RESEARCH

Comparing the efficacy and safety of duloxetine and amitriptyline in the treatment of fibromyalgia: overview of systematic reviews

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Abstract

Background: Duloxetine and amitriptyline are antidepressants used in the treatment of fibromyalgia. In published systematic reviews, there is no agreement about which drug is more effective and safer. This study aimed to compare evidence of the efficacy and safety of duloxetine compared with amitriptyline in the treatment of adult patients with fibromyalgia. This work contributes to guiding clinicians on the use of duloxetine or amitriptyline for the treatment of fibromyalgia and provides information for public health decision-makers.

Methods: Overview of systematic reviews of clinical trials comparing duloxetine and amitriptyline in the treatment of fibromyalgia. The reviews were screened in Cochrane, PubMed, EMBASE, and SRDR with no restrictions on language and year of publication, considering that the research was conducted in July 2018 and updated until May 2020. The selection was based on the following criteria: adult patients with a diagnosis of fibromyalgia treated with duloxetine or amitriptyline, comparing the efficacy and safety in pain, fatigue, sleep, and mood disorder symptoms and quality of life, in addition to the acceptability of these antidepressants. The methodological quality and strength of evidence were assessed using the AMSTAR and GRADE instruments.

Results: Eight systematic reviews were selected. Amitriptyline had low evidence for pain, moderate evidence for sleep and fatigue, and high evidence for quality of life. Duloxetine had high quality of evidence in patients with mood disorders. With low evidence, duloxetine has higher acceptability, but is safer in older patients, while amitriptyline is safer for non-elderly individuals.

Conclusion: Both antidepressants are effective in the treatment of fibromyalgia, differing according to the patient's symptoms and profile.

Registration: PROSPERO: CRD42019116101.

Keywords: Fibromyalgia, Duloxetine, Amitriptyline, Systematic review, Overview

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Background

Fibromyalgia is a syndrome whose etiology is still not fully understood. It is multifactorial and is characterized by chronic, widespread, diffuse musculoskeletal pain, often associated with fatigue, sleep and mood disorders, and a consequent adverse impact on the quality of life. Its diagnosis is very complex, and treatment is multidisciplinary, which can be pharmacological or not [1]. The global prevalence of fibromyalgia is 2.7%, ranging from 0.4% in Greece to 9.3% in Tunisia. Mean prevalence is 3.1% in the Americas, 2.5% in Europe, and 1.7% in Asia [2]. In Brazil, a study by Senna et al. [3] recorded a 2.5% prevalence of the disease, affecting women in more than 90% of cases.

Pharmacotherapy of fibromyalgia can include diverse therapeutic classes and, among the antidepressants, there are several studies citing duloxetine hydrochloride and amitriptyline. Compared to amitriptyline, launched in 1961, duloxetine is a more recent drug available in the market, released in 2004, and has in its favor a safety profile with fewer anticholinergic effects such as dry mouth, tachycardia, constipation, weight increase, increased intraocular pressure, among others [4].

Systematic reviews are indicating that both duloxetine and amitriptyline are effective in the treatment of fibromyalgia [5, 6]. However, based on individual analysis of these reviews, one cannot conclude whether these drugs have the same efficacy and safety in the treatment of the symptoms of the illness, such as fatigue, sleep, mood disorder and quality of life.

When selecting pharmacological therapy, it is relevant to consider drug cost analysis as part of the final decision. However, there is a lack of economic studies comparing antidepressants in fibromyalgia [7]. It is known that the one-year treatment with duloxetine in the dosages indicated for fibromyalgia is 2.7 times greater than amitriptyline [8]. In addition, it is important not to neglect patients' social preferences to support the final decision [9].

This study aimed to synthesize evidence on the efficacy, safety, and acceptability of duloxetine in the treatment of adult patients diagnosed fibromyalgia, compared with the effects of amitriptyline, based on systematic reviews of clinical trials.

Methods

Protocol and registration

The research protocol was defined and registered in the PROSPERO database (registration number CRD42019116101). The study was reported according to the initial version of the Preferred Reporting Items for OoSRs-PRIO-harms [10].

Study design

We conducted an overview of systematic reviews. Overview is a method that selects, gathers, and synthesizes results and improves the accessibility of existing evidence. It is used when there are several systematic reviews on similar or related topics [11].

Criteria of eligibility

The research question was based on the PICO method. We included all systematic reviews of clinical trials that assessed the efficacy and safety of duloxetine and amitriptyline to treat fibromyalgia symptoms (pain, fatigue, sleep and mood disorders, quality of life) and the acceptability of these drugs by adult patients with this disease. Idiom and year of publication were not restricted.

The main outcome of interest was the efficacy of duloxetine and amitriptyline in the treatment of major fibromyalgia-related symptoms. The secondary outcomes were associated with the safety of these drugs, including adverse responses, and adherence to the treatment (acceptability).

Search strategy

The reviews were identified in the following databases: Cochrane Central Register of Controlled Trials, MED-LINE, EMBASE, and The Systematic Review Data Repository (SRDR). The search was carried out using the following MeSH (Medical Subject Headings) and DHS (Descriptors in Health Sciences) terms: (fibromyalgia); (duloxetine); (amitriptyline); (systematic review). An additional search strategy was performed in the Epistemonikos platform, specific for systematic reviews, using the terms (title:(abstract:(fibromyalgia AND duloxetine AND amitriptyline AND systematic review)) OR abstract:(abstract:(fibromyalgia AND duloxetine AND amitriptyline AND systematic review))). Database searches were performed in July 2018 and were updated until May 2020.

Gray literature was also searched in the Sociedade Médica de Reumatologia [Medical Society of Rheumatology] and academic dissertations in Google Scholar databases.

Selection of studies and data extraction

The titles and abstracts were read by two authors (AF and LE), who also read the full text of the studies included. Afterward, old reviews that had been updated were excluded, and the latest one was considered. Other reviews that, when reading, did not meet the eligibility criteria were also disregarded. The data were extracted independently by the reviewers. Any disagreements were resolved by consensus between the two authors or with the senior researchers (TA and TDP).

General information on the reviews, scoring utilized, and the outcomes related to pain, sleep, fatigue, quality of life, acceptability, and safety were collected from the reviews included.

Data on reviews were extracted and entered into Microsoft Excel® datasheets. It was not necessary to contact the selected review's authors to obtain data.

Assessment of the methodological and evidence quality

The methodological quality of the reviews included in the overview was assessed by two independent researchers, as recommended by the Cochrane Handbook for overviews [12], using the Assessment of Multiple Systematic Reviews – AMSTAR instrument [13]. The results of the methodological quality assessed in AMSTAR are rated as "very low quality" (≤ 9 scores), "low quality" (10–11 scores), "moderate quality" (12–13 scores), and "high quality" (14–16 scores). The scores resulting from the assessment of the requirements that were met, as proposed by the instrument.

The quality of evidence of the reviews included was assessed according to the Grading of Recommendations Assessment, Development and Evaluation – GRADE – [14]. In the case of overviews, the GRADE is adapted as described in the Cochrane Handbook for Systematic Reviews of Interventions [12]. We did not re-evaluate each individual study of the selected reviews. The overview reviewers assessed and documented the criteria presented in the reviews included, and descriptively reported the quality of the reviews' datasets, using the analysis made by the reviews' authors. The criteria used to determine the reduced quality of the evidence were: risk of bias in the studies included, inconsistency, indirect evidence, imprecision, and publication bias. Due to subjectivity in the application of the criteria, a calculation was developed to allow a reproducible attribution of the GRADE's evidence levels. For each outcome, the above five criteria in the reviews selected were assessed. The reviewers worked to ensure consensus and consistency of entering objective data related to these criteria into a worksheet, and according to the number of evidence downgrades in the number of reviews that addressed the outcome, the following rating was used: 0–1.00: not serious; 1.01–1.50: serious; 1.51–2.00: very serious. This classification was applied to the narrative table available in the Software GRADE Pro GDT [15] and was adapted to allow an interpretation of the results, determining the grading of the evidence found as high, moderate, low, or very low.

Calculation of overlapping

One of the major challenges of an overview is the overlap of studies, that is, when there are individual studies present in more than one review. We calculated the corrected covered area – CCA, a method that divides the total number of individual studies by the product between the number of reviews and the number of non-repeated studies [16].

Results

A total of 123 abstracts were found, and after exclusion of those that did not meet the criteria of eligibility, 14 articles remained. One of them [17] was out because it is not published yet. A total of 13 articles were read in full. Out of these, five articles were excluded, remaining eight analyzed reviews [5, 6, 18–23].

Figure 1 is a flowchart of the searches and exclusions. Table 1 describes the main characteristics of the studies included, and Table 2 shows the reviews excluded and justifications.

The methodological qualities of the included reviews varied largely, as shown in Table 3. Table 4 presents the assessment of the quality of evidence, according to GRADE.
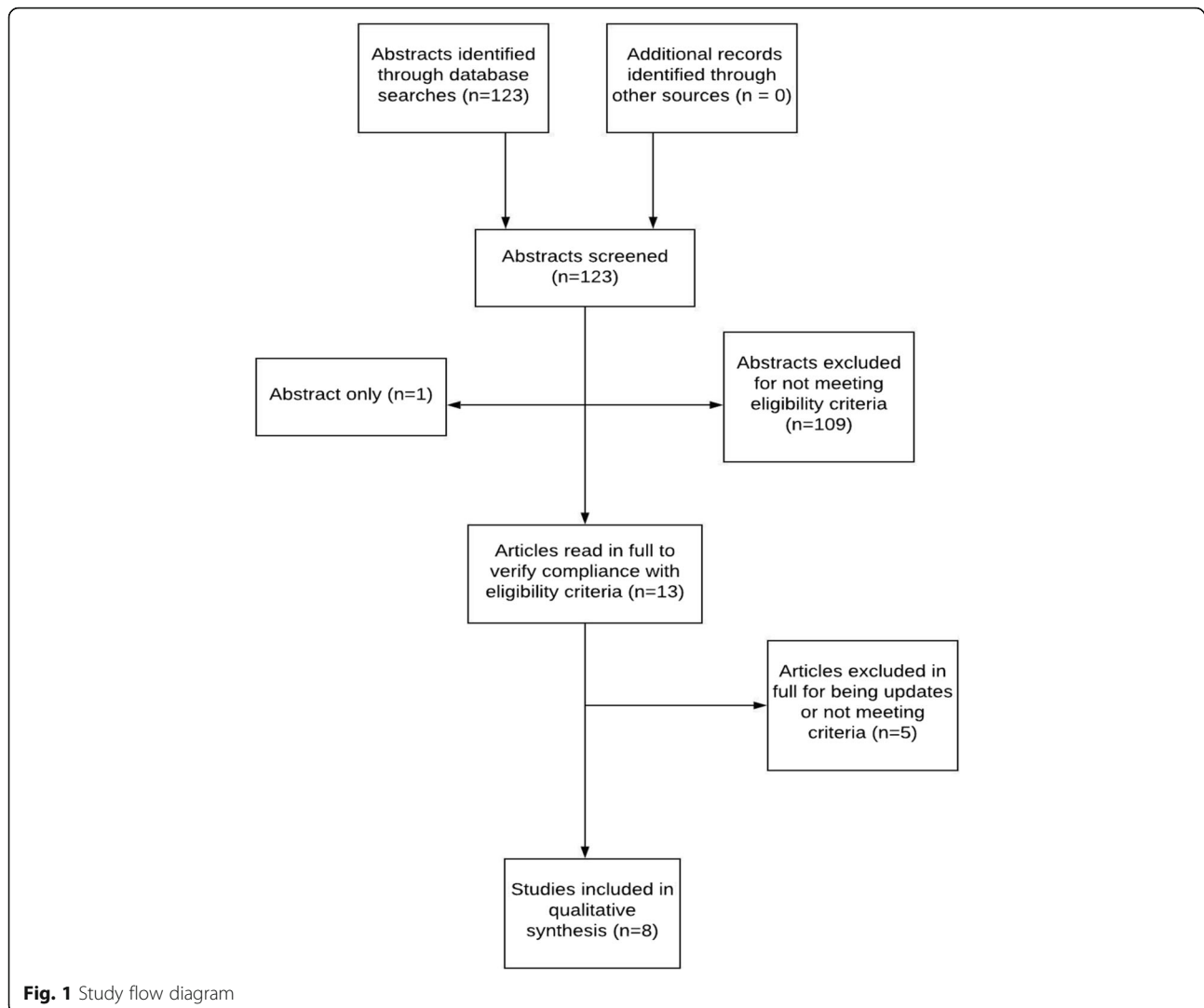
Regarding overlapping, the calculation of the area covered and corrected for this overview indicated 40% of overlap in individual studies. The result indicates that there may be duplicates in the systematic reviews, which may have an impact on data extraction, because the results of the overlapped studies may influence the overall analyses of results. For this reason, a systematic review must be conducted when there are no reviews with the same objective or when the existing ones are outdated [16].

Discussion and conclusions

This overview summarized the results of eight systematic reviews on efficacy, safety and acceptability of duloxetine in the treatment of adult patients diagnosed with fibromyalgia, compared with amitriptyline. Differences in efficacy varied depending on the symptom.

Regarding pain, amitriptyline was more effective in three (37.5%) of the selected reviews [5, 19, 21]. However, the evidence was considered of low quality in the GRADE analysis, and it should be emphasized that four reviews [6, 20, 22, 23] did not find a significant difference between the two drugs used in the management of this symptom. Both drugs are recommended by the European League Against Rheumatism [24], *Sociedade Brasileira de Reumatologia* [1] [Brazilian Society of Rheumatology], and the Canadian Guidelines for the Diagnosis and Management of Fibromyalgia Syndrome [25]. The findings are consistent with a study [26], which point out that antidepressants, in general, have not yet shown quality evidence that they have a significant effect on pain in fibromyalgia. It would seem that the results are related to the difficulty of measuring the real drug-induced potentiation of descending pathways that inhibit pain in the central nervous system [27].

Regarding the sleep disorders outcome, amitriptyline was more effective in five (62.5%) of the selected

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Fig. 1 Study flow diagram

reviews [5, 18, 19, 21, 23] with moderate quality of evidence. Duloxetine did not exhibit proven efficacy in sleep in any of the reviews. This corroborates the findings of specific research on sleep disorders in fibromyalgia [28], which concluded that amitriptyline is more efficacious than duloxetine for this specific symptom probably due to its actions on cortical areas from the central nervous system that regulate sleep.

Regarding fatigue, six (75%) reviews [5, 18, 19, 21–23] favored amitriptyline. Duloxetine did not have proven efficacy for fatigue in any of the reviews examined. The quality of evidence was considered moderate. However, fatigue has an extremely complex pathophysiology that requires a comprehensive approach that goes beyond the use of antidepressants and it is not possible to explain the results found definitively.

Regarding mood disorders, 50% of the reviews selected [5, 18, 19, 22] addressed this outcome, and all of them showed that duloxetine is more efficacious than amitriptyline in the management of depression-related symptoms and mood disorders with high quality of evidence. Therefore, duloxetine would be the first option when this is the main symptom of patients with fibromyalgia. A systematic review carried out in 2016 [29] indicated an average prevalence of 52% of depression in patients with fibromyalgia; therefore, it is necessary to consider the potentiality of indication for treatment with duloxetine if a mood disorder is, in fact, the major symptom. The results are in agreement with the findings of a study conducted in 2005 [30], which indicated that fibromyalgia-associated depression will often require non-selective reuptake inhibitors, such as duloxetine.

Table 1 Characteristics of the systematic reviews included

Author, year	Number of Studies DLX	Number of Studies AMT	Participants Included	Objectives	Criteria for Inclusion	Criteria for Exclusion	Scales
Thorpe et al., 2018 [18]	2	1	133	To assess the efficacy, safety and tolerability of combination of drugs with monotherapy or placebo, or both, in the treatment of FMS	Double-blind RCT comparing combinations of two or more drugs with placebo or other comparatives, or both, in the treatment of FMS	Single-blind studies, complementary studies to those already selected, non-randomized, studies with other therapies and with patients having diverse fibromyalgia diseases	VAS, NPS, pain reduction of 30% or more and 50% or more, FIQ, NNTH
Sommer et al., 2017 [19]	10	14	6038	To assess the efficacy and safety of drugs and non-drug therapy in the treatment of FMS	Randomized clinical trials with drugs used to treat FMS, in databases, non-published articles and specialists' opinion	Studies with downgraded quality evidence according to the application of the GRADE method used by the authors	50% pain reduction, NNTB, VAS, FIQ
Smith et al., 2011 [20]	9	24	1368	To compare the efficacy and harms of drugs used in the treatment of FMS	Studies with patients with FMS, according to the ACR criteria of 1990 and 2010, involving the use of diverse drugs and direct and indirect comparisons, assessing efficacy and damages	Studies with ineligible results, intervention, population, publication and study design	50% pain reduction, MFI, MAF, VAS, FIQ
Häuser et al., 2011 [5]	4	10	2023	To assess and compare the efficacy and acceptability of amitriptyline (AMT), duloxetine (DLX) and milnacipran (MLN) antidepressants in the treatment of FMS	RCT comparing AMT, DLX or MLN with placebo, assessing at least one FMS key domain: pain, sleep, fatigue or health-related quality of life; treatment discontinuation rate	RCTs with combination of drugs with any other treatment	VAS, 30% pain reduction, NPS, NNTB, Cohen's category, VAS, FIQ
Üçeyler et al., 2008 [22]	2	13	891	To review systematically the efficacy of antidepressants in the treatment of FMS	FMS or CWP diagnosis based on recognized criteria, controlled study design with a control group who received placebo, usual treatment or any other well-defined treatment; treatment with antidepressants, and measurement of specific symptom results	Studies with cyclobenzaprine, which combines characteristics of antidepressant with relaxant, and studies with S-adenosylmethionine, because this substance is officially available in two countries only (UK and Italy) as food supplement	VAS, tender point count, VAS, BDI, HAM-D, FIQ
Roskell et al., 2011 [6]	2	5	538	To compare pain response to licensed drugs or drugs commonly used in fibromyalgia, also addressing treatment discontinuation due to adverse reactions	Randomized Controlled Clinical Trials with at least 4-week duration with patients aged 18 years or over with clinical FMS diagnosis, using Duloxetine (60 mg / day), Fluoxetine (40 to 50 mg / day), Gabapentin (2400 mg / day), Milnacipran (100 or 200 mg / day), Placebo, Pramipexol (4.5 mg / day), Pregabalin (300 or 450 mg / day), TCA (amitriptyline 25 to 75 mg / day or cyclobenzaprine 1030 mg / day), Tramadol with paracetamol (200 to 300 mg / day)	Treatment of no interest for meta-analysis, no major outcome reported, different treatment doses, study not properly controlled, duplicated or of short duration, poor quality testing and when the article was irretrievable	FIQ, BDI
Häuser et al., 2009 [5]	3	7	927	To determine the efficacy of antidepressants in the treatment of FMS through meta-analysis and randomized controlled clinical trials	Patients effectively diagnosed FMS, RCT with one control group receiving placebo and one group treated with antidepressants (TCA, SSRIs,	Studies assessing cyclobenzaprine, S-adenosylmethionine, or antidepressant combinations. Studies where only categorial data were	VAS, FIQ, NRS, HRQOL scale

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Table 1 Characteristics of the systematic reviews included *(Continued)*

Author, year	Number of Studies DLX	Number of Studies AMT	Participants Included	Objectives	Criteria for Inclusion	Criteria for Exclusion	Scales
					SNRIs or MAOIs)	provided and studies with incomplete data	
Perrot et al., 2008 [23]	2	4	910	To review evidences of use of antidepressants in painful rheumatological conditions	Articles published between 1966 and 2007 in 5 European idioms, addressing the use of antidepressants in various rheumatological conditions, including FMS. The authors attributed a rating scale based on the Jadad method (0–5), including studies with scoring above 2	Articles that were scored below 2 in the Jadad scale	VAS, FIQ, NRS

^a*FMS* Fibromyalgia, *DLX* Duloxetine, *AMT* Amitriptyline, *RCT* Randomized Clinical Trial, *ACR* American College of Rheumatology, *CWP* Chronic Widespread Pain, *TCA* Tricyclic Antidepressant, *SSRIs* Selective Serotonin Reuptake Inhibitor, *SNRIs* Serotonin and Noradrenaline Reuptake Inhibitor, *MAOIs* Monoamine Oxidase Inhibitors, *VAS* Visual Analog Scale, *NPS* Numeric Pain Scale, *FIQ* Fibromyalgia Impact Questionnaire, *NNTB* Number needed to treat for an additional benefit, *NNTH* Number needed to treat to prevent one additional harm, *MAF* Multidimensional Assessment of Fatigue, *MFI* Multidimensional Fatigue Inventory, *BDI* Beck Depression Inventory, *HAM-D* Hamilton Depression Scale, *BDI* Brief Pain Inventory, *NRS* Numeric Rating Scale, *HRQL* Health-related Quality of Life

These drugs have fewer adverse reactions than the tricyclic antidepressants and are much more effective in the control of depression.

Regarding the quality of life, in two out of five reviews that addressed this outcome, amitriptyline had a better result [19, 21]. The evidence was considered of high quality. However, for the specialists who developed the *Consenso Brasileiro de Fibromialgia* [1] [Brazilian Consensus on Fibromyalgia], both medicines are recommended with the same level of evidence for the management of quality of life. It would seem that divergence in results occur due to the subjectivity of perception of the quality of life, which, for many patients, can be directly associated with their level of pain or in the way pain interferes with the emotional aspect [31].

Regarding acceptability and safety, the studies pointed out that was treatments with duloxetine had less discontinuation of therapy due to adverse reactions, but amitriptyline was slightly favored regarding safety. However, the evidence was considered of low quality and highlighted that the reviews with the best quality that addressed safety and acceptability [20, 21] did not find significant differences between both medicines. Both drugs have diverse adverse reactions, and these outcomes must be considered with caution, case by case when making a clinical decision.

It should be noted that according to the American Geriatrics Society [32], there is a strong recommendation with high quality of evidence against amitriptyline in older adults, which should be avoided because of its anticholinergic effect, causing sedation and orthostatic hypotension. Thus, for older patients, duloxetine would be the safer choice.

This overview has some limitations. The majority of the studies were conducted before 2010, before changes in the fibromyalgia diagnosis criteria, which

Table 2 Studies excluded for not having met the eligibility criteria

Study excluded	Exclusion code
HÄUSER W, WOLFE F, TÖLLE T, ÜÇEYLER N, SOMMER C. The Role of Antidepressants in the Management of Fibromyalgia Syndrome: A Systematic Review and Meta-Analysis. CNS Drugs. 2012 Apr; 26 (4):297–307.	4
CHOY E, MARSHALL D, GABRIEL ZL, MITCHELL SA, GYLEE E, DAKIN HA. A Systematic Review and Mixed Treatment Comparison of the Efficacy of Pharmacological Treatments for Fibromyalgia. Seminars in Arthritis and Rheumatism. 2011 Dec; 41 (3):335–345.e6.	4
SULTAN A, GASKELL H, DERRY S, MOORE RA. Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic review of randomised trials. BMC Neurol. 2008 Dec; 8 (1):29.	2

a) Complete articles considered for inclusion, but excluded for not having met the criteria. Exclusion codes: 1 = ineligible outcome, 2 = ineligible intervention, 3 = ineligible population, 4 = ineligible methodology.
b) The other two papers were old versions of the study of Sommer et al., (2017).

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Table 3 Methodological quality of the systematic reviews included in the overview

Author, year	Methodological quality (AMSTAR)
Thorpe et al., 2018 [18]	12/16 – moderate
Sommer et al.,2017 [19]	10/16 – low
Smith et al., 2011 [20]	15/16- high
Roskell et al., 2011 [6]	13/16 – moderate
Häuser et al., 2011 [21]	14/16 – high
Häuser et al., 2009 [5]	14/16 – high
Üçeyler et al., 2008 [22]	9/16 – very low
Perrot et al., 2008 [23]	7/16 – very low

basically considered palpation of tender points. Some patients probably were excluded, considering the new form of diagnosis, which considers the pain intensity associated with the degree of severity of other symptoms [33], which could lead to a selection bias.

There are challenges in common with the routine of systematic reviews and overviews, such as the management of large volumes of information and extracted datasets as well as the time available, resources, and the ability to make consensual decisions between the authors and reviewers. In the overview case, we still have the aggravating issue of studies overlapping, inherent to the level of analysis, which encompasses systematic reviews and not individual studies [34].

It was observed that, in some reviews, studies with amitriptyline are of lower methodological quality compared with those with duloxetine. This finding can be explained by the fact that they are older studies, considering that clinical trials have improved over time, making use of the policy of application of trial registration and study assessment tools [35].

In conclusion, both drugs can be used in the treatment of fibromyalgia, depending on the set of predominant key symptoms. The results of analyses indicate recommendation in favor of amitriptyline with low evidence for pain, moderate evidence for sleep and fatigue, and high evidence for the quality of life. Duloxetine is recommended with high quality of evidence when the patients have mood disorder as a major symptom, has more acceptability, and is the first choice for older patients for safety reasons. The

Table 4 Quality of evidence of the reviews included according to GRADE

No. studies	Study design	Risk of Bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Impact	Confidence	Importance
Pain									
8	SR of CT	Not serious	Serious [a]	Not serious	Not serious	Highly suspicious	Favors AMT	++ Low	Critical
Sleep									
6	SR of CT	Not serious	Serious [a]	Not serious	Not serious	None	Favors AMT	+++ Moderate	Critical
Fatigue									
7	SR of CT	Not serious	Not serious	Not serious	Not serious	Highly-suspicious publication bias	Favors AMT	+++ Moderate	Critical
Mood Disorder									
4	SR of CT	Not serious	Not serious	Not serious	Not serious	None	Favors DLX	++++ High	Critical
Quality of life									
5	SR of CT	Not serious	Not serious	Not serious	Not serious	None	Favors AMT	++++ High	Critical
Safety and acceptability									
7	SR of CT	Not serious	Serious [b]	Not serious	Not serious	Highly suspicious publication bias	DLX with higher acceptability and safety for elderlies; AMT with higher safety for non-elderlies	++ Low	Critical

SR Systematic Review, *CT* Clinical Trial; [a] most of the reviews do no detail the results of the heterogeneity tests and, in some of them, the rates were high; [b] diverging results with rare approaches to explain heterogeneity; scarce safety data; *AMT* Amitriptyline, *DLX* Duloxetine

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results are aligned with the already-recognized complexity of this disease. This overview contributes to guiding clinicians and decision-makers in public health policies based on systematic reviews that addressed the use of antidepressants in the management of fibromyalgia.

Authors' contributions
AF conceived the study, performed data collection, analysis, review and interpretation, and drafted the manuscript. LE conducted data collection, analysis, review and interpretation and contributed to the writing of the manuscript. TA conceived the study, conducted data analysis and interpretation and contributed to the writing of the manuscript. TDP contributed to the study conception and the writing of the manuscript. The authors read and approved the final manuscript.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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