Effect of pharmacotherapy on fibromyalgia: an overview of systematic reviews

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
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. Although relatively common, it is still a controversial condition in respect of its etiology, pathophysiology, diagnosis and treatment. This syndrome affects an estimated 2.10% of the world’s population, and is four times more prevalent in women. 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. 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.

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. 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. In clinical practice, a maximum of 25% of fibromyalgia patients experience significant pain-related improvements when using any drug treatment, 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.

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) and also the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA). 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.

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).

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). To assist in this process, we used the Rayyan tool. For any unavailable full articles, the corresponding authors were contacted via ResearchGate (www.researchgate.net) or by e-mail. For ongoing studies, assessments were made using the 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, 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

| P | Fibromyalgia patients | Fibromyalgia [MeSHTerms]; Fibromyalgias; Fibromyalgia-Fibromyositis Syndrome; Fibromyalgia-Fibromyositis Syndrome; Fibromyalgia-Fibromyositis Syndromes; Syndrome, Fibromyalgia-Fibromyositis; Rheumatism, Muscular; Muscular Rheumatism; Fibrosis; Fibrotides; Myofascial Pain Syndrome, Diffuse; Diffuse Myofascial Pain Syndrome; Fibromyositis Fibromyalgia Syndrome; Fibromyositis Fibromyalgia Syndrome; Syndromes, Fibromyositis-Fibromyalgia; Fibromyalgia, Secondary; Fibromyalgias, Secondary; Secondary Fibromyalgia; Fibromyalgia, Primary; Fibromyalgias, Primary
| I | Pharmacotherapy | Pharmacotherapy; Cannabinoids; Neuromodulators; Tricyclic antidepressants; Muscle relaxants; Selective serotonin reuptake inhibitors; Antidepressants; Antiparkinsonian; Simple analgesics; Light opiates
| C | Reduction of Fibromyalgia signs and symptoms | Treatment, outcome; Outcome, Treatment; Clinical Effectiveness; Clinical Effectivenesses; 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
| O | Systematic reviews | Systematic Reviews; 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.14

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 Pharmacy15 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.16,17 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.8 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,18-20 and 7.93% (n= 5) had high quality,21-25 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.14

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,26 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.27 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 2011,18-20,23-25 one used the Cochrane Risk of Bias Tool published in 2008,21 and one used the Review Manager 5.22 The ROBINS-I tool was used to assess the risk of bias in an observational study.20

**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.22 presented five primary studies with milnacipran28-32 the review by Häuser et al.19 included the same five studies with milnacipran28-32 and also evaluated duloxetine.33-37 Cording et al.24 included seven primary studies with milnacipran.28,32,38,39 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%).19,22,24 Duloxetine was superior to milnacipran in reducing mean pain.19

Only Häuser et al.19 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,19,22,24 although the imputation method used in analyses of the primary outcomes could overestimate treatment effect.2

**Anticonvulsants**

Two of the systematic reviews analyzed the use of the anticonvulsants for the treatment of fibromyalgia.18,21 Hearn et al.21 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.18 analyzed eight primary studies: five studies with pregabalin,40-44 one study with gabapentin,45 one study with levetiracetam (NCT00254657) and one with lacosamide (NCT00401830), the same included in the review by Hearn et al.21 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.18,21

Only Üçeyler et al.18 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.18 Most risks of bias were low, except for incomplete outcome data and selective non-reporting by some studies.19,21 All pregabalin studies had a low risk of bias.18
## Chart 2. Characteristics of included systematic reviews

<table>
<thead>
<tr>
<th>Systematic Reviews</th>
<th>Primary studies (Total participants)</th>
<th>Intervention (Number of participants)</th>
<th>Comparison (Number of participants)</th>
<th>Duration</th>
<th>Gender and Mean Age of the Participants</th>
<th>Settings</th>
<th>Design of Included Studies</th>
<th>Quality of Systematic review (AMSTAR 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cording(^2) 2015</td>
<td>7 studies (4575)</td>
<td>Milnacipran 100mg (1220)</td>
<td>Placebo (1746)</td>
<td>8 to 24 weeks</td>
<td>92 to 97% female 47 to 50 years</td>
<td>Multicenter - Community</td>
<td>Randomized controlled trials: Parallel group</td>
<td>High quality</td>
</tr>
<tr>
<td>Derry(^2) 2012</td>
<td>5 studies (4138)</td>
<td>Milnacipran 100mg (1141)</td>
<td>Placebo (1614)</td>
<td>8 to 24 weeks</td>
<td>93 to 97% female 47 to 50 years</td>
<td>Outpatient centers/ Outpatient clinical/ Research centers</td>
<td>Randomized controlled trials: Parallel group</td>
<td>High quality</td>
</tr>
<tr>
<td>Häuser(^3) 2013</td>
<td>10 studies (6038)</td>
<td>Milnacipran 100 to 200mg/day (2524)</td>
<td>Duloxetine 60 to 120mg/day (1087)</td>
<td>12 to 27 weeks</td>
<td>92 to 100% female 47 to 51 years</td>
<td>Research centers</td>
<td>Randomized controlled trials: Parallel group</td>
<td>Moderate quality</td>
</tr>
<tr>
<td>Heam(^3) 2012</td>
<td>1 study (159)</td>
<td>Lacosamide 400mg/day (81)</td>
<td>Placebo (78)</td>
<td>12 weeks</td>
<td>93% female 50 years</td>
<td>Multicenter - Community</td>
<td>Randomized controlled trials: Parallel group</td>
<td>High quality</td>
</tr>
<tr>
<td>Tort(^3) 2012</td>
<td>2 studies (230)</td>
<td>Pirindole 150mg/day (50)</td>
<td>Placebo (95)</td>
<td>4 to 12 weeks</td>
<td>85 to 100% female 39 to 49 years</td>
<td>Outpatient clinics</td>
<td>Randomized controlled trials: Parallel group</td>
<td>High quality</td>
</tr>
<tr>
<td>Üçeyler(^3) 2013</td>
<td>8 studies (3579)</td>
<td>Gabapentin 1200 to 2400mg/day (75)</td>
<td>Placebo (1099)</td>
<td>13 weeks</td>
<td>89 to 96% Female 47 to 50 years</td>
<td>Research centers</td>
<td>Randomized controlled trials: Parallel group</td>
<td>Moderate quality</td>
</tr>
<tr>
<td>Stockings(^3) 2018</td>
<td>7 studies (403)</td>
<td>Plant-based cannabis (72)</td>
<td>Placebo (118)</td>
<td>4 to 144 weeks</td>
<td>0 to 95% female 45 to 57 years</td>
<td>No reported</td>
<td>Randomized controlled trials; Quasi-experimental and Observational studies</td>
<td>Moderate quality</td>
</tr>
<tr>
<td>Welsch(^5) 2018</td>
<td>3 studies (606)</td>
<td>Dronabinol (32)</td>
<td>Placebo (272)</td>
<td>7 to 14 weeks</td>
<td>86 to 95 % female 43 to 45 years</td>
<td>Multiple research centers</td>
<td>Randomized controlled trials: Parallel group and cross-over</td>
<td>High quality</td>
</tr>
</tbody>
</table>
**Chart 3. Evaluation measures used in the studies included in the systematic reviews**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Systematic reviews that reported</th>
<th>Evaluation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Cording19; Derry23; Häuser19; Hear19; Tort23; Üçeyler19; Stockings20; Welsch25</td>
<td>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)</td>
</tr>
<tr>
<td>Patient perceived improvement</td>
<td>Cording19; Derry23; Häuser19; Hear19; Tort23; Üçeyler19; Stockings20; Welsch25</td>
<td>PGIC (NRS 1-7), CGI of severity (0 to 7), SCL-90-R (0-5)</td>
</tr>
<tr>
<td>Adverse reaction</td>
<td>Cording19; Derry23; Häuser19; Hear19; Tort23; Üçeyler19; Stockings20; Welsch25</td>
<td>Spontaneous report of participants, physical exams, electrocardiograms, laboratory tests.</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>Cording19; Derry23; Tort23</td>
<td>Spontaneous report of participants</td>
</tr>
<tr>
<td>Sleep</td>
<td>Häuser19; Tort23; Üçeyler19; Welsch25</td>
<td>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)</td>
</tr>
<tr>
<td>Depression</td>
<td>Häuser19; Üçeyler 2013; Welsch25</td>
<td>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)</td>
</tr>
<tr>
<td>Disability</td>
<td>Häuser19; Tort23; Üçeyler18</td>
<td>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)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Häuser19; Üçeyler18; Welsch25</td>
<td>FIQ (VAS 0-10), SF-36 (VAS 0-100), MAF (NRS 1-50), MFI general fatigue (NRS 4-20), MFI total (NRS 20-100)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Häuser19; Üçeyler18</td>
<td>FIQ single-item scale for anxiety (VAS 0-10); BAI total score (NRS 0-63), STAI (NRS 20-80), HADS (NRS 21)</td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td>Häuser19; Tort23; Üçeyler18</td>
<td>FIQ (VAS 0-100), FIQ total score (0-80), SF-36, NHP (0-100)</td>
</tr>
<tr>
<td>Cognitive disturbances</td>
<td>Häuser19</td>
<td>MFI (NRS 4-20), MASQ (NRS 38-190).</td>
</tr>
<tr>
<td>Sexual fuction</td>
<td>Häuser19</td>
<td>ASEX (NRS 5-30)</td>
</tr>
<tr>
<td>Tenderness</td>
<td>Häuser19</td>
<td>Measurement of tender point pain threshold</td>
</tr>
</tbody>
</table>

**Monoamine Oxidase Inhibitors (MAOIs)**

Tort et al. evaluated the use of the monoamine oxidase inhibitors pirlindole and moclobemide, and was the only review to include a study that used a reference drug, amitriptyline, in addition to a placebo. 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 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.

**Tetracyclic antidepressant**

The review by Welsch et al. evaluated tetracyclic antidepressants and comprised three primary studies of mirtazapine (JapicCTI-101176). 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.

### Cannabis and Cannabinoids

The cannabis and cannabinoids were evaluated by Stockings et al., which presented a total of one hundred and four studies, but only seven examined fibromyalgia, six of which were observational studies, and only one was a randomized controlled trial. 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 adjuncts to other painkillers.

### Data Interpretation

The expert committee used nominal group methodology 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.

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. 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

<table>
<thead>
<tr>
<th>Review</th>
<th>Quantitative results related to drug effectiveness in fibromyalgia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cordingley (2015)</td>
<td>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 10.0 [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 10.0 [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].</td>
</tr>
<tr>
<td>Derry (2012)</td>
<td>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 1.5. 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 10.0 [7 to 18]; Substantial benefit 28%, RR 1.4 [1.2 to 1.5], RR 1.5 [1.4 to 1.9], NNT 6.1 [4.8 to 8.2].</td>
</tr>
<tr>
<td>Häuser (2013)</td>
<td>DLX 60/120mg/day – Pain: SMD -0.32 [-0.41 to -0.22] (p&lt;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 -0.39 [-0.39 to -0.20]. Sleep: SMD -0.24 [-0.37 to -0.12]. Depression: SMD -0.26 [-0.37 to -0.16]. Fatigue: SMD -0.33 [-0.43 to -0.24]. Anxiety: SMD -0.23 [-0.29 to -0.17]. 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&lt;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].</td>
</tr>
<tr>
<td>Hean et al. (2012)</td>
<td>LCM 400mg/day – Pain: Change pain score 1.8 ± 2.1; Placebo 1.3 ± 1.9, Statistic NR. Patient perceived improvement: PGIC NS.</td>
</tr>
<tr>
<td>Tort (2013)</td>
<td>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.</td>
</tr>
<tr>
<td>Üçeyler (2013)</td>
<td>GBP 1200/2400mg/day – Pain: SMD -0.49 [-0.86 to -0.13] (p&lt;0.008); Moderate benefit 50.7% (p=0.02), RR 1.65 [1.10 to 2.48]; Substantial benefit 22.7% (p=0.04), RR 1.70 [1.01 to 2.53]. Sleep: SMD -0.71 [-1.08 to -0.24] (p&lt;0.001). Depression: SMD -0.52 [-0.89 to -0.16] (p&lt;0.001). Disability: SMD -0.49 [1.32 to -0.56] (p&lt;0.001). Health-related quality of life: SMD -0.66 [-1.03 to -0.29] (p&lt;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&lt;0.001); Moderate benefit 40%, RR 1.37 [1.22 to 1.53] (p&lt;0.001). Substantial benefit 22.2%, RR 1.59 [1.33 to 1.90] (p&lt;0.001), NNT 12 [9 to 21]. Patient perceived improvement: PGIC: 39.4%, RR 1.38 [1.23 to 1.55] (p&lt;0.001), NNT 9 [7 to 13]. Sleep: SMD -0.35 [-0.43 to -0.27] (p&lt;0.001). Depression: SMD -0.09 [-0.16 to -0.01] (p&lt;0.001). Disability: NS. Fatigue: NS. Anxiety: SMD -0.12 [-0.20 to -0.04] (p&lt;0.001). Health-related quality of life: SMD -0.17 [-0.26 to -0.09] (p&lt;0.001).</td>
</tr>
<tr>
<td>Welsch (2018)</td>
<td>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].</td>
</tr>
</tbody>
</table>

MLN: Milnacipran; Moderate benefit: 230% 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; LT: 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**

<table>
<thead>
<tr>
<th>Review</th>
<th>Quantitative results related to safety and drug adherence in fibromyalgia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cordingley et al. 2015</td>
<td><strong>MLN 100mg/day</strong> – Any adverse reaction: 85%, RR 1.1 [1.05 to 1.1], NHN 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], NHN 23 [12 to 140]. Adverse reaction withdrawals: 19%, RR 1.6 [1.3 to 2.0], NHN 14 [10 to 24].</td>
</tr>
<tr>
<td>Derry et al. 2012</td>
<td><strong>MLN 100mg/day</strong> – Any adverse reaction: 86%, RR 1.1 [1.06 to 1.14], NHN 13 [9.3 to 22]. Serious adverse reaction: 1.4%, RR 0.9 [0.5 to 1.7]. Lack of efficacy withdrawals: 8.6%, 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], NHN of 23 [12 to 210]. Adverse reaction withdrawals: 19%, RR 1.6 [1.3 to 2.0], NHN 14 [10 to 24].</td>
</tr>
<tr>
<td>Häuser et al. 2013</td>
<td><strong>DLX 60/120mg/day</strong> – Serious adverse reaction: RR 0.63 [0.34 to 1.16]. Adverse reaction withdrawals: RR 1.65 [1.3 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].</td>
</tr>
<tr>
<td>Hearni et al. 2012</td>
<td><strong>LCM 400mg/day</strong> – 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].</td>
</tr>
<tr>
<td>Tort et al. 2012</td>
<td><strong>AMT 25/37.5mg/day</strong> – 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, NHN 7 [4 to 33]. All case withdrawals: 34%, statistic NR. Adverse reaction withdrawals: RR 1.96 [0.52 to 7.34].</td>
</tr>
<tr>
<td>Üçeyler et al. 2013</td>
<td><strong>GBP 1200/2400mg/day</strong> – Adverse reaction withdrawals: 16%, RR 1.71 [0.71 to 4.11] (p&lt;0.23). LCM 400mg/day – Serious adverse reaction: NS. LVT 3000mg/day – Adverse reaction withdrawals: NS. PGB 150/300/450/600mg/day – Serious adverse reaction: 5.2%, RR 1.03 [0.71 to 1.49] (p=0.09). Adverse reaction withdrawals: 19.4%, RR 1.68 [1.36 to 2.07] (p&lt;0.001).</td>
</tr>
<tr>
<td>Welsch et al. 2018</td>
<td><strong>MTN 15/30/45mg/day</strong> – Any adverse reaction: 76%, RD 0.12 [-0.01 to 0.02]. 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].</td>
</tr>
</tbody>
</table>

**MLN: Milnacipran; RR: Relative Risk [95% Confidence Interval]; NHN: Number Needed to Harm [95% Confidence Interval]; NNT: Number Needed to Treat [95% Confidence Interval]; DLX: Duloxetine; LCM: Lacosamide; AMT: Amitriptyline; NS: 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 often also attributed to the low methodological quality of other systematic reviews in the literature. 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 the disease in the case of fibromyalgia is the diagnosis. Fibromyalgia shares symptoms with other functional somatic problems and there is often an overlap in diagnosis. In addition, the variability of outcome measures in clinical trials makes it difficult to assess treatment evidence. We identified the diagnostic criteria of the primary studies in which there was uniformity with the American College of Rheumatology (1990) criteria. 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. 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.

In this overview, in common with Canadian and Israeli guidelines, the European League Against Rheumatism (EULAR) recommendations, and the last Brazilian consensus, 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. 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, while pregabalin showed efficacy in relation to fatigue, depression, quality of life, anxiety and sleep-related problems. Amitriptyline also showed improvement in sleep.
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.\(^5\)\(^,\)\(^10\) Thus, the evidence was insufficient to determine the benefit of amitriptyline, cannabis and cannabinoids, leviteracetam, gabapentin, and mirtazapine for pain reduction in fibromyalgia.\(^18\)\(^,\)\(^20\)\(^,\)\(^23\)\(^,\)\(^25\) These findings were consistent with the EULAR recommendations, but not with the Brazilian consensus, which recommends amitriptyline for the control of fibromyalgia pain.\(^63\)\(^,\)\(^66\) 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.\(^18\)\(^,\)\(^21\)\(^,\)\(^23\)\(^,\)\(^24\)

Again, the Brazilian consensus provides different information, with moclobemide being recommended for use in fibromyalgia.\(^56\)

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.\(^18\)\(^,\)\(^19\)\(^,\)\(^21\)\(^,\)\(^22\)\(^,\)\(^24\) Pirlindole and mirtazapine demonstrated safety in this parameter.\(^23\)\(^,\)\(^25\) For amitriptyline, leviteracetam 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.\(^53\) Among the medicines in which serious adverse reactions were reported (pregabalin, duloxetine, milnacipran and mirtazapine), there was not a significant difference from placebo,\(^18\)\(^,\)\(^19\)\(^,\)\(^22\)\(^,\)\(^24\)\(^,\)\(^25\) which were similar to EULAR recommendations.\(^53\) Milnacipran and lacosamide presented at least one significant adverse reaction compared to placebo,\(^21\)\(^,\)\(^22\)\(^,\)\(^24\) for pirlindole, moclobemide and mirtazapine the difference was not significant.\(^23\)\(^,\)\(^25\) No results were given for pregabalin, duloxetine, gabapentin, and leviteracetam. 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.\(^53\)\(^,\)\(^67\)

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, leviteracetam, mirtazapine and duloxetine this result was not reported. Milnacipran had a significant difference in withdrawals compared to placebo.\(^22\)\(^,\)\(^24\) According to the EULAR, the highest frequency of dropouts was among patients taking milnacipran, and the lowest among those taking amitriptyline.\(^63\)\(^,\)\(^69\) 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.\(^68\) 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.\(^69\)

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, leviteracetam 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.

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**Figure 2. Flowchart of choice for fibromyalgia treatment**

- **Need**: Evaluate through the diagnostic criteria and tools used to assess clinical outcomes for Fibromyalgia.

- **Effectiveness**:
  - **Pain**: Duloxetine, Milnacipran, Pirlindole
  - **Depression**: Duloxetine, Milnacipran, Pirlindole
  - **Quality of life**: Duloxetine, Milnacipran, Pirlindole
  - **Fatigue**: Duloxetine, Milnacipran, Pirlindole
  - **Disability**: Duloxetine, Milnacipran
  - **Cognitive impairment**: Duloxetine, Milnacipran
  - **Sleep**: Amitriptyline, Pirlindole
  - **Anxiety**: Pregabalin

- **Safety**:
  - **Withdrawals by adverse reactions**:
    - **Yes**: Duloxetine, Milnacipran, Pirlindole
    - **No**: Pirlindole
  - **Serious adverse reactions**:
    - **Yes**: Milnacipran
    - **No**: Pirlindole

- **Drug Adherence**:
  - All case withdrawals with significant difference compared to placebo: Milnacipran

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\(\text{\footnotesize \text{We were unable to compare data for all pharmacotherapeutic options used in fibromyalgia.}}\)

\(\text{\footnotesize \text{Some limitations in systematic reviews have decreased the ability for better treatment comparability.}}\)
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).

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