









## Effect of pharmacotherapy on fibromyalgia: an overview of systematic reviews

*Efeito da farmacoterapia na fibromialgia: uma overview de revisões sistemáticas*

 Alana Teles Costa<sup>1</sup>,  Renata Ferraz Figueiredo<sup>1</sup>,  Rafaella de Oliveira Santos Silva<sup>1</sup>,  Tatiana Damasceno da Silva<sup>1</sup>,  
 Thaciana dos Santos Alcantara<sup>1</sup>,  Mairim Russo Serafini<sup>1</sup>,  Divaldo Pereira de Lyra Júnior<sup>1</sup>,  Cristiani Isabel Banderó Walker<sup>1</sup>

**ABSTRACT**

Fibromyalgia is a debilitating and chronic pain processing disorder, in which the proportion of patients who achieve good results with pharmacotherapy is small. However, choosing the best available evidence on pharmacotherapy can optimize patient clinical outcomes. **Objective:** This overview aimed to identify in systematic reviews the effects of pharmacotherapy on fibromyalgia, considering the quality of the reviews and the efficacy of the outcomes. **Methods:** This search was performed in seven databases: PubMed, Web of Science, COCHRANE, Lilacs, Embase, Scopus and IPA. The methodological quality was evaluated using A MeaSurement Tool to Assess Systematic Reviews 2. The protocol was registered in the PROSPERO database (CRD42018095943). **Results:** A total of 63 systematic reviews were selected after reading full texts, but only 8 of them were of moderate to high quality and were included in this overview. All included reviews were published in English, between 2012 and 2018, performed meta-analysis, used the American College of Rheumatology (1990) diagnostic criteria for fibromyalgia, and jointly assessed pain improvement, adverse reactions, and withdrawal. Most reviews included only randomized controlled trials. Of the fourteen drugs addressed in systematic reviews evaluated, duloxetine, milnacipran, and pregabalin showed evidence of improvement in pain (Moderate: ≤30%) and other fibromyalgia symptoms, as depression and fatigue. However, these medications presented significant withdrawals due to adverse reactions (mainly nausea, headache, dizziness and constipation). The rate of treatment withdrawal reached 36%. **Conclusion:** Few studies have high quality and sufficient evidence on the effect of medicines on fibromyalgia, resulting in a lack of support for prescribers to choose drugs that meet criteria for need, effectiveness, safety and compliance.

**Keywords:** Rheumatic Diseases, Fibromyalgia, Pain, Drug Therapy, Treatment Outcome

**RESUMO**

Fibromialgia é um distúrbio de processamento da dor debilitante e crônico, em que a proporção de pacientes que obtêm bons resultados com a farmacoterapia é pequena. No entanto, escolher a melhor evidência disponível sobre a farmacoterapia pode otimizar os resultados clínicos do paciente. **Objetivo:** Esta overview teve como objetivo identificar em revisões sistemáticas os efeitos da farmacoterapia na fibromialgia, considerando a qualidade das revisões e a eficácia dos resultados. **Métodos:** Esta busca foi realizada em sete bases de dados: PubMed, Web of Science, COCHRANE, Lilacs, Embase, Scopus e IPA. A qualidade metodológica foi avaliada usando A MeaSurement Tool to Assess Systematic Reviews 2. O protocolo foi registrado no PROSPERO (CRD42018095943). **Resultados:** Um total de 63 revisões sistemáticas foram selecionadas após a leitura de textos completos, mas apenas 8 delas eram de qualidade moderada a alta e foram incluídas nesta overview. Todas as revisões incluídas foram publicadas em inglês, entre 2012 e 2018, realizaram meta-análises, utilizaram os critérios de diagnósticos do American College of Rheumatology (1990) para fibromialgia e avaliaram conjuntamente a melhora da dor, reações adversas e retiradas. A maioria das revisões incluiu apenas ensaios clínicos randomizados. Dos quatorze medicamentos abordados nas revisões sistemáticas avaliadas, duloxetina, milnaciprano e pregabalina mostraram evidências de melhora da dor (moderada: ≤30%) e de outros sintomas da fibromialgia como depressão e fadiga. No entanto, esses medicamentos apresentaram retiradas significativas devido a reações adversas (principalmente náusea, cefaleia, tontura e constipação). A taxa de abandono ao tratamento chegou a 36%. **Conclusão:** Poucos estudos apresentam evidências suficientes e de alta qualidade sobre o efeito dos medicamentos na fibromialgia, resultando na falta de apoio para os prescritores escolherem medicamentos que atendam aos critérios de necessidade, eficácia, segurança e adesão.

<sup>1</sup> Universidade Federal de Sergipe - UFS

**Address for correspondence**

Cristiani Isabel Banderó Walker  
E-mail: [bandewalk@hotmail.com](mailto:bandewalk@hotmail.com)

Submitted: November 17, 2020

Accepted: June 27, 2022

**How to cite**

Costa AT, Figueiredo RF, Silva ROS, Silva TD, Alcantara TS, Serafini MR, et al. Effect of pharmacotherapy on fibromyalgia: an overview of systematic reviews. *Acta Fisiatr.* 2022;29(3):232-244.



10.11606/issn.2317-0190.v29i3a178254



©2022 by Acta Fisiátrica

This work is licensed under a Creative Commons - Attribution 4.0 International

**Palavras-chaves:** Doenças Reumáticas, Fibromialgia, Dor, Tratamento Farmacológico, Resultado do Tratamento

## INTRODUCTION

Fibromyalgia is defined as a severe, chronic, non-articular rheumatic condition characterized by diffuse musculoskeletal pain, hyperalgesia, and generalized tender points in the absence of inflammatory or structural musculoskeletal abnormalities.<sup>1</sup> Although relatively common, it is still a controversial condition in respect of its etiology, pathophysiology, diagnosis and treatment.<sup>2</sup> This syndrome affects an estimated 2.10% of the world's population, and is four times more prevalent in women.<sup>3</sup> Patients affected by fibromyalgia commonly present, in addition to generalized chronic pain, symptoms such as fatigue, non-restorative sleep, gastrointestinal complaints, and cognitive and mood problems, among others.<sup>4</sup> Due to the heterogeneity of the symptoms and the fact that the pathogenesis has not yet been fully elucidated, fibromyalgia therapy remains a challenge for physicians.<sup>5</sup>

Different medicines are recommended for fibromyalgia by different published guidelines, with only three being approved by the Food and Drug Administration - pregabalin, duloxetine and milnacipran, and none by the European Medicines Agency.<sup>6</sup> The current pharmacotherapeutic management of fibromyalgia includes the use of neurotransmission modulating drugs that act on pain, reward and emotional circuits. Although many drugs have been used, the evidence for pharmacotherapy intervention effectiveness is still weak.<sup>5</sup> In clinical practice, a maximum of 25% of fibromyalgia patients experience significant pain-related improvements when using any drug treatment,<sup>7</sup> which is usually 10% to 25% more than placebo. Many patients discontinue drug treatments because of their limited effectiveness and the incidence of adverse reactions.<sup>8</sup>

The treatment of fibromyalgia is, therefore, challenging. In recent years, there have been systematic reviews conducted for almost all commonly used treatment strategies. However, it is necessary to assess the quality of these systematic reviews and to provide a summary of the best evidence for decision makers, health professionals and researchers.

## OBJECTIVE

This overview aimed to identify and provide a summary of the systematic reviews on the effects of pharmacotherapy on fibromyalgia in the literature, evaluate the quality of the reviews, and the efficacy of the outcomes.

## METHODS

The question of this overview of systematic reviews was "What data do systematic reviews present about the effect of pharmacotherapy used by patients with fibromyalgia?". Based on this question, it will be possible to assess the quality and compile the best evidence to support the decision-making for choice of medicines that meet well-defined criteria for need, effectiveness, safety and, compliance.

This overview followed the recommendations of A MeaSurement Tool to Assess Systematic Reviews (AMSTAR 2)<sup>9</sup> and also the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA).<sup>10</sup>

This overview was registered with the International Prospective Register of Systematic Reviews (PROSPERO), n.

CRD42018095943 (This protocol gave rise to two articles).

To be considered eligible for this overview, the reviews were required to meet the following criteria:

- Type of reviews – systematic reviews, with or without a meta-analysis, of any study design, in any language, investigating some pharmacotherapy for fibromyalgia.
- Type of participant – adults diagnosed with fibromyalgia.
- Type of intervention – any pharmacotherapy for fibromyalgia, by any route of administration and at any dosage.
- Type of comparator – any placebo or active medicine.
- Type of outcome – improvement of the patient's painful condition or other symptoms associated with fibromyalgia, identified through any tool.

The exclusion criteria were systematic reviews that: were unavailable in full; evaluated pharmacotherapy for other morbidities; were overviews and case reports; did not present specific results for the fibromyalgia group; had a low or critically low AMSTAR 2 rating.<sup>11</sup>

## Search strategy

The following databases were searched from their inception to January 2020 to identify systematic reviews with or without meta-analysis: COCHRANE, Scopus, PubMed, Lilacs, Embase, Web of Science, and International Pharmaceutical Abstracts (IPA), using a combination of Medical Subject Headings (MESH) and key word terms. The PICOS strategy was used to determine the words that would be used in the search (Chart 1).<sup>12</sup>

The selection process was performed in three steps:

- 1) the exclusion of duplicate articles;
- 2) screening of titles, abstract and finally full texts;
- 3) manual screening of references of systematic reviews included after reading the full articles.

The studies were independently selected by two evaluators (RFF and TSD), and any disagreements were resolved by a third evaluator (TSA).<sup>10</sup> To assist in this process, we used the Rayyan tool.<sup>13</sup> For any unavailable full articles, the corresponding authors were contacted via ResearchGate ([www.researchgate.net](http://www.researchgate.net)) or by e-mail. For ongoing studies, assessments were made using the [clinicaltrials.gov](http://clinicaltrials.gov) portal.

## Methodological quality assessment

The studies were independently analyzed by two evaluators (RFF and TSD) and any disagreements were resolved by consensus through a senior evaluator (ROSS). This analysis was performed using the AMSTAR 2 tool,<sup>9</sup> used with Microsoft Office Excel (2016) to produce a table specifying the critical and non-critical domains of the AMSTAR 2 tool. The overall quality in the included studies was classified as:

- High – One or no non-critical weakness and no critical weakness.
- Moderate – No critical weakness and more than one non-critical weakness.
- Low – A critical weakness with or without non-critical weaknesses.
- Critically low – More than one critical weakness with or without non-critical weaknesses.

**Chart 1.** PICOS strategy

<b>P</b>	Fibromyalgia patients	Fibromyalgia [MeSHTerms]; Fibromyalgias; Fibromyalgia-Fibromyositis Syndrome; Fibromyalgia Fibromyositis Syndrome; Fibromyalgia-Fibromyositis Syndromes; Syndrome, Fibromyalgia-Fibromyositis; Syndromes, Fibromyalgia-Fibromyositis; Rheumatism, Muscular; Muscular Rheumatism; Fibrositis; Fibrositides; Myofascial Pain Syndrome, Diffuse; Diffuse Myofascial Pain Syndrome; Fibromyositis Fibromyalgia Syndrome; Fibromyositis Fibromyalgia Syndrome; Fibromyositis-Fibromyalgia Syndromes; Syndrome, Fibromyositis Fibromyalgia; Syndromes, Fibromyositis-Fibromyalgia; Fibromyalgia, Secondary; Fibromyalgias, Secondary; Secondary Fibromyalgia; Secondary Fibromyalgias; Fibromyalgia, Primary; Fibromyalgias, Primary
<b>I</b>	Pharmacotherapy	Pharmacotherapy; Cannabinoids; Neuromodulators; Tricyclic antidepressants; Muscle relaxants; Selective serotonin reuptake inhibitors; Antidepressants; Antiparkinsoniano; Simple analgesics; Light opiates
<b>C</b>	-	-
<b>O</b>	Reduction of Fibromyalgia signs and symptoms	Treatment, outcome; Outcome, Treatment; Clinical Effectiveness; Clinical Effectiveness; Effectiveness, Clinical; Effectivenesses, Clinical; Patient Relevant Outcome; Outcome, Patient-Relevant; Outcomes, Patient-Relevant; Patient Relevant Outcome; Patient-Relevant Outcomes; Efficacy, Clinical; Treatment Effectiveness; Effectiveness, Treatment; Treatment Efficacy; Efficacy, Treatment; Rehabilitation Outcome; Outcome, Rehabilitation
<b>S</b>	Systematic reviews	Systematic Reviews; Systematic Review; Systematic Literature Review; Systematic Literature Reviews; Meta-analysis

*P: Patient or Problem; I: Intervention; C: Comparison; O: Outcomes; S: Study design*

### Data extraction

The following data were extracted independently by two evaluators (ATC and RFF): authors; year of publication; number of primary studies included in the systematic review or meta-analysis; design of primary studies and systematic reviews; practice scenarios; types of study participants; pharmacotherapy evaluated in each study; comparator group; tools used to evaluate clinical outcomes; all clinical outcomes evaluated for fibromyalgia; limitations and risk of bias. Disagreements were resolved by a third reviewer (CIBW). If additional information was required, the authors were contacted by email.

### Analysis of the degree of agreement

To measure the degree of agreement between the evaluators for each of the overview stages, Cohen's Kappa index (k) was used. The degree of agreement was stratified:  $k < 0.10$ , no agreement;  $k < 0.40$ , poor agreement;  $0.40 < k < 0.75$ , good agreement;  $k > 0.75$ , excellent agreement.<sup>14</sup>

### Data Interpretation

In order to facilitate the understanding of the implications of the evidence presented in relation to practical decisions, a nominal group was formed to interpret the results found in the systematic reviews. The expert committee from the nominal group was formed by professionals (ATC, RFF, ROSS, CIBW, and DPLJ), with experience and expertise in the clinical and research area.

The hypotheses proposed by the nominal group related the variables extracted in the systematic reviews of fibromyalgia to the steps recommended by The American College of Clinical Pharmacy<sup>15</sup> for choosing the appropriate treatment. The nominal group meeting was conducted by senior moderators (CIBW and DPLJ). The process was carried out in six stages: explanation of the theme and purpose of the nominal group;

silent generation of hypotheses; hypothesis sharing; discussion of hypotheses; ranking and prioritization; discussion and re-ranking.<sup>16,17</sup> At the end of the nominal group, we listed which variables were related to the needs or appropriateness, effectiveness, safety and adherence of treatment in fibromyalgia.

### RESULTS

A total of 4,107 articles were identified by searching the EMBASE, Scopus, Web of Science, PubMed, Cochrane and IPA databases. For the full text reading, 201 articles were selected. After this step, 63 systematic reviews were evaluated for quality using the AMSTAR 2 tool.<sup>9</sup> The excluded full texts (138), all the steps of the selection process are described in Figure 1.

According to AMSTAR 2, 87.30% (n= 55) of the selected systematic reviews showed poor or critically low quality and therefore were not included in this overview, 4.76% (n= 3) had moderate quality,<sup>18-20</sup> and 7.93% (n= 5) had high quality,<sup>21-25</sup> and were included in the overview. Critical items that were frequently omitted by the studies were item 2 (review protocol), item 15 (list of excluded articles and reasons), and item 7 (risk of bias).

The kappa index (k) for measuring the degree of agreement between the two raters was greater than 0.75 at all stages (Study selection: 0.77 in the first stage, and 0.87 in the second stage; the AMSTAR 2 evaluation was: 0.81 in the first stage, and 0.92 in the second stage) which indicate excellent agreement.<sup>14</sup>

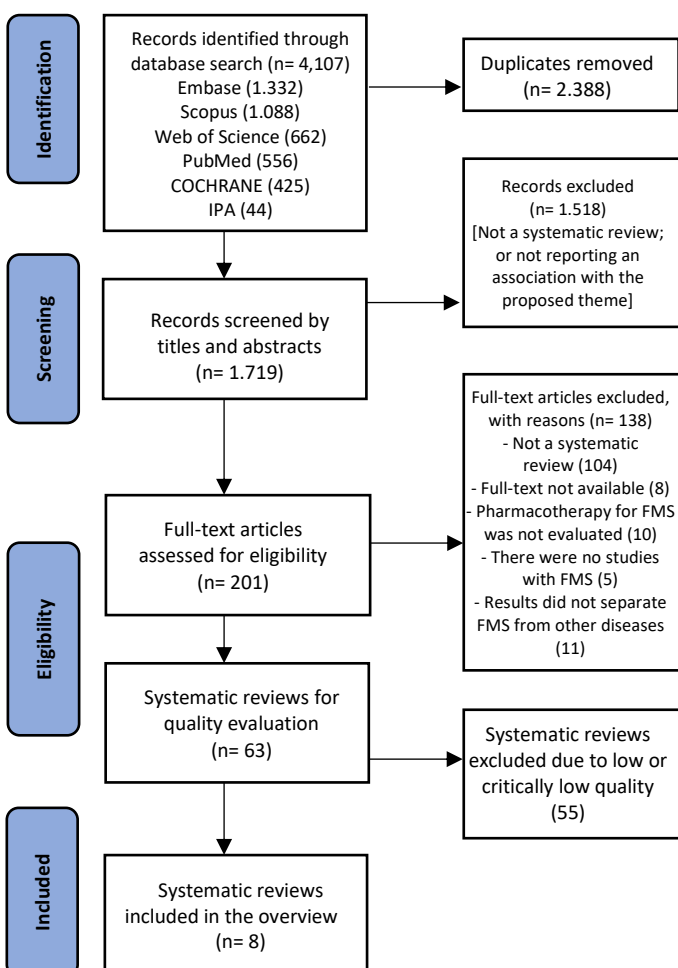
### Characteristics of the included studies

This overview included eight systematic reviews with meta-analysis of moderate to high quality, which investigated fourteen pharmacotherapies for fibromyalgia. The total sum of participants in 32 studies within the included reviews was 11,293. All reviews were published in English, between 2012 and 2018, using the American College of Rheumatology (1990) diagnostic criteria for fibromyalgia,<sup>26</sup> and jointly assessed pain

improvement, adverse reactions, and withdrawal. The characteristics of the systematic reviews are presented in Chart 2. There was great variation in the tools used to evaluate the clinical outcomes. The complete list of tools used to evaluate the clinical outcomes is described in Chart 3.

The assessment of pain intensity was performed in all reviews 100% using different pain scales. However, the assessment of pain intensity in all studies was interpreted in accordance with the definitions of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.<sup>27</sup> The frequency with which adverse reactions and withdrawals occurred were also analyzed by all reviews. Moreover, anxiety, disability, fatigue, problems related to sexual function, cognitive disorders, quality of life, depression and sleep were addressed in the minority of the reviews.

Regarding the assessment of the risk of bias in primary studies, six of the eight systematic reviews used the Cochrane Risk of Bias Tool published in 2011,<sup>18-20,23-25</sup> one used the Cochrane Risk of Bias Tool published in 2008,<sup>21</sup> and one used the Review Manager 5.22 The ROBINS-I tool was used to assess the risk of bias in an observational study.<sup>20</sup>



**Figure 1.** PRISMA diagram of study selection process

### Pharmacotherapy for fibromyalgia

#### Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Of the eight systematic reviews evaluated in this overview, three evaluated the SNRIs: Derry et al.<sup>22</sup> presented five primary

studies with milnacipran;<sup>28-32</sup> the review by Häuser et al.<sup>19</sup> included the same five studies with milnacipran<sup>28-32</sup> and also evaluated duloxetine.<sup>33-37</sup> Cording et al.<sup>24</sup> included seven primary studies with milnacipran.<sup>28-32,38,39</sup> According to these reviews, milnacipran is only effective for a minority in the treatment of fibromyalgia pain, supplying moderate levels of pain relief (at least 30%). There were insufficient data to assess substantial levels of pain relief (at least 50%).<sup>19,22,24</sup> Duloxetine was superior to milnacipran in reducing mean pain.<sup>19</sup>

Only Häuser et al.<sup>19</sup> evaluated other outcomes such as anxiety, sleep, depression, fatigue, disability, health-related quality of life, sexual function problems, and cognitive impairment. In this review, duloxetine was superior to milnacipran in reducing sleep-related problems. When comparing milnacipran and duloxetine with placebo there were only reduction in anxiety, sleep related problems and sexual function problems but they were not statistically significant.

The potential benefit of duloxetine and milnacipran is counterbalanced by their potential harms, as increased adverse reactions and adverse reaction withdrawals, which were significantly greater for the higher dose. Headache, constipation and nausea were the most common reactions. There was no significant difference in serious adverse reactions between either duloxetine or milnacipran and placebo. The studies had a low risk of bias and good quality in general,<sup>19,22,24</sup> although the imputation method used in analyses of the primary outcomes could overestimate treatment effect.<sup>2</sup>

#### Anticonvulsants

Two of the systematic reviews analyzed the use of the anticonvulsants for the treatment of fibromyalgia.<sup>18,21</sup> Hearn et al.<sup>21</sup> studied six primary studies with lacosamide, five of which comprised participants with chronic neuropathic pain, but only one primary study (NCT00401830) comprised participants who had a diagnosis for fibromyalgia. Üçeyler et al.<sup>18</sup> analyzed eight primary studies: five studies with pregabalin,<sup>40-44</sup> one study with gabapentin,<sup>45</sup> one study with levetiracetam (NCT00254657) and one with lacosamide (NCT00401830), the same included in the review by Hearn et al.<sup>21</sup> There is high-quality evidence that pregabalin had little benefit compared with placebo in reducing pain. The amount and quality of evidence are insufficient to be sure in the conclusions on the efficacy and safety of gabapentin, lacosamide and levetiracetam in fibromyalgia.<sup>18,21</sup>

Only Üçeyler et al.<sup>18</sup> evaluated other outcomes. Pregabalin had little benefit over placebo in reducing sleep problems. There is high-quality evidence that the effects of pregabalin compared with placebo in reducing fatigue, depression, anxiety and quality of life are significant but not substantial. There is high-quality evidence that there is no significant difference between pregabalin and placebo in the reduction of disability.

The adverse reactions withdrawals were higher with pregabalin use than with placebo use. There was no significant difference in serious adverse reactions between pregabalin and placebo use. Dizziness was a particularly frequent adverse reaction seen with pregabalin use.<sup>18</sup> Most risks of bias were low, except for incomplete outcome data and selective non-reporting by some studies.<sup>18,21</sup> All pregabalin studies had a low risk of bias.<sup>18</sup>

Chart 2. Characteristics of included systematic reviews

Systematic Reviews	Primary studies (Total participants)	Intervention (Number of participants)	Comparison (Number of participants)	Duration	Gender and Mean Age of the Participants	Settings	Design of included Studies	Quality of Systematic review (AMSTAR 2)
Cording <sup>24</sup> 2015	7 studies (4575)	Milnacipran 100mg (1220) Milnacipran 200mg (1609)	Placebo (1746)	8 to 24 weeks	92 to 97% female 47 to 50 years	Multicenter - Community	Randomized controlled trials: Parallel group	High quality
Derry <sup>22</sup> 2012	5 studies (4138)	Milnacipran 100mg (1141) Milnacipran 200mg (1383)	Placebo (1614)	8 to 24 weeks	93 to 97% female 47 to 50 years	Outpatient centers/ Outpatient clinical/ Research centers	Randomized controlled trials: Parallel group	High quality
Häuser <sup>19</sup> 2013	10 studies (6038)	Milnacipran 100 to 200mg/day (2524) Duloxetine 60 to 120mg/day (1087)	Placebo (2427)	12 to 27 weeks	92 to 100% female 47 to 51 years	Research centers	Randomized controlled trials: Parallel group	Moderate quality
Hearn <sup>21</sup> 2012	1 study (159)	Lacosamide 400mg/day (81)	Placebo (78)	12 weeks	93% female 50 years	Multicenter - Community	Randomized controlled trials: Parallel group	High quality
Tort <sup>23</sup> 2012	2 studies (230)	Pirindole 150mg/day (50) Moclobemide 450 to 600mg/day (43)	Placebo (95) Amitriptyline 25/37.5mg/day (42)	4 to 12 weeks	85 to 100% female 39 to 49 years	Outpatient clinics	Randomized controlled trials: Parallel group	High quality
Üçeyler <sup>18</sup> 2013	8 studies (3579)	Gabapentin 1200 to 2400mg/day (75) Lacosamide 400mg/day (81) Levetiracetam 3000mg/day (40) Pregabalin 150 to 600mg/day (2319)	Placebo (1099)	13 weeks	89 to 96% Female 47 to 50 years	Research centers	Randomized controlled trials: Parallel group	Moderate quality
Stockings <sup>20</sup> 2018	7 studies (403)	Plant-based cannabis (72) Nabilone (133) THC-extract (48)	Placebo (118) None	4 to 144 weeks	0 to 95% female 45 to 57 years	No reported	Randomized controlled trials; Quasi-experimental and Observational studies	Moderate quality
Welsch <sup>25</sup> 2018	3 studies (606)	Dronabinol (32) Mirtazapine 15 to 45mg/day (334)	Placebo (272)	7 to 14 weeks	86 to 95 % female 43 to 45 years	Multiple research centers	Randomized controlled trials: Parallel group and cross-over	High quality

**Chart 3.** Evaluation measures used in the studies included in the systematic reviews

Outcome	Systematic reviews that reported	Evaluation measures
Pain	Cording <sup>24</sup> ; Derry <sup>22</sup> ; Häuser <sup>19</sup> ; Hearn <sup>21</sup> ; Tort <sup>23</sup> ; Üçeyler <sup>18</sup> ; Stockings <sup>20</sup> ; Welsch <sup>25</sup>	BPI (0-10) 24 mean pain score, electronic diary 24-hours recall pain (VAS 0-100), (VAS 0-100) without reporting the time frame, daily diary mean pain (NRS 0-10), PGIC (NRS 1-7), tender point score (0 to 36), tender points (0 to 18), MPQ (NRS 0-10), MPQ (NRS 0-100), Gracely logarithmic scale (0-20)
Patient perceived improvement	Cording <sup>24</sup> ; Derry <sup>22</sup> ; Häuser <sup>19</sup> ; Hearn <sup>21</sup> ; Tort <sup>23</sup> ; Üçeyler <sup>18</sup> ; Stockings <sup>20</sup> ; Welsch <sup>25</sup>	PGIC (NRS 1-7), CGI of severity (0 to 7), SCL-90-R (0-5)
Adverse reaction	Cording <sup>24</sup> ; Derry <sup>22</sup> ; Häuser <sup>19</sup> ; Hearn <sup>21</sup> ; Tort <sup>23</sup> ; Üçeyler <sup>18</sup> ; Stockings <sup>20</sup> ; Welsch <sup>25</sup>	Spontaneous report of participants, physical exams, electrocardiograms, laboratory tests.
Withdrawal	Cording <sup>24</sup> ; Derry <sup>22</sup> ; Tort <sup>23</sup>	Spontaneous report of participants
Sleep	Häuser <sup>19</sup> ; Tort <sup>23</sup> ; Üçeyler <sup>18</sup> ; Welsch <sup>25</sup>	BPI sleep interference (NRS 0-10), MOS Sleep Problems Index I (NRS 0-100), diary sleep interference (NRS 0-10), JSS total score (NRS 0-20), PSQI (NRS 0-21), ISI (NRS 0-28)
Depression	Häuser <sup>19</sup> ; Üçeyler 2013; Welsch <sup>25</sup>	BDI total score (NRS 0-63), HDRS (NRS 0-52), HADS (NRS 0-21); MDRS (NRS 0-60); FIQ single item depression scale (0-10)
Disability	Häuser <sup>19</sup> ; Tort <sup>23</sup> ; Üçeyler <sup>18</sup>	BPI mean interference scale (NRS 0-10), MDHAQ disability subscale score, physical functioning scale of the SF-36 (0-50), FIQ disability scale (VAS 0-10), SDS (0-10), physical functioning (NRS 50-0)
Fatigue	Häuser <sup>19</sup> ; Üçeyler <sup>18</sup> ; Welsch <sup>25</sup>	FIQ (VAS 0-10), SF-36 (VAS 0-100), MAF (NRS 1-50), MFI general fatigue (NRS 4-20), MFI total (NRS 20-100)
Anxiety	Häuser <sup>19</sup> ; Üçeyler <sup>18</sup>	FIQ single-item scale for anxiety (VAS 0-10); BAI total score (NRS 0-63), STAI (NRS 20-80), HADS (NRS 0-21)
Health-related quality of life	Häuser <sup>19</sup> ; Tort <sup>23</sup> ; Üçeyler <sup>18</sup>	FIQ (VAS 0-100), FIQ total score (0-80), SF-36, NHP (0-100)
Cognitive disturbances	Häuser <sup>19</sup>	MFI (NRS 4-20), MASQ (NRS 38-190).
Sexual function	Häuser <sup>19</sup>	ASEX (NRS 5-30)
Tenderness	Häuser <sup>19</sup>	Measurement of tender point pain threshold

BPI: Brief Pain Inventory; VAS: Visual Analogue Scale; NRS: Numeric Rating Scale; PGIC: Patient Global Impression of Change; MPQ: McGill Pain Questionnaire; CGI: Clinical Global Impression; SCL-90-R: Symptom Checklist-90 Revised; MOS: Medical Outcomes Study; JSS: Jenkins Sleep Survey; PSQI: Pittsburgh Sleep Quality Index; ISI: Insomnia Severity Index; BDI: Beck Depression Inventory; HDRS: Hamilton Depression Rating Scale; HADS: Hospital Anxiety and Depression Scale; MDRS: Montgomery Depression Rating Scale; FIQ: Fibromyalgia Impact Questionnaire; MDHAQ: Multidimensional Health Assessment Questionnaire; SF-36: Short-Form Health Survey; SDS: Sheehan's disability scales; MAF: Multidimensional Assessment of Fatigue; MFI: Multidimensional Fatigue Inventory; BAI: Beck Anxiety Inventory; STAI: State-Trait Anxiety Inventory; NHP: Nottingham Health Profile; MASQ: Multiple Ability Self-report Questionnaire; ASEX: Arizona sexual experience scale

### Monoamine Oxidase Inhibitors (MAOIs)

Tort et al.<sup>23</sup> evaluated the use of the monoamine oxidase inhibitors pirlindole<sup>46</sup> and moclobemide, and was the only review to include a study that used a reference drug, amitriptyline, in addition to a placebo.<sup>47</sup> Pirlindole showed statistically significant results compared with placebo for pain, classified as a moderate effect size on pain, whereas moclobemide did not show statistically significant differences between groups. Pirlindole showed statistically significant results compared with placebo for tender points and overall assessment by the patient and the physician, whereas moclobemide did not show statistically significant differences between groups. There was a statistically significant difference in sleep and global assessment by the physician favoring amitriptyline compared to moclobemide. The most frequent adverse reactions of MAOIs were headache and insomnia, although there were no statistically significant differences with

placebo. Drop outs due to adverse reactions did not differ either compared with placebo. The most frequent adverse reactions with pirlindole were nausea and vomiting. The most common adverse reactions with moclobemide were headache and difficulties in falling asleep. The most typical adverse reactions with amitriptyline were dry mouth and fatigue. The studies had an inconsistent risk of bias and a small number of patients.<sup>23</sup>

### Tetracyclic antidepressant

The review by Welsch et al.<sup>25</sup> evaluated tetracyclic antidepressants and comprised three primary studies of mirtazapine (JapicCTI-101176).<sup>48,49</sup> Mirtazapine showed a clinically-relevant benefit compared to placebo in moderate pain improvement (30% pain relief) and in the reduction of mean pain intensity. Mirtazapine did not show a statistically significant benefit compared to placebo in substantial pain

improvement (50% pain relief). Mirtazapine showed a clinically-relevant benefit compared to placebo in relation to sleep problems. Mirtazapine did not show a statistically significant benefit compared to placebo in participant-reported improvement of health-related quality of life, or in reduction of fatigue and negative mood. There were no statistically significant differences between mirtazapine and placebo in the frequency of withdrawals due to adverse reactions or due to lack of efficacy, serious adverse reactions and any adverse reaction. There was a clinically-relevant harm from taking mirtazapine compared to placebo in the number of participants with somnolence, weight gain, and elevated alanine aminotransferase. The authors concluded that there is low-quality evidence that some people with fibromyalgia will experience moderate pain relief and reduced sleep problems from taking mirtazapine, because of poor study quality, indirectness, imprecision, risk of publication bias, and sometimes low numbers of reactions.<sup>25</sup>

### Cannabis and Cannabinoids

The cannabis and cannabinoids were evaluated by Stockings et al.<sup>20</sup> which presented a total of one hundred and four studies, but only seven examined fibromyalgia, six of which were observational studies,<sup>50-55</sup> and only one was a randomized controlled trial.<sup>56</sup> The studies used plant-based cannabis, nabilone, THC-extract, or dronabinol as a treatment at varying doses and routes of administration, as the first or second line of treatment. In all studies, pain improvement was classified as significant. A significant difference in other outcomes as anxiety were reported. There were no serious adverse reactions, but the majority of patients reported at least one adverse reaction (dry mouth, sedation, dizziness, confusion). The review authors concluded that there is little evidence and poor quality in studies of cannabinoids used for fibromyalgia. In addition, they stressed that the results presented would need to be considered amid several potential limitations, including a high risk of bias in many studies because of the small number of participants, lack of information on study design and in the rigor of controls, and also because most studies evaluated cannabinoids as adjuvants to other painkillers.<sup>20</sup>

### Data Interpretation

The expert committee used nominal group methodology<sup>16</sup> to interpret the data in a stratified and sequential way, according to the criteria described below: Need or appropriateness - diagnostic criteria and tools used to assess clinical outcomes; Effectiveness - pain, (patient perceived improvement), sleep, depression, disability, fatigue, anxiety, quality of life, cognitive disorders, sexual function, sensitivity; Safety - frequency and gravity of adverse reactions. Adherence - withdrawal from treatment.<sup>15</sup>

The quantitative results related to drug effectiveness in fibromyalgia, extracted from systematic reviews, are presented in Chart 4. The quantitative results related to safety and drug adherence in fibromyalgia, extracted from systematic reviews, are presented in Chart 5. The review of Stockings et al.<sup>20</sup> is not included in Chart 4 and Chart 5, because the meta-analysis was not done separately for fibromyalgia.

**Chart 4.** Data of systematic reviews related to drug effectiveness in fibromyalgia

Review	Quantitative results related to drug effectiveness in fibromyalgia
Cording <sup>24</sup> 2015	MLN 100mg/day – Pain: Moderate benefit 41%, RR 1.4 [1.2 to 1.6], NNT 9.0 [6.5 to 15]; Substantial benefit 27%, RR 1.6 [1.3 to 2.0], NNT 10 [6.7 to 20]. Patient perceived improvement: PGIC 38%, RR 1.5 [1.3 to 1.7]. MLN 200mg/day – Pain: Moderate benefit 39%, RR 1.4 [1.2 to 1.5], NNT 10 [7.0 to 18]; Substantial benefit 29%, RR 1.6 [1.3 to 1.8], NNT 11 [7.9 to 16]. Patient perceived improvement: PGIC 36%, RR 1.6 [1.3 to 1.8].
Derry <sup>22</sup> 2012	MLN 100mg/day – Pain: Moderate benefit 41%, RR 1.4 [1.2 to 1.6], NNT 8.6 [6.3 to 14]; Substantial benefit 28%, RR NR. Patient perceived improvement: PGIC 39%, RR 1.5 [1.3 to 1.7], NNT 7.6 [5.7 to 11]. MLN 200mg/day – Pain: Moderate benefit 39%, RR 1.4 [1.2 to 1.5], NNT 10 [7.0 to 18]; Substantial benefit 28%, RR NR. Patient perceived improvement: PGIC 40%, RR 1.6 [1.4 to 1.9], NNT 6.1 [4.8 to 8.2].
Häuser <sup>19</sup> 2013	DLX 60/120mg/day – Pain: SMD -0.32 [-0.41 to -0.22] (p=0.04); Moderate benefit RR 1.33 [1.18 to 1.51]; Substantial benefit RR 1.59 [1.35 to 1.88]. Patient perceived improvement: SMD -0.29 [-0.39 to -0.20]. Sleep: SMD -0.24 [-0.37 to -0.12]. Depression: SMD -0.26 [-0.37 to -0.16]. Disability: SMD -0.33 [-0.43 to -0.24]. Fatigue: SMD -0.12 [-0.23 to -0.02]. Anxiety: SMD -0.05 [-0.22 to 0.13]. Cognitive disturbances reduction: SMD -0.27 [-0.38 to -0.16]. Tenderness: SMD -0.23 [-0.35 to -0.12]. MLN 100/200mg/day – Pain: SMD -0.20 [-0.26 to -0.13] (p=0.04); Moderate benefit RR 1.38 [1.25 to 1.51]; Substantial benefit RR 1.44 [1.28 to 1.62]. Patient perceived improvement: SMD -0.25 [-0.33 to -0.17]. Sleep: SMD 0.02 [-0.05 to 0.10]. Depression: SMD -0.11 [-0.17 to -0.04]. Disability: SMD -0.16 [-0.23 to -0.10]. Fatigue: SMD -0.14 [-0.21 to -0.08]. Anxiety: SMD -0.04 [-0.23 to 0.1]. Cognitive disturbances reduction: SMD -0.11 [-0.18 to -0.05].
Hearn <sup>21</sup> 2012	LCM 400mg/day – Pain: Change pain score 1.8 ± 2.1; Placebo 1.3 ± 1.9, Statistic NR. Patient perceived improvement: PGIC NS.
Tort <sup>23</sup> 2012	AMT 25/37.5mg/day – Patient perceived improvement: NS. MCB 450/600mg/day – Pain: MD -0.70 [-2.07 to 0.67]. Patient perceived improvement: NS. Sleep: NS. PLD 150mg/day – Pain: MD -2.00 [-2.91 to -1.09]. Patient perceived improvement: MD -1.60 [-2.74 to -0.46]. Sleep: NS.
Üçeyler <sup>18</sup> 2013	GBP 1200/2400mg/day – Pain: SMD -0.49 [-0.86 to -0.13] (p=0.008); Moderate benefit 50.7% (p=0.02), RR 1.65 [1.10 to 2.48]; Substantial benefit 42.7% (p=0.04), RR 1.60 [1.01 to 2.53]. Sleep: SMD -0.71 [-1.08 to -0.24] (p<0.001). Depression: SMD -0.52 [0.89 to -0.16] (p<0.001). Disability: SMD -0.94 [1.32 to -0.56] (p<0.001). Health-related quality of life: SMD -0.66 [-1.03 to -0.29] (p<0.001). LCM 400mg/day – Pain: NS. Patient perceived improvement: NS. Sleep: NS. Depression: NS. Disability: NS. Fatigue: NS. Anxiety: NS. Health-related quality of life: NS. LVT 3000 mg/day – Pain: NS. Sleep: NS. PGB 150/300/450/600 mg/day – Pain: SMD -0.28 [-0.35 to -0.20] (p<0.001); Moderate benefit 40%, RR 1.37 [1.22 to 1.53] (p<0.001); Substantial benefit 22.2%, RR 1.59 [1.33 to 1.90] (p<0.001), NNT 12 [9 to 21]. Patient perceived improvement: PGIC: 39.4%, RR 1.38 [1.23 to 1.55] (p<0.001), NNT 9 [7 to 13]. Sleep: SMD -0.35 [-0.43 to -0.27] (p<0.001). Depression: SMD -0.09 [-0.16 to -0.01] (p<0.001). Disability: NS. Fatigue: SMD -0.17 [-0.25 to -0.09] (p<0.001). Anxiety: SMD -0.12 [-0.20 to -0.04] (p<0.001). Health-related quality of life: SMD -0.17 [-0.26 to -0.09] (p<0.001).
Welsch <sup>25</sup> 2018	MTN 15/30/45mg/day – Pain: SMD -0.29 [-0.46 to -0.13]; Moderate benefit 47%, RD 0.13 [0.05 to 0.21], NNT 8 [5 to 20]; Substantial benefit 22%, RD 0.05 [-0.01 to 0.12]. Sleep: SMD -0.23 [-0.39 to -0.06]. Depression: SMD 0.67 [-1.44 to 0.10]. Fatigue: SMD -0.02 [-0.19 to 0.16]. Health-related quality of life: HRQoL ≥ 20% (58%), RD 0.08 [-0.01 to 0.16].

MLN: Milnacipran; Moderate benefit: ≥30% improvement; RR: Relative Risk [95% Confidence Interval]; NNT: Number Needed to Treat [95% Confidence Interval]; Substantial benefit: ≥50% improvement; PGIC: Patient Global Impression of Change scale; NR: Not Reported; DLX: Duloxetine; SMD: Standardized Mean Difference [95% Confidence Interval]; LCM: Lacosamide; NS: Not Significant; AMT: Amitriptyline; MCB: Moclobemide; MD: Mean Difference [95% Confidence Interval]; PLD: Pirlindole; GBP: Gabapentin; LVT: Levetiracetam; PGB: Pregabalin; HRQoL: Health-related quality of life; MTN: Mirtazapine; RD: Risk Difference [95% Confidence Interval].

**Chart 5.** Data of systematic reviews related to safety and drug adherence in fibromyalgia

Review	Quantitative results related to safety and drug adherence in fibromyalgia
Cording <sup>24</sup> 2015	MLN 100mg/day – Any adverse reaction: 85%, RR 1.1 [1.05 to 1.1], NNH 15 [10 to 27]. Serious adverse reaction: 1.5%, RR 0.90 [0.47 to 1.7]. Lack of efficacy withdrawals: 7%, RR 0.72 [0.55 to 0.94], NNT 41 [22 to 470]. All case withdrawals: 35%, RR 1.1 [1.01 to 1.3], NNH 23 [12 to 140]. Adverse reaction withdrawals: 19%, RR 1.6 [1.3 to 2.0], NNH 14 [10 to 24]. MLN 200mg/day – Any adverse reaction: 87%, RR 1.1 [1.06 to 1.15], NNH: 11 [8.2 to 16]. Serious adverse reaction: 1.9%, RR 0.91 [0.52 to 1.6]. Lack of efficacy withdrawals: 7.2%, RR 0.66 [0.51 to 0.87], NNT 41 [21 to 400]. All case withdrawals: 36%, RR 1.4 [1.2 to 1.6], NNH 8.8 [6.7 to 13]. Adverse reaction withdrawals: 24%, RR 2.5 [2.0 to 3.1], NNH 7.0 [5.8 to 8.7].
Derry <sup>22</sup> 2012	MLN 100mg/day – Any adverse reaction: 86%, RR 1.1 [1.06 to 1.14], NNH 13 [9.3 to 22]. Serious adverse reaction: 1.4%, RR 0.9 [0.5 to 1.7]. Lack of efficacy withdrawals: 6.8%, RR 0.8 [0.6 to 1.0], NNT 45 [22 to 5850], All case withdrawals: 34%, RR 1.1 [1.02 to 1.3], NNH of 23 [12 to 210]. Adverse reaction withdrawals: 19%, RR 1.6 [1.3 to 2.0], NNH 14 [10 to 24]. MLN 200mg/day – Any adverse reaction: 87%, RR 1.1 [1.06 to 1.14], NNH 11 [8.2 to 16]. Serious adverse reaction: 1.9%, RR 0.9 [0.5 to 1.6]. Lack of efficacy withdrawals: 7.2%, RR 0.66 [0.51 to 0.87], NNT 41 [21 to 400]. All case withdrawals: RR 1.4 [1.2 to 1.6], NNH 8.8 [6.7 to 13]. Adverse reaction withdrawals: 24%, RR 2.5 [2.0 to 3.1], NNH 7.0 [5.8 to 8.7].
Häuser <sup>19</sup> 2013	DLX 60/120mg/day – Serious adverse reaction: RR 0.63 [0.34 to 1.16]. Adverse reaction withdrawals: RR 1.65 [1.30 to 2.09]. MLN 100/200mg/day – Serious adverse reaction: RR 0.88 [0.57 to 1.37]. Adverse reaction withdrawals: RR 2.00 [1.47 to 2.73].
Hearn <sup>21</sup> 2012	LCM 400mg/day – Any adverse reaction: 13.9%, RR 1.38 [1.05 to 1.80]. Serious adverse reaction: 8.9%, RR 0.15 [0.01 to 2.82]. Lack of efficacy withdrawals: 46%, RR 0.47 [0.17 to 1.30]. All case withdrawals: 26.8%, RR 1.07 [0.73 to 1.57]. Adverse reaction withdrawals: 25.8%, RR 1.87 [0.92 to 3.79].
Tort <sup>23</sup> 2012	AMT 25/37.5mg/day – Any adverse reaction: 74%, statistic NR. All case withdrawals: 24%, statistic NR. Adverse reaction withdrawals: 12%, statistic NR. MCB 450/600mg/day – Any adverse reaction: 77%, statistic NR. All case withdrawals: 30%, statistic NR. Adverse reaction withdrawals: 14%, statistic NR. PLD 150mg/day – Any adverse reaction: 40%, statistic NR, NNH 7 [4 to 33]. All case withdrawals: 34%, statistic NR. Adverse reaction withdrawals: RR 1.96 [0.52 to 7.34].
Üçeyler <sup>18</sup> 2013	GBP 1200/2400mg/day – Adverse reaction withdrawals: 16%, RR 1.71 [0.71 to 4.11] (p=0.23). LCM 400mg/day – Serious adverse reaction: NS. LVT 3000 mg/day – Adverse reaction withdrawals: NS. PGB 150/300/450/600 mg/day – Serious adverse reaction: 5.2%, RR 1.03 [0.71 to 1.49] (p=0.99). Adverse reaction withdrawals: 19.4%, RR 1,68 [1,36 to 2,07] (p<0.001).
Welsch <sup>25</sup> 2018	MTN 15/30/45mg/day – Any adverse reaction: 76%, RD 0.12 [-0.01 to 0.26]. Serious adverse reaction: 0.3%, RD -0.00 [-0.01 to 0.02]. Lack of efficacy withdrawals: 1.5%, RD 0.01 [-0.01 to 0.02]. Adverse reaction withdrawals: 3.3%, RD 0.00 [-0.02 to 0.03].

MLN: Milnacipran; RR: Relative Risk [95% Confidence Interval]; NNH: Number Needed to Harm [95% Confidence Interval]; NNT: Number Needed to Treat [95% Confidence Interval]; DLX: Duloxetine; LCM: Lacosamide; AMT: Amitriptyline; NR: Not Reported; MCB: Moclobemide; PLD: Pirlindole; GBP: Gabapentin; NS: Not Significant; LVT: Levetiracetam; PGB: Pregabalin; MTN: Mirtazapine; RD: Risk Difference [95% Confidence Interval]

## DISCUSSION

Only systematic reviews with moderate to high methodological quality were included in this overview in order to compile the best evidence to support the choice of

medicines that met well-defined criteria for need, efficacy, safety and adherence to treatment of fibromyalgia. It was not possible to address all pharmacotherapeutic options due to the low or critically low quality of the other systematic reviews. The main reasons for the low quality of the excluded studies were: failure to investigate or discuss risk of bias; lack of information on excluded articles and the reasons for this; and for changing the review protocol without giving any explanation. These reasons are also often attributed to the low methodological quality of other systematic reviews in the literature.<sup>57-60</sup>

Therefore, we compiled data from eight systematic reviews with moderate to high quality that evaluated fourteen pharmacotherapies. We used these reviews to build a flowchart of choice for fibromyalgia treatment (Figure 2), which provides a clear view of therapies that can be tailored to the needs of each patient.

To assess the need for the medicines the diagnostic criteria and the tools used to assess clinical outcomes were considered. The first challenge in treating the disease in the case of fibromyalgia is the diagnosis.<sup>61</sup> Fibromyalgia shares symptoms with other functional somatic problems and there is often an overlap in diagnosis.<sup>1,5,62</sup> In addition, the variability of outcome measures in clinical trials makes it difficult to assess treatment evidence.<sup>27</sup> We identified the diagnostic criteria of the primary studies in which there was uniformity with the American College of Rheumatology (1990) criteria.<sup>26</sup> We also identified the tools used by the primary studies to assess each of the outcomes, in which there was variability. The systematic reviews included in this overview evaluated 13 outcomes using 52 different means. As for the tools used to assess outcomes, ten types were used to assess pain, and seven to assess sleep. This heterogeneity does not facilitate the process of grouping data from different studies, which is necessary to provide a basis for significant comparisons between treatments and the clinical importance of the results.

Regarding effectiveness, fibromyalgia treatment should improve not only pain, but also the other symptoms that cause suffering to patients. Although pain is the dominant symptom in fibromyalgia, other symptoms such as fatigue, sleep disturbance and cognitive impairment are common and have an important influence on the quality of life of patients.<sup>63</sup> The evidence on the effectiveness of the fibromyalgia pharmacotherapy was, therefore, determined based on significant improvement in the outcomes for each medicine evaluated in relation to the placebo confirmed by meta-analysis.<sup>9,10</sup>

In this overview, in common with Canadian and Israeli guidelines, the European League Against Rheumatism (EULAR) recommendations, and the last Brazilian consensus,<sup>63-66</sup> we find evidence that supports the efficacy of the milnacipran, duloxetine, and pregabalin for a minority of patients in the treatment of pain in fibromyalgia.<sup>18,19,22,24</sup> Pirlindole showed a moderate effect to reduce pain compared to placebo. In addition, milnacipran and duloxetine showed efficacy in relation to fatigue, depression, quality of life, disability and cognitive impairment,<sup>19</sup> while pregabalin showed efficacy in relation to fatigue, depression, quality of life, anxiety and sleep-related problems.<sup>18</sup> Amitriptyline also showed improvement in sleep.<sup>23</sup>

On the other hand, insufficient or low evidence on the



effectiveness of fibromyalgia pharmacotherapy was determined based on the following criteria: the inclusion of studies of different designs in systematic reviews, primary studies with a high risk of bias and/or a low number of participants, as well as the absence of a goal-analysis to assess the significant improvement in the outcomes for each medicine studied in relation to the placebo.<sup>9,10</sup> Thus, the evidence was insufficient to determine the benefit of amitriptyline, cannabis and cannabinoids, levetiracetam, gabapentin, and mirtazapine for pain reduction in fibromyalgia.<sup>18,20,23,25</sup> These findings were consistent with the EULAR recommendations, but not with the Brazilian consensus, which recommends amitriptyline for the control of fibromyalgia pain.<sup>63,66</sup> Finally, there was a low level of evidence for the effectiveness of lacosamide and moclobemide, which presented no significant difference when compared to placebo in respect of pain improvement, or in any of the secondary endpoints for fibromyalgia treatment.<sup>18,21,23</sup>

Again, the Brazilian consensus provides different information, with moclobemide being recommended for use in fibromyalgia.<sup>66</sup>

To evaluate the safety of fibromyalgia pharmacotherapy, the parameters used were the frequency of adverse reactions, serious adverse reactions, and withdrawals due to adverse reactions. Milnacipran, duloxetine, pregabalin and lacosamide had significant withdrawals due to adverse reactions compared to placebo, the most common being nausea, headache, dizziness, and constipation.<sup>18,19,21,22,24</sup> Pirlindole and mirtazapine demonstrated safety in this parameter.<sup>23,25</sup> For amitriptyline, levetiracetam and gabapentin the data were not presented or were not sufficient to draw conclusions. This parameter was also classified as significant compared to placebo for pregabalin, duloxetine and milnacipran in the EULAR recommendations.<sup>63</sup> Among the medicines in which serious adverse reactions were reported (pregabalin, duloxetine, milnacipran and mirtazapine), there was not a significant difference from placebo,<sup>18,19,22,24,25</sup> which were similar to EULAR recommendations.<sup>63</sup> Milnacipran and lacosamide presented at least one significant adverse reaction compared to placebo,<sup>21,22,24</sup> for pirlindole, moclobemide and mirtazapine the difference was not significant.<sup>23,25</sup> No results were given for pregabalin, duloxetine, gabapentin, and levetiracetam. This is a very important data that should not be neglected, as, according to studies, experiencing an adverse reaction is the reason for abandoning treatment in 40% of cases, so health professionals need this information to be able to consider not only effectiveness, but also safety when choosing a treatment option.<sup>61,67</sup>

After assessing whether treatment is necessary, effective and safe, characteristics that may interfere with good adherence, or compliance, by patients should be evaluated. The criteria used in this study to assess non-adherence was the general number of withdrawals. For pregabalin, gabapentin, levetiracetam, mirtazapine and duloxetine this result was not reported. Milnacipran had a significant difference in withdrawals compared to placebo.<sup>22,24</sup> According to the EULAR, the highest frequency of dropouts was among patients taking milnacipran, and the lowest among those taking amitriptyline.<sup>63,65</sup> The adherence model proposed by the World Health Organization highlights a number of factors that should be considered that relate to the health professionals, the

treatment itself, the disease, the patient and, socioeconomic factors.<sup>68</sup> Pharmacological treatment adherence to fibromyalgia is considered low worldwide with many patients refusing treatment, and less than half of new users adhering to treatment. However, evidence shows that quality of life is higher in fibromyalgia patients who adhere to their pharmacotherapy.<sup>69</sup>

It is important to emphasize that some limitations in the systematic reviews hamper the ability to compare treatments. Many results were not presented separately for each drug evaluated by the systematic reviews, but as a therapeutic class.

Symptoms of fibromyalgia other than pain were not evaluated in all studies. The number of participants in the studies of amitriptyline, pirlindole, moclobemide, lacosamide, levetiracetam and gabapentin was small compared to the others studies. The moclobemide and amitriptyline studies were short term. Quantitative results for cannabis and cannabinoids could not be compared because they were presented in conjunction with other diseases.

Future studies should consider all the physical and emotional factors involved in fibromyalgia. However, health professionals should not expect a specific drug to have positive results for all outcomes in order to classify it as effective for fibromyalgia. The purpose of a holistic assessment of outcomes is to help prescribers choose the pharmacotherapy that best meets the needs of each patient, particularly given the low adherence to pharmacotherapy of patients with fibromyalgia.

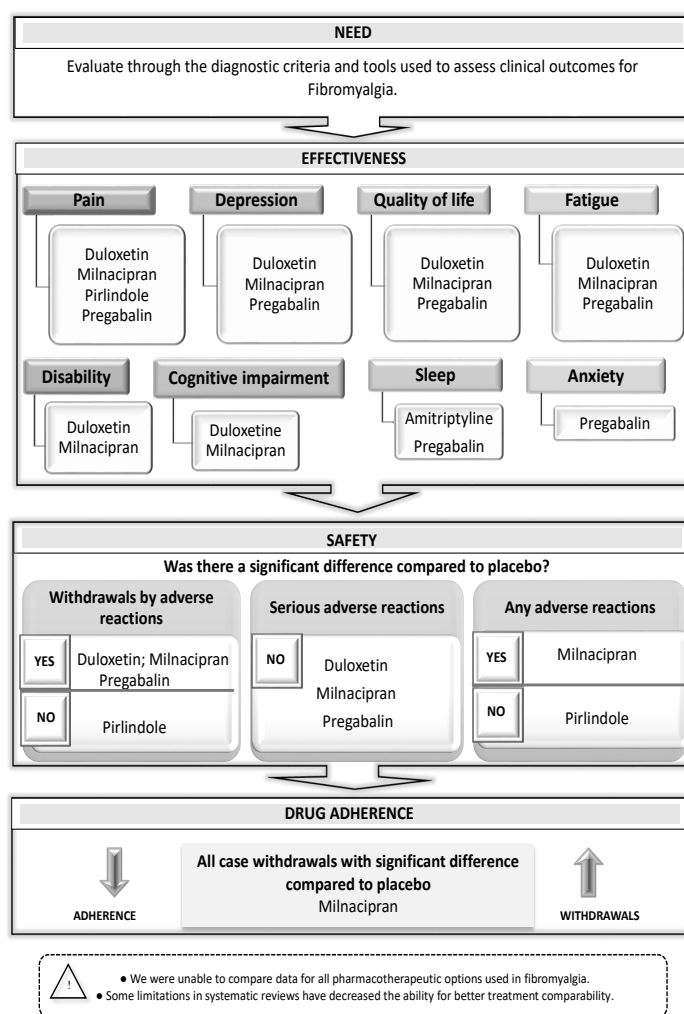


Figure 2. Flowchart of choice for fibromyalgia treatment

## LIMITATIONS

This overview of systematic reviews has some strengths and limitations. Among the strengths is the fact that, to the best of our knowledge, this is the first overview to use a sequential and stratified approach to identify the best pharmacotherapy for each patient according to an analysis of the need, effectiveness, safety and compliance to treatment.

Other strengths include the following methodological aspects: planning and reporting of the overview based on the recommendations of AMSTAR-2; prior registration of the review protocol; an extensive search in the literature in respect of the number of databases and terms used in the search; as well as selection of studies and quality assessment by two independent reviewers. However, this overview also presents limitations. There was no search in the gray literature. The evaluation of the effect of the pharmacotherapy of fibromyalgia was performed only in systematic reviews, resulting in overlapping primary studies. We were unable to compare data for all pharmacotherapeutic options used in fibromyalgia, due to the decision to exclude systematic reviews with low or very low quality.

## CONCLUSION

In conclusion, few systematic reviews have sufficient evidence on the effect of medicines on fibromyalgia, resulting in a lack of support for prescribers to choose drugs that meet criteria for need, effectiveness, safety and compliance. The vast majority of systematic reviews published on the pharmacotherapy used in fibromyalgia have low or critically low quality, did not investigate or discuss the risk of study bias, did not state which articles had been excluded and for which reasons, and did not justify important changes from the review protocol. There was great variation in the tools chosen to assess each of the outcomes, which can make it difficult to compile the data and do the correlation between them.

Of the fourteen medicines that were evaluated in the systematic reviews analyzed in this overview, only duloxetine, milnacipran, pregabalin and pirlindole showed evidence of moderate pain improvement in fibromyalgia. Duloxetine, milnacipran and pregabalin also showed evidence of improved quality of life, depression, fatigue and other symptoms of fibromyalgia. Regarding safety, milnacipran, duloxetine, and pregabalin did not cause serious adverse reactions, but presented significant withdrawals because of adverse reactions. In conclusion, pharmacotherapy for fibromyalgia has limited benefit, and is associated with unwanted effects, which contribute to low adherence to treatment.

## FUNDING

This work was based on the Masters Dissertation of the first author (ATC). This work was supported by the Fundação de Apoio à Pesquisa e a Inovação Tecnológica do Estado de Sergipe, FAPITEC-SE (Edital 11/2016 - PROEF); and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, CAPES (Finance Code 001).

## REFERENCES

1. Conversano C, Carmassi C, Bertelloni CA, Marchi L, Micheloni T, Carbone MG, et al. Potentially traumatic events, post-traumatic stress disorder and post-traumatic stress spectrum in patients with fibromyalgia. *Clin Exp Rheumatol*. 2019;37(1):39-43.
2. Perrot S. Fibromyalgia: A misconnection in a multiconnected world? *Eur J Pain*. 2019;23(5):866-73. Doi: <https://doi.org/10.1002/eip.1367>
3. Cabo-Meseguer A, Cerdá-Olmedo G, Trillo-Mata JL. Fibromyalgia: Prevalence, epidemiologic profiles and economic costs. *Med Clin (Barc)*. 2017;149(10):441-8. Doi: <https://doi.org/10.1016/j.medcli.2017.06.008>
4. Talotta R, Bazzichi L, Di Franco M, Casale R, Batticciotto A, Gerardi MC, et al. One year in review 2017: fibromyalgia. *Clin Exp Rheumatol*. 2017;35 Suppl 1(3):6-12.
5. Atzeni F, Talotta R, Masala IF, Giacomelli C, Conversano C, Nucera V, et al. One year in review 2019: fibromyalgia. *Clin Exp Rheumatol*. 2019;37(1):3-10.
6. Calandre EP, Rico-Villademoros F, Slim M. An update on pharmacotherapy for the treatment of fibromyalgia. *Expert Opin Pharmacother*. 2015;16(9):1347-68. Doi: <https://doi.org/10.1517/14656566.2015.1047343>
7. Häuser W & Fitzcharles MA. Facts and myths pertaining to fibromyalgia. *Dialogues Clin Neurosci*. 2018;20(1):53–62. Doi: <https://doi.org/10.31887/DCNS.2018.20.1/whauser>
8. Lawson K. Potential drug therapies for the treatment of fibromyalgia. *Expert Opin Investig Drugs*. 2016;25(9):1071-81. Doi: <https://doi.org/10.1080/13543784.2016.1197906>
9. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008. Doi: <https://doi.org/10.1136/bmj.j4008>
10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*. 2009;6(7):e1000097. Doi: <https://doi.org/10.1371/journal.pmed.1000097>
11. Lorenz RC, Matthias K, Pieper D, Wegewitz U, Morche J, Nocon M, et al. A psychometric study found AMSTAR 2 to be a valid and moderately reliable appraisal tool. *J Clin Epidemiol*. 2019;114:133-40. Doi: <https://doi.org/10.1016/j.jclinepi.2019.05.028>
12. Santos CMD, Pimenta CADM, Nobre MRC. The PICO strategy for the research question construction and evidence search. *Rev Latino-Am Enferm*. 2007;15(3):508–11. Doi: <http://dx.doi.org/10.1590/S0104-11692007000300023>
13. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan - a web and mobile app for systematic reviews. *Syst Rev*. 2016;5(1):210. Doi: <https://doi.org/10.1186/s13643-016-0384-4>

14. Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley; 1989. Doi: <https://doi.org/10.1002/sim.4780100718>
15. McClurg MR, Sorensen TD, Carroll J, Blanchard CM, Livet M, Yannayon M, et al. The Patient Care Process for Delivering Comprehensive Medication Management (CMM): optimizing medication use in patient-centered, team-based care settings. Washington, DC: American College of Clinical Pharmacy (ACCP); 2018.
16. McMillan SS, King M, Tully MP. How to use the nominal group and Delphi techniques. *Int J Clin Pharm.* 2016;38(3):655–62. Doi: <https://doi.org/10.1007/s11096-016-0257-x>
17. Delbecq AL, Van de Ven AH. A Group Process Model for Problem Identification and Program Planning. *J Appl Behav Sci.* 1971;7(4):466-92. Doi: <https://doi.org/10.1177/002188637100700404>
18. Üçeyler N, Sommer C, Walitt B, Häuser W. Anticonvulsants for fibromyalgia. *Cochrane Database Syst Rev.* 2013;2013(10):CD010782. Doi: <https://doi.org/10.1002/14651858>
19. Häuser W, Urrútia G, Tort S, Üçeyler N, Walitt B. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome. *Cochrane Database Syst Rev.* 2013;2(2):CD010292. Doi: <https://doi.org/10.1002/14651858>
20. Stockings E, Campbell G, Hall WD, Nielsen S, Zagic D, Rahman R, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions. *Pain.* 2018;159(10):1932-54. Doi: <https://doi.org/10.1097/j.pain.0000000000001293>
21. Hearn L, Derry S, Moore RA. Lacosamide for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev.* 2012;2012(5):CD009485. Doi: <https://doi.org/10.1002/14651858>
22. Derry S, Gill D, Phillips T, Moore RA. Milnacipran for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev.* 2012;3(3):CD008244. Doi: <https://doi.org/10.1002/14651858>
23. Tort S, Urrútia G, Nishishinya MB, Walitt B. Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome. *Cochrane Database Syst Rev.* 2012;(4):CD009807. Doi: <https://doi.org/10.1002/14651858.CD009807>
24. Cording M, Derry S, Phillips T, Moore RA, Wiffen PJ. Milnacipran for pain in fibromyalgia in adults. *Cochrane Database Syst Rev.* 2015;2015(10):CD008244. Doi: <https://doi.org/10.1002/14651858>
25. Welsch P, Bernardy K, Derry S, Moore RA, Häuser W. Mirtazapine for fibromyalgia in adults. *Cochrane Database Syst Rev.* 2018;2018(8):CD012708. Doi: <https://doi.org/10.1002/14651858>
26. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum.* 1990;33(2):160-72. Doi: <https://doi.org/10.1002/art.1780330203>
27. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. *J Pain.* 2008;9(2):105-21. Doi: <https://doi.org/10.1016/j.jpain.2007.09.005>
28. Arnold LM, Gendreau RM, Palmer RH, Gendreau JF, Wang Y. Efficacy and safety of milnacipran 100 mg/day in patients with fibromyalgia: Results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2010;62(9):2745-56. Doi: <https://doi.org/10.1002/art.27559>
29. Branco JC, Zachrisson O, Perrot S, Mainguy Y. A European multicenter randomized double-blind placebo-controlled monotherapy clinical trial of milnacipran in treatment of fibromyalgia. *J Rheumatol.* 2010;37(4):851-9. Doi: <https://doi.org/10.3899/jrheum.090884>
30. Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y. Milnacipran for the treatment of fibromyalgia in adults: A 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. *Clin Ther.* 2008;30(11):1988–2004. Doi: <https://doi.org/10.1016/j.clinthera.2008.11.009>
31. Mease PJ, Clauw DJ, Gendreau RM, Rao SG, Kranzler J, Chen W, et al. The efficacy and safety of milnacipran for treatment of fibromyalgia. A randomized, double-blind, placebo-controlled trial. *J Rheumatol.* 2009;36(2):398–409. Doi: <https://doi.org/10.3899/jrheum.080734>
32. Vitton O, Gendreau M, Gendreau J, Kranzler J, Rao SG. A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. *Hum Psychopharmacol Clin Exp.* 2004;19(S1):S27-35. Doi: <https://doi.org/10.1002/hup.622>
33. Arnold LM, Lu Y, Crofford LJ, Wohlreich M, Detke MJ, Iyengar S, et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis Rheum.* 2004;50(9):2974-84. Doi: <https://doi.org/10.1002/art.20485>
34. Arnold LM, Rosen A, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S, et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain.* 2005;119(1–3):515. Doi: <https://doi.org/10.1016/j.pain.2005.06.031>
35. Arnold LM, Clauw D, Wang F, Ahl J, Gaynor PJ, Wohlreich MM. Flexible dosed duloxetine in the treatment of fibromyalgia: A randomized, double-blind, placebo-controlled trial. *J Rheumatol.* 2010;37(12):2578–86. Doi: <https://doi.org/10.3899/jrheum.100365>
36. Chappell AS, Bradley LA, Wiltse C, Detke MJ, Souza DND, Spaeth M. A six-month double-blind, placebo-controlled, randomized clinical trial of duloxetine for the treatment of fibromyalgia. *Int J Gen Med.* 2008;1:91-102. Doi: <https://doi.org/10.2147/ijgm.s3979>

37. Russell JJ, Mease PJ, Smith TR, Kajdasz DK, Wohlreich MM, Detke MJ, et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. *Pain*. 2008;136(3):432-44. Doi: <https://doi.org/10.1016/j.pain.2008.02.024>
38. Bateman L, Palmer RH, Trugman JM, Lin Y. Results of switching to milnacipran in fibromyalgia patients with an inadequate response to duloxetine: A phase IV pilot study. *J Pain Res*. 2013;6:311-8. Doi: <https://doi.org/10.2147/JPR.S43395>
39. Clauw DJ, Mease PJ, Palmer RH, Trugman JM, Wang Y. Continuing efficacy of milnacipran following long-term treatment in fibromyalgia: a randomized trial. *Arthritis Res Ther*. 2013;15(4):R88. Doi: <https://doi.org/10.1186/ar4268>
40. Arnold LM, Russell JJ, Diri EW, Duan WR, Young JP, Sharma U, et al. A 14-week, Randomized, Double-Blinded, Placebo-Controlled Monotherapy Trial of Pregabalin in Patients With Fibromyalgia. *J Pain*. 2008;9(9):792-805. Doi: <https://doi.org/10.1016/j.jpain.2008.03.013>
41. Crofford LJ, Rowbotham MC, Mease PJ, Russell JJ, Dworkin RH, Corbin AE, et al. Pregabalin for the treatment of fibromyalgia syndrome: Results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2005;52(4):1264-73. Doi: <https://doi.org/10.1002/art.20983>
42. Mease PJ, Russell JJ, Arnold LM, Florian H, Young JP Jr, Martin SA et al. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. *J Rheumatol*. 2008;35(3):502-14.
43. Ohta H, Oka H, Usui C, Ohkura M, Suzuki M, Nishioka K. A randomized, double-blind, multicenter, placebo-controlled phase III trial to evaluate the efficacy and safety of pregabalin in Japanese patients with fibromyalgia. *Arthritis Res Ther*. 2012;14(5):R217. Doi: <https://doi.org/10.1186/ar4056>
44. Pauer L, Winkelmann A, Arsenault P, Jespersen A, Whelan L, Atkinson G, et al. An international, randomized, double-blind, placebo-controlled, phase III trial of pregabalin monotherapy in treatment of patients with fibromyalgia. *J Rheumatol*. 2011;38(12):2643-52. Doi: <https://doi.org/10.3899/jrheum.110569>
45. Arnold LM, Goldenberg DL, Stanford SB, Lalonde JK, Sandhu HS, Keck PE, et al. Gabapentin in the treatment of fibromyalgia: A randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum*. 2007;56(4):1336-44. Doi: <https://doi.org/10.1002/art.22457>
46. Ginsberg F, Joos E, Geczy J, Bruhwyler J, Vandekerckhove K FJ. A pilot randomized placebo-controlled study of pirlindole in the treatment of primary fibromyalgia. *J Musculoskelet Pain*. 1998;6(2):5-17. Doi: [https://doi.org/10.1300/J094v06n02\\_02](https://doi.org/10.1300/J094v06n02_02)
47. Hannonen P, Malminiemi K, Yli-Kerttula U, Isomeri R, Roponen P. A randomized, double-blind, placebo-controlled study of moclobemide and amitriptyline in the treatment of fibromyalgia in females without psychiatric disorder. *Br J Rheumatol*. 1998;37(12):1279-86. Doi: <https://doi.org/10.1093/rheumatology/37.12.1279>
48. Miki K, Murakami M, Oka H, Onozawa K, Yoshida S, Osada K. Efficacy of mirtazapine for the treatment of fibromyalgia without concomitant depression. *Pain*. 2016;157(9):2089-96. Doi: <https://doi.org/10.1097/j.pain.0000000000000622>
49. Yeephu S, Suthisisang C, Suttiruksa S, Prateepavanich P, Limampai P, Russell JJ. Efficacy and Safety of Mirtazapine in Fibromyalgia Syndrome Patients: A Randomized Placebo-Controlled Pilot Study. *Ann Pharmacother*. 2013;47(7-8):921-32. Doi: <https://doi.org/10.1345/aph.1R725>
50. Fiz J, Durán M, Capellà D, Carbonell J, Farré M. Cannabis use in patients with Fibromyalgia: Effect on symptoms relief and health-related quality of life. *PLoS One*. 2011;6(4):3-7. Doi: <https://doi.org/10.1371/journal.pone.0018440>
51. Gerardi MC, Batticciotto A, Talotta R, Ditto MC, Atzeni F S-PP. Efficacy of cannabis flos in patients with fibromyalgia: a monocentric observational study. *Arthritis Rheumatol*. 2016;68:72-4.
52. Ko GD, Bober SL, Mindra S MJ. Medical cannabis – the Canadian perspective. *J Pain Res*. 2016;9:735-44. Doi: <https://doi.org/10.2147/JPR.S98182>
53. Schley M, Legler A, Skopp G, Schmelz M, Konrad C, Rukwied R. Delta-9-THC based monotherapy in fibromyalgia patients on experimentally induced pain, axon reflex flare, and pain relief. *Curr Med Res Opin*. 2006;22(7):1269-76. Doi: <https://doi.org/10.1185/030079906x112651>
54. Weber J, Schley M, Casutt M, Gerber H, Schuepfer G, Rukwied R, et al. Tetrahydrocannabinol (Delta 9-THC) Treatment in Chronic Central Neuropathic Pain and Fibromyalgia Patients: Results of a Multicenter Survey. *Anesthesiol Res Pract*. 2009;2009:1-9. Doi: <https://doi.org/10.1155/2009/827290>
55. Chung SA, Hossain NK, Blackman AS SC. Can the cannabinoid nabilone help with pain and sleep in fibromyalgia patients? *Sleep*. 2009;32:A325-6.
56. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the Treatment of Pain in Fibromyalgia. *J Pain*. 2008;9(2):164-73. Doi: <https://doi.org/10.1016/j.jpain.2007.09.002>
57. Sideri S, Papageorgiou SN, Eliades T. Registration in the international prospective register of systematic reviews (PROSPERO) of systematic review protocols was associated with increased review quality. *J Clin Epidemiol*. 2018;100:103-10. Doi: <https://doi.org/10.1016/j.jclinepi.2018.01.003>

58. Raza A, Kale S, Bulent B, Komandur T, Kannadath BS, Patil P et al. Methodological Quality Assessment of Meta-Analyses and Systematic Reviews of Rectal Indomethacin in the Prophylaxis of Post-ERCP Pancreatitis Using AMSTAR 2. *Am J Gastroenterol.* 2018;113(S56):104. Doi: <https://doi.org/10.14309/00000434-201810001-00104>
59. Almeida MO, Yamato TP, Parreira PCS, Costa LOP, Kamper S, Saragiotto BT. Overall confidence in the results of systematic reviews on exercise therapy for chronic low back pain: a cross-sectional analysis using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR)2 tool. *Brazilian J Phys Ther.* 2019;24:103-17. Doi: <https://doi.org/10.1016/j.bjpt.2019.04.004>
60. Bobrovitz N, Heneghan C, Onakpoya I, Fletcher B, Collins D, Tompson A, et al. Medications that reduce emergency hospital admissions: an overview of systematic reviews and prioritisation of treatments. *BMC Med.* 2018;16(1):115. Doi: <https://doi.org/10.1186/s12916-018-1104-9>
61. Oliveira Júnior JO, Ramos JVC. Adherence to fibromyalgia treatment: challenges and impact on the quality of life. *Brazilian J Pain.* 2019;2(1):81-7. Doi: <https://doi.org/10.5935/2595-0118.20190015>
62. Borchers AT, Gershwin ME. Fibromyalgia: A Critical and Comprehensive Review. *Clin Rev Allergy Immunol.* 2015;49(2):100-51. Doi: <https://doi.org/10.1007/s12016-015-8509-4>
63. Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Flub E, et al. EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis.* 2017;76(2):318-28. Doi: <https://doi.org/10.1136/annrheumdis-2016-209724>
64. Fitzcharles M-A, Ste-Marie PA, Goldenberg DL et al. 2012 Canadian Guidelines for the diagnosis and management of fibromyalgia syndrome: Executive summary. *Pain Res Manag.* 2013;18(3):119-26. Doi: <https://doi.org/10.1155/2013/918216>
65. Carville SF, Arendt-Nielsen S, Bliddal H, Blotman F, Branco JC, Buskila D, et al. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. *Ann Rheum Dis.* 2007;67(4):536-41. Doi: <https://doi.org/10.1136/ard.2007.071522>
66. Heymann RE, Paiva EDS, Helfenstein M, Pollak DF, Martinez JE, Provenza JR, et al. Brazilian consensus on the treatment of fibromyalgia. *Rev Bras Reumatol.* 2010;50(1):56-66. Doi: <https://doi.org/10.1590/S0482-50042010000100006>
67. Arnold LM, Clauw DJ. Challenges of implementing fibromyalgia treatment guidelines in current clinical practice. *Postgrad Med.* 2017;129(7):709-14. Doi: <https://doi.org/10.1080/00325481.2017.1336417>
68. World Health Organization. Adherence to long-term therapies: Evidence for action. Geneva: WHO; 2003.
69. Xhaxho D, Soler JF, Calleja N, Borg A, Mercieca C. Determinants Influencing Patient Decision to Start Pharmacological Treatment in Fibromyalgia. *Rheumatology.* 2016;55(Suppl 1):180. Doi: <https://doi.org/10.1093/rheumatology/kew187.001>