (McIntyre et al., 2014; Miki et al., 2016; Murakami et al., 2015; Ohta et al., 2012). In three studies, significant reductions in depressive and anxiety symptoms were observed for duloxetine (60 mg/d), mirtazapine, and quetiapine XR compared to each matching placebo. In the study in which pregabalin (300 or 450mg/day) and placebo were compared, no evidence was observed for this outcome.

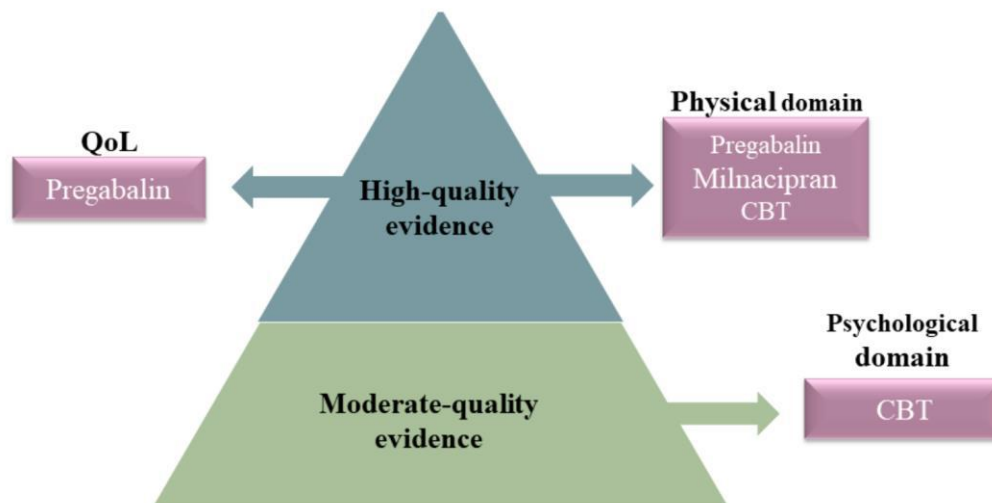
Three studies evaluated the effect of psychological interventions (Alda et al., 2011; Kashikar-Zuck et al., 2012; Lumley et al., 2017). For positive outcomes related to the mental domain in FM, EAET and CBT showed lower anxiety and depression rates compared to the control. Similarly, in two other studies, CBT produced improvements in symptoms when compared to pharmacological therapies (RPT and TAU) and education in fibromyalgia. However, at follow-up, the TCC and RPT groups reported positive effects.

Benefits in favor of acupuncture were reported in one study (Vas et al., 2016). After ten weeks of intervention, significant improvements were reported for anxiety compared to the control group. For depression, no significant reduction was found. No significant findings were also reported for MBSR.

## **4. Discussion**

Our study provides a review of recent evidence of the effectiveness of therapeutic interventions that improve the QoL of patients with FM. We have gathered moderate to high-quality evidence supporting the use of interventions with antidepressants (milnacipran) for the physical domain of QoL, CBT for the physical (pain and physical function) and psychological (anxiety and depression) domains, and the anticonvulsant pregabalin for overall QoL and physical domain (pain and physical function) specifically (Figure 4).

**Figure 4:** Evidence-synthesis found in this study for the therapeutic interventions that improve the different domains of QoL in patients with fibromyalgia.



Source: Authors.

#### 4.1 General Quality of Life

Evidence-based recommendations suggest that non-pharmacological approaches such as physical exercise are initially prescribed for FM management (Macfarlane et al., 2017). Our investigation suggests clinically relevant associations between resistance exercise and improvements in QoL, although these findings were not supported during follow-up. A previous systematic review (AJ et al., 2013) provides, although to a limited extent, support that moderate to moderate-high intensity resistance training can improve multidimensional function and other symptoms of FMS. Although consistent with the results found in this review, future investigations will likely lead us to other important findings for this result.

We have collected different drug interventions that have been shown to improve the QoL of individuals with FMS, including two of them, pregabalin and duloxetine are approved by the Food and Drug Administration (FDA) and recommended by the European League Against Rheumatism (EULAR) for the management of FMS (Macfarlane et al., 2017). A previous review gathered several clinical trials to assess the effect of mirtazapine on QoL (Welsch et al., 2018). Consistent with our findings, it was shown that only a few individuals experienced relief from FMS symptoms, although the evidence was limited. Our review also found evidence to support good results for improving QoL with drugs as duloxetine, (Lunn et al., 2014) pregabalin (M. J. Arnold, 2017) and quetiapine (Seehusen & Bain, 2017). Although we have found high-quality evidence only for pregabalin. We believe that other high-quality studies can be performed and confirm our findings that suggest the effectiveness of these therapies.

Previous studies with moderate evidence suggest that acupuncture does not provide positive results on the QoL of patients with FM or only provides a brief improvement during the initial phase of treatment, (Bai et al., 2014; Deare et al., 2013) which was not observed in the present review. A possible explanation for this is that the analyzed trial reports that patients used antidepressant and analgesic drugs during the intervention period, and this interferes with the results obtained. We admit that possibly the positive results found here were generated by the interference of these drugs and should be

interpreted with great caution. Another complementary therapy from traditional Chinese medicine (TCM), craniopuncture showed some results for QoL compared to other complementary treatments. However, we were unable to compare this intervention based on the literature due to the scarcity of available studies. This is an important question for future research because, despite initially promising results, questions remain.

#### **4.2 Pain and physical ability**

Amplification of pain sensitivity and functional changes are commonly found in individuals with fibromyalgia (Lorena et al., 2016). Increases in pain levels are associated with greater functional limitations and, consequently, greater negative impacts on different perspectives of QoL. For this reason, the initial management of these symptoms is highlighted as a priority to reduce the impacts of the syndrome (Staud & Rodriguez, 2006) and compelling, high-quality recommendations emphasize pain management through non-pharmacological measures such as exercise in fibromyalgia. (Fitzcharles et al., 2013; Macfarlane et al., 2017; Buckhardt et al., 2005). In the present study, resistance exercise was associated with significant reductions in pain and improvements in physical capacity. These findings have also been noted in previous (AJ et al., 2013; Busch et al., 2007) studies that also suggest improvements in pain and physical capacity in different exercise modalities, including resistance exercise. This evidence, however, was reduced due to present methodological limitations, but we believe that future investigations with better quality will support this intervention.

In our review, we assessed the effects of each drug intervention individually. Although we found evidence of pain reductions with mirtazapine, a previous review provided us findings that only a minority experience this outcome (Welsch et al., 2018). We admit that this inconsistency can be explained by the non-pharmacological therapies maintained in the clinical trial simultaneously with the intervention. Consistent with previous findings, we found indications of reductions in pain levels and improvements in physical capacity with SNRIs such as milnacipran (Cording et al., 2015) and duloxetine (Lunn et al., 2014). Although only milnacipran has been supported by high-quality evidence, overall, these results provide us support that serotonin and norepinephrine play analgesic roles independent of their antidepressant activity, as seen in previous studies (Larsson et al., 2015; Obata, 2017; Perahia et al., 2006). These are undoubtedly clinically important findings for FM pain therapy. High-quality evidence also supported pregabalin for pain reduction and improved physical function (M. J. Arnold, 2017) and, for quetiapine XR, reduced evidence for fibromyalgia pain reduction (Seehusen & Bain, 2017). In our analysis for quetiapine XR, one source of uncertainty for this result is that half of the patients used stable doses of analgesic medications (opioids) during the trial. It is noteworthy that these findings are potential sources of bias.

Psychological interventions are one of the pillars of therapy for FMS, and their results are even compared to analgesic drug therapy (Glombiewski et al., 2010; Schiltenswolf et al., 2017; Theadom et al., 2015). We found positive associations for pain reduction and physical capacity improvement with CBT (K. Bernardy et al., 2018). These results are consistent with previous studies that suggest benefits of these therapies in managing fibromyalgia pain and are further supported by high-quality evidence.

Previous studies have reported moderate and high-quality evidence supporting acupuncture for pain management in fibromyalgia (Deare et al., 2013; Zhang et al., 2019). These results support the findings of our investigation, however, the results showed that acupuncture does not differ from sham acupuncture in pain benefits.

#### **4.3 Anxiety and depression**

Anxiety and Depression FMS is often associated with psychiatric comorbidities that negatively impact the QoL of these patients. Emotional distress, although subjective, reflects a neuropsychological impairment that predicts significant functional and cognitive impairment. We found several positive effects of drugs for psychological symptoms in our review.

Although the effects of mirtazapine on anxiety and depression in FM patients remain controversial, mirtazapine will likely provide benefits for some patients during the acute phase of the depressive episode (Nakagawa et al., 2007; Welsch et al., 2018). Quetiapine and duloxetine appear to be effective in these conditions, however, they are found with limited evidence. (Curran, 2009; Seehusen & Bain, 2017).

CBT also showed moderate evidence of psychological benefits in patients with fibromyalgia, confirming the results obtained in our analysis (Glombiewski et al., 2010; Kathrin Bernardy et al., 2010).

The multiplicity of chronic symptoms not resolved by standard therapy together with a difficult prognosis are some of the possible reasons that induce FMS patients to resort to complementary and alternative interventions (Perry et al., 2017; Terhorst et al., 2011). Acupuncture therapy, although it shows us promising data for anxious conditions and depression, is not addressed in studies with high methodological quality, which limit our suggestions about the therapeutic efficacy of this intervention (Pilkington, 2010).

#### **4.4 Strengths and Limitations**

The findings of this review have noteworthy strengths. We conducted this review following the recommendations of the Cochrane manual, which makes our investigation with great methodological rigor. In addition, we analyzed current evidence on which interventions improve the different dimensions that make the QoL of patients with FMS. As it is a syndrome, any of these domains can be affected alone or together in addition to pain, and the management of these symptoms becomes clinically relevant to consolidate an effective treatment that improves QoL.

However, this report has some limitations, such as: due to the diversity of interventions analyzed, we were faced with great clinical heterogeneity, which did not allow us to carry out a meta-analysis. Furthermore, studies published after 2010 were included in this research. However, it is unlikely that we missed potential studies to be analyzed because the ACR criteria were updated this year, and previously, only tender points were assessed and no other symptoms that also impact the QoL. The studies that used the less current criteria, from 1990, still used other measurement instruments to encompass the other symptoms of the syndrome. Another limitation could be that we use multidisciplinary therapies as an exclusion criterion, to limit our research scope and recover interventions used isolated. We admit that multimodal treatments are of great importance, but we do not know if all patients would respond well or would need joint therapies. However, as previously reported, multifaceted interventions were not our focus. Finally, we consider the inclusion of trials with a possible risk of bias and the absence of long-term follow-up in most of the investigated interventions as strong limitations, after all, this point is of great importance when dealing with chronic diseases. Thus, such limitations point to gaps that can be filled in future studies. Noteworthy, although we have some low evidence on interventions in FM, most are recommended in the main guidelines for this disease management. In addition, we highlight the different interventions that alleviate the manifestations of FM, but which have a lesser impact on QoL.

#### **5. Conclusion**

In general, there is limited, poor-quality evidence on the effectiveness of therapeutic interventions on the QoL of patients with FM. In this investigation, we found high-quality evidence supporting pregabalin for overall QoL and the physical domain (pain and function), CBT, and milnacipran for the physical domain of QoL (pain and function), and moderate-quality evidence supporting CBT for the domain psychological (anxiety and depression).



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