Effective Health Care Program

Comparative Effectiveness Review
Number 148

Treatments for Fibromyalgia in Adult Subgroups

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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Treatments for Fibromyalgia in Adult Subgroups

Structured Abstract

Objective. We conducted a systematic literature review of clinical trials to assess the comparative effectiveness of treatments for fibromyalgia in subgroups of highly affected or clinically complex adults. We focused on patient subgroups rather than overall treatment effects to complement a large systematic review being conducted on fibromyalgia treatments at McMaster University.

Data sources. We searched Medline®, Embase®, PsycINFO®, AMED, and the Cochrane Central Register of Controlled Trials (CENTRAL) plus reference lists of included studies and recent systematic reviews.

Methods. Two investigators screened abstracts of identified references for eligibility (enrolled adults with fibromyalgia, examined treatment effects, had a control group, and assessed outcomes at least 3 months after treatment initiation). Full-text articles were reviewed to identify outcomes reporting for at least one adult subgroup: women, older or obese adults, individuals with coexisting mental health conditions, high severity or longer fibromyalgia duration, multiple medical comorbidities, or other chronic pain conditions. Primary outcomes included pain, symptom improvement, function, fatigue, sleep quality, participation, and health-related quality of life. We extracted data, assessed risk of bias of individual studies, and evaluated strength of evidence for each comparison and outcome.

Results. We identified 22 randomized controlled trials (RCTs), 8 pooled analyses of patient-level RCT data, and 4 observational studies that met inclusion criteria; 59 percent were drug trials. Adults with fibromyalgia and major depressive disorder (MDD) were studied most often; drug studies also reported outcomes by age, sex, race, and anxiety. Most drug trials examined duloxetine effects on pain and global improvement; trial duration was typically 3 months. Low-strength evidence for duloxetine suggests that subgroups of adults with fibromyalgia and MDD do not experience differential short-term treatment effects. Other subgroup evidence is largely insufficient. For nearly all comparisons, treatment-by-subgroup interactions were not significant. Most interaction results were reported in text; only two RCTs and five pooled RCT analyses displayed data on subgroup outcomes. Losses to followup were considerable; dropout reporting was not subgroup specific. Adverse effects were reported for the MDD subgroup in one duloxetine pooled analysis; these were similar to overall adverse effects. Studies were not powered to detect subgroup effects.

Conclusion. Despite the prevalent belief that fibromyalgia treatments may behave differently in subgroups, evidence to date is largely insufficient for fibromyalgia subgroup effects of interventions other than duloxetine in adults with concomitant MDD. Future studies should be designed to support subgroup analysis to improve clinical applicability.

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Executive Summary

Background

Fibromyalgia is a chronic diffuse musculoskeletal pain syndrome that has no clearly identified etiology.[1-4] It affects mostly adults[5] and is characterized by chronic widespread pain, abnormal processing of and heightened sensitivity to pain, chronic fatigue, sleep disorders, and emotional distress or depression.[5,6] Fibromyalgia reduces quality of life and productivity, and is associated with functional disability, lost worktime, and increased use of health care services.[5,7-9] Based on diagnostic criteria developed in 1990 by the American College of Rheumatology (ACR), fibromyalgia affects more than 5 million Americans,[10] most of whom are middle-aged women.

The diagnostic criteria for fibromyalgia have evolved[11,12] since their first publication by the ACR in 1990. The original criteria included palpation of myofascial "tender points" during physical examination and the presence of widespread pain for at least 3 months.[13] In 2010 the ACR eliminated the criterion of tender points examination and added (1) physician-rated severity on two scales, the Widespread Pain Index and the Symptom Severity Scale, and (2) a requirement of symptoms for at least 3 months and the absence of another disorder that would account for the symptoms.[11,14] A survey version of the 2010 ACR criteria was released for research purposes in 2011.[12] Compared with the 1990 criteria, the 2010 ACR preliminary diagnostic criteria capture a broader population of fibromyalgia patients, which affects prevalence estimates and patient heterogeneity in more recent studies.[14-16] Alternative diagnostic criteria are under consideration.[17]

Treatments for fibromyalgia syndrome include drugs and nonpharmacologic therapies to help mitigate symptoms and improve function.[5] Treatment goals are to mitigate diffuse musculoskeletal pain, maximize physical and cognitive function, optimize patient self-management and self-efficacy, and manage comorbid medical and psychiatric disorders. Treatment typically involves multidisciplinary approaches and providers. Treatment components may include drugs, exercise programs, cognitive behavioral therapy (CBT), patient education (self-management, sleep hygiene, importance of exercise, etc.), and the treatment of comorbid medical and mental health conditions.[5,18] Complementary and alternative medicine approaches are also common.[18,19] The U.S. Food and Drug Administration (FDA) has approved three oral medications for fibromyalgia since 2007: pregabalin, duloxetine, and milnacipran. In addition, numerous drugs approved for other conditions are currently used off label in patients with fibromyalgia, such as antidepressants, analgesics, opioid analgesics, anti-inflammatories, and skeletal muscle relaxants. Nondrug treatments for fibromyalgia include psychological, physical (active or passive), multicomponent, lifestyle-modification, and other therapies, including nutraceuticals, with the goal of improving physical function, endurance, and self-efficacy in fibromyalgia management, both short and long term.

Many clinical trials suggest a modest benefit from treatments for a general population of fibromyalgia patients.[1,18] Although clinicians believe that treatment effectiveness may vary in subgroups,[20-22] less is known about the efficacy and comparative effectiveness of fibromyalgia treatments in subgroups of adults (defined by the number and type of coexisting syndromes or conditions, severity of pain or impairment at baseline,[11] presence of a concomitant mood or other mental health disorder, or demographic or other related factors). Understanding subgroup effects might help to better inform clinical treatment decisions. This systematic review provides information for both patients and providers on treatment outcomes in fibromyalgia subgroups;

such patients typically present with multiple chronic symptoms or conditions and pose significant treatment dilemmas for providers.

Scope and Key Questions

This systematic review examined whether specific subgroups would benefit from being treated differently from the general fibromyalgia patient population. We limited this review to subgroup effects because McMaster University in Canada is currently conducting a comprehensive systematic review of randomized controlled trials (RCTs) on interventions for fibromyalgia in adults.[23] Our review adds unique information by examining outcomes in fibromyalgia patient subgroups and by including observational literature. The patient subgroups, chosen a priori from the literature and with input from experts and other stakeholders, are: women;[24-28] older[29,30] or obese[31] adults; individuals with coexisting mental health conditions;[5,10,32-34] and those with high-severity[34-37] or longer (vs. shorter) fibromyalgia duration,[38] multiple medical comorbidities,[5,38,39] or other chronic pain conditions.[5,10,18,33,40] We also examined subgroups not identified a priori but for whom information is available in the literature. Because fibromyalgia is largely a chronic condition in adults, we limited our analysis to studies of individuals age 18 or older that compared treatments for fibromyalgia in subgroups of adults and reported outcomes at least 3 months after treatment initiation.

The following two Key Questions were the focus of this systematic review:

Key Question 1. What are the efficacy and comparative effectiveness of treatments for fibromyalgia in each of these specific adult subpopulations?

- Women
- Individuals with coexisting mental health conditions
- Individuals with high fibromyalgia symptom severity (Fibromyalgia Impact Questionnaire [FIQ] 59-100 = severe fibromyalgia)
- Older adults
- Obese adults
- People with multiple medical comorbidities
  - Concurrent rheumatic disease: rheumatoid arthritis, lupus, ankylosing spondylitis, etc., including osteoarthritis
  - Other comorbidities
- Individuals with other significant chronic pain conditions (low back pain, headache, irritable bowel syndrome, etc.)
- Individuals with longer duration of fibromyalgia symptoms

Key Question 2. What are the harms of treatments for fibromyalgia in each of these specific adult subpopulations?

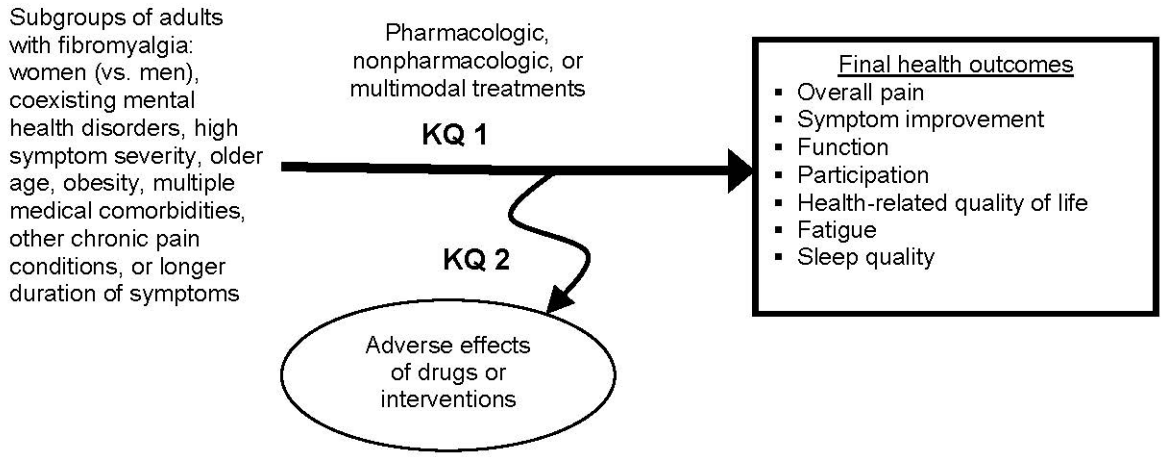
- Women
- Individuals with coexisting mental health conditions
- Individuals with high fibromyalgia symptom severity (FIQ 59-100 = severe fibromyalgia)
- Older adults
- Obese adults

- Individuals with multiple medical comorbidities:
  - Concurrent rheumatic disease: rheumatoid arthritis, lupus, ankylosing spondylitis, etc., including osteoarthritis
  - Other comorbidities
- Individuals with other significant chronic pain conditions (low back pain, headache, irritable bowel syndrome, etc.)
- Individuals with longer duration of fibromyalgia symptoms

Analytic Framework

The analytic framework for the Key Questions is depicted in Figure A. The figure illustrates how the use of pharmacologic, nonpharmacologic, or multimodal treatments may improve outcomes for adults with fibromyalgia.

Figure A. Analytic framework for treatments for fibromyalgia in adult subgroups



Note: KQ = Key Question

Methods

The methods for this Comparative Effectiveness Review follow the methods suggested in the Agency for Healthcare Research and Quality "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (available at www.effectivehealthcare.ahrq.gov/methodsguide.cfm). A complete description of the methods can be found in the full report.

Literature Search Strategy

We searched Ovid MEDLINE®, Embase®, Ovid PsycINFO®, AMED (Allied and Complementary Medicine), and the Cochrane Central Register of Controlled Trials (CENTRAL) from 1985 through August 2014 to identify RCTs, systematic reviews, and observational studies with control groups on treatments for adults with fibromyalgia. We supplemented bibliographic database searches with backward citation searches of highly relevant systematic reviews.

Eligibility

We included RCTs, pooled analyses of individual patient-level RCT data, and observational studies published in English that examined one or more treatments for fibromyalgia in adults, used a comparator group, and reported treatment outcomes in at least one subgroup 3 months or more after the initiation of treatment. We excluded studies of drugs not FDA approved in the United States for any condition; studies that included patients with different health conditions and that did not separately report baseline and outcomes in fibromyalgia patients; studies that did not use established fibromyalgia diagnostic criteria for subject selection (ACR[11-13] or Yunus[41] criteria for fibrositis from 1985-90); and pharmaceutical RCTs in which patients were unblinded to treatment for any part of the study.

Two independent investigators independently determined study eligibility and resolved disagreements through discussions; when needed, a third investigator was consulted until consensus was achieved.

Data Extraction

We extracted data from included studies into evidence tables by the type of study design. Extracted data included the relevant population, intervention, baseline, and outcomes data on the adult subgroups of interest. Initial data abstraction was quality checked by a second investigator.

Quality (Risk-of-Bias) Assessment of Individual Studies

The risk of bias of eligible studies was assessed by two independent investigators using instruments specific to each study design. Two investigators consulted to reconcile any discrepancies in overall risk-of-bias assessments and, when needed, a third investigator was consulted to reconcile the summary judgment. For RCTs we assessed the risk of bias using a modified Cochrane risk-of-bias tool.[42] We used additional items based on Sun et al.[43] to assess the credibility of subgroup analysis of individual RCTs. Overall summary risk-of-bias assessments for each study were classified as low, moderate, or high based on the collective risk of bias inherent in each domain and confidence that the results are believable given the study's limitations.[42] A consolidating algorithm was not used. We developed an instrument to assess risk of bias for observational studies using the RTI item bank on risk of bias and precision in observational studies,[44] with weighted emphasis on selection and attrition bias.

Data Synthesis

We summarized the results into evidence tables and qualitatively synthesized evidence by the type of study (RCT, observational, pooled RCT) for each unique population, comparison, and outcome combination within specific followup periods. Studies were grouped by intervention category and then subgroup. We summarized within-study[43] outcomes comparisons on pain, global improvement, fatigue, function, and quality of life for patient-centered subgroups. Pooling was planned for measures that assessed the same outcome and had comparable scoring characteristics (such as the FIQ[45] and revised Fibromyalgia Impact Questionnaire [FIQR][46]). However, a quantitative analysis pooled across studies was not possible due to differences in subgroup-treatment-outcome combinations.

Wherever possible, we report data and/or interaction results that assessed whether treatment effects varied in subgroups. If interaction results were not reported and data were presented for within-stratum results—such as stratum-specific change in pain for those with MDD (treated vs.

controls) and for those without MDD (treated vs. controls)—we report within-stratum information.

When available, we identified minimal clinically important outcomes differences for measures specific to fibromyalgia patients. Additionally, when subgroup data were provided, we calculated the difference in mean change from baseline between treated and control groups by subgroup strata as a general measure of the magnitude of treatment effect relative to the control (placebo) group.

Strength of the Body of Evidence

We evaluated the overall strength of evidence for selected clinical outcomes based on four domains: (1) study limitations (internal validity); (2) directness (single direct link between the intervention and outcome); (3) consistency (similarity of effect direction and size); and (4) precision (degree of certainty around an estimate), with the study limitations domain having considerable importance.[47] Study limitations were rated as low, moderate, or high according to study design and conduct. The possible strength-of-evidence grades[47] were—

- High: High confidence that the evidence reflects the true effect. Further research is unlikely to change the estimates.
- Moderate: Moderate confidence that the estimate reflects the true effect. Further research may change estimates and our confidence in the estimates.
- Low: Limited confidence that the estimate of effect lies close to the true effect. Further research is likely to change confidence in the estimate of effect and may change the estimate.
- Insufficient: Evidence is either unavailable or does not permit a conclusion.

Applicability

Applicability of studies was determined according to the PICOTS (populations, interventions, comparators, outcomes, timing, settings) framework. Adults in clinical trials of fibromyalgia treatments may be higher functioning, be less impaired, and have fewer or less severe concomitant medical or mental health conditions than the fibromyalgia patient population as a whole, which impacts the generalizability of clinical trial results to the broader fibromyalgia population.

Results

Overview

We included several types of studies. RCTs with mixed patient samples are studies that identified a patient subgroup after randomization (such as adults with fibromyalgia, a proportion of whom had depression). RCTs that selected within particular subgroups (such as sedentary women or postmenopausal women) comprised another group of included studies. We refer to this collection of studies as pure subgroup RCTs. A third type of study was a pooled analysis of individual patient data from several RCTs to report subgroup outcomes. We refer to these pooled within-study comparisons as pooled analyses of individual patient data (IPD) from RCTs, or pooled IPD RCT analyses. All such studies investigated pharmaceutical interventions. Finally, observational studies with comparator groups were included. Detailed tables and synthesis can be found in the full report.

Results of Literature Searches

We identified 6,401 citations from all databases combined. We examined the full text of 516 articles (391 RCTs, 24 pooled analyses of patient-level RCT data, and 101 observational studies) to assess for subgroup reporting. Of those, 34 studies were included in the analysis: 22 RCTs, 8 analyses that pooled IPD from RCTs,[20,21,33,48-52] and 4 observational studies.[53-56] The two types of RCTs included 10 studies with mixed patient samples[3,4,22,57-63] and 12 RCTs of pure subgroups.[64-75] Of the 22 RCTs, 10 were placebo-controlled trials. Twenty studies were drug trials (59%). All included studies were published in 2001 or later, with the eight pooled IPD RCT analyses all published since 2009. Table A summarizes the included studies by design.

Table A. Included fibromyalgia subgroup studies, by study design

Study Design	Count
Randomized controlled trials	10
Randomized controlled trials of pure subgroups	12
Pooled analyses of individual patient data from randomized controlled trials	8
Observational studies	4
Total of included studies for report	**34**

Key Question 1. Treatment Effectiveness in Fibromyalgia Subgroups

Overview

Given the sparse evidence for specific treatment-subgroup-outcome combinations, we were unable to conduct meta-analyses. Results from qualitative synthesis are provided here.

Key Points

- Evidence is largely insufficient to determine subgroup effects for interventions other than duloxetine in adults with fibromyalgia.
- For duloxetine, patient subgroups do not experience significantly different fibromyalgia treatment effects relative to other adults with fibromyalgia (low-strength evidence).
- The most commonly addressed subgroup was adults with fibromyalgia and major depressive disorder (MDD), especially for the effects of duloxetine on pain. Less information is available on treatment effects for other subgroups (such as age, sex, race, anxiety), for other outcomes, or for nondrug interventions.
- All but two individual RCTs had high risk of bias; all RCTs used in pooled IPD analyses had high risk of bias.
- Evidence is overwhelmingly short term (3 months).

Pharmacologic Therapies

The majority of included studies reported the effects of pharmacologic therapies on pain and other outcomes in subgroups of adults with fibromyalgia. All eight pooled analyses of patient-level RCT data were drug studies. Duloxetine effects were studied most often.[3,4,20-22,48,57,58,63] Subgroups we determined a priori that were found in drug studies included depression (12 studies), age (7 studies), sex (6 studies), anxiety (4 studies), obesity/body mass index (BMI) (2 studies), and medical comorbidities (1 study). Additional subgroups in drug studies were race (4 studies), baseline fatigue level (1 study), prior antidepressant use (1 study), postmenopausal

women (2 studies), and 1 study that used baseline Visual Analog Scale (VAS) pain ratings for subgroup definition.

The literature set for pharmacologic interventions consists exclusively of studies with high risk of bias due to high attrition, lack of attrition reporting for subgroups or treatment groups, and small subgroup sample sizes in nonpooled analyses. Overall attrition in drug trials ranged from 4 percent in one off-label international trial[65] to 47 percent,[3] with most studies having 30- to 40-percent overall attrition. Only two off-label pharmaceutical trials reported overall attrition of less than 25 percent.[64,65]

Industry funded 85 percent of the 17 drug trials that reported the source of study funding. Industry study involvement included data management, statistical support, manuscript drafting, construction of tables, and study management. Corresponding and other authors in drug trials were often industry employees.

Subgroup Outcomes

In this section, we first examine the effect of drugs on various subgroups and then address the effects of other treatments. Those subgroup-intervention-outcome comparisons with at least low strength of evidence are provided first. Brief details for the subgroups with insufficient evidence are provided second.

Comorbid Mental Health Conditions

Depression

Adults with fibromyalgia and MDD or a history thereof were the most frequently assessed subgroup for treatment interactions in drug studies and across all other types of treatments. Eleven drug studies (including 8 RCTs [7 FDA approved, 1 off label]; 2 pooled IPD RCT analyses; and 1 observational study) assessed treatment-by-MDD interactions on the outcomes of pain, global improvement, fibromyalgia impact, and depression. One additional pooled IPD RCT analysis reported stratum-specific changes in pain rather than an interaction effect.[51]

Drug treatments did not appear to have differential effects in adults with fibromyalgia and depression versus those without depression. Low-strength evidence from six RCTs and one pooled IPD analysis[20] of duloxetine suggest that pain outcomes for adults with fibromyalgia with or without depression do not differ.[3,4,20,22,57,58,63] Pain was the most common outcome assessed in adults with fibromyalgia and comorbid depression, including six RCTs (5 of duloxetine[3,4,22,57,63] and 1 of milnacipran[59]) plus two pooled RCT analyses,[20,21] both of duloxetine. All treatment-by-MDD interactions for pain were either not significant or not reported. Five different measures were used to assess pain in the MDD subgroup; the Brief Pain Inventory (BPI) average pain severity score was used most often. Two RCTs with high risk of bias[3,63] and one pooled IPD RCT analysis of four RCTs of duloxetine with high risk of bias[20] presented data on MDD subgroup BPI average pain severity scores. The interaction result was not reported; the text implies that it was not significant.[3]

Treatment-by-MDD interaction results for all other outcomes were found in article text only, with or without p-values; these were either not significant or the results were not specifically reported. For the MDD subgroup, two studies (1 RCT[4] and 1 pooled IPD[20]) showed no difference on the FIQ total score with duloxetine.[4,20] Two RCTs (1 of duloxetine[4] and 1 of fluoxetine[60]) examined the FIQ and FIQ pain subscales as primary outcomes; neither treatment-by-MDD interactions on the FIQ pain subscales[4,60] nor FIQ total scores[4] were significant.

Low-strength evidence from three studies of duloxetine (2 RCTs[3,58] and 1 pooled analysis[20]) showed no difference among subgroups on the Patient Global Impression of Improvement (PGI-I).[76] For the PGI-I outcome, the duloxetine-by-MDD interaction was not statistically significant[20,58] or not reported.[3] The RCT by Russell et al. (2008)[3] displayed MDD subgroup data for the PGI-I. Study authors noted similar improvements in PGI-I in treated patients versus controls regardless of MDD status but did not report the interaction result. However, dropouts were assigned a PGI-I score of 4 (corresponding to no change) for the analysis, which assumed no treatment benefit or decrement for patients who did not complete the 3- or 6-month treatment phases.[3]

Insufficient information on duloxetine effects on the Hamilton Rating Scale for Depression[3,20] and the Beck Depression Inventory[57] was available for analysis.

These reported results should be considered in light of issues common to this set of studies. At baseline, MDD subgroup sample sizes were small in all RCTs, excluding the pooled IPD RCT analyses. The number of patients with MDD at final followup in both treatment and control groups was not determinable due to incomplete reporting of denominator values and dropouts in subgroups or in treatment groups after baseline. The lack of denominator values after baseline was common in both RCTs and pooled analyses.

Anxiety

Three RCTs provided insufficient evidence for duloxetine treatment and generalized anxiety disorder on the outcomes of BPI average pain severity and PGI-I.[57,58,63] One pooled IPD RCT analysis provided insufficient evidence for pregabalin on pain.[51]

Other Subgroups

Age

Three RCTs with low-strength evidence found no differences by age for duloxetine on the BPI average pain severity score for 3 to 6 months.[3,57,63] Two RCTs with low-strength evidence found no differences by age on duloxetine effects on the PGI-I.[3,58] One study provided insufficient evidence for the effect of pregabalin on weekly pain by age.[52]

Sex

Four RCTs that assessed duloxetine effects by sex offered insufficient evidence of a mixed pattern for the BPI average pain severity score; in four there was no difference by sex at 3[3,57] and 6 months,[55,63] but in one study females improved more than males at 3 months.[4] When PGI-I was the outcome, low-strength evidence from two duloxetine studies showed no differences by sex in 3-[55] and 6-month treatment effects.

Race

Race showed insufficient evidence of mixed effects of duloxetine. Two of three RCTs found no difference in BPI average pain severity by race,[3,63] but in one RCT that was not powered for subgroup effects, nonwhites improved more than whites in BPI average pain severity scores.[57] Two RCTs with low-strength evidence reported no difference by race when PGI-I was the outcome.[3,58]

Obesity

Two pooled IPD analyses, one of duloxetine[48] and one of milnacipran,[49] provided insufficient evidence for the outcomes of stiffness[48] (FIQ subscale) and weight loss for subgroups determined by BMI at baseline.[49]

Other Subgroup Outcomes

One duloxetine RCT with high risk of bias reported 6-month changes in BPI average pain severity for patients stratified by prior antidepressant use at baseline.[63] The interaction was significant, whereby treated patients with previous antidepressant use had greater improvements in BPI average pain than those without prior antidepressant use ($p = 0.028$).

Bradley et al.[21] conducted a pooled analysis of IPD RCT data to determine whether duloxetine effects on the BPI average pain score varied by baseline level of fatigue using the FIQ tiredness subscale. The interaction term was not significant.

Within-subgroup changes from baseline in pain were reported by Bhadra et al.[51] in a pooled study of varying doses of pregabalin, although no interaction effects were assessed.

No other subgroups were separately reported in included studies.

Physical Treatments

Five pure subgroup RCTs examined the effects of physical interventions[66-68,70,74] and one of dietary changes[69] on outcomes in subgroups of adults with fibromyalgia. Four RCTs examined exercise interventions:[66,68,70,74] two studies had moderate risk of bias,[66,67] and the others had high risk of bias.[66,69,68,74] Sample sizes ranged from 21 to 83 adults at enrollment, for a total of 311 subjects across all six studies. The strength of evidence was insufficient to compare treatment outcomes for physical interventions from these RCTs.

Psychological Therapies

Four studies examined the effects of psychological therapies in subgroups of adults with fibromyalgia: one mixed-sample RCT,[61] two pure subgroup RCTs,[71,72] and one observational study.[55] Study duration ranged from 3 months to 1 year, which was the longest followup of any study included in this report. Sample sizes were small. All assessed unique outcomes in disparate subgroups and all had high risk of bias. The strength of evidence was insufficient to compare subgroup treatment effects for psychological interventions.

Mixed Types of Treatments

Four studies assessed combination therapies, and each study had high risk of bias.[56,62,73,75] The strength of evidence was insufficient to compare treatment outcomes for mixed types of fibromyalgia treatments. All four studies assessed unique treatment-subgroup-outcome combinations.

Key Question 2. Adverse Treatment Effects in Fibromyalgia Subgroups

The clinical trial literature on adults with fibromyalgia that reported on subgroup treatment effects was nearly devoid of adverse effect (AE) reporting for subgroups.

Key Points

- AEs were rarely reported by subgroup.

- Evidence was insufficient to determine whether AEs of treatments for adults with fibromyalgia vary in adult subgroups or whether subgroups experience atypical AEs for a given treatment.
- When reported, AEs did not markedly differ in subgroups.

Adverse Effects Reporting

None of the 10 mixed-sample RCTs with subgroup outcomes separately reported AEs by subgroups.[3,4,22,57-63] Of the 12 pure subgroup RCTs, only 3 reported any information on adverse treatment effects: 2 off-label drug studies[64,65] and 1 test of an exercise intervention.[66] The most common side effect with exercise was muscle pain.[66] AEs were reported for subgroups in one pooled analysis of duloxetine effects on fibromyalgia patients with MDD.[20] The treatment-by-MDD interaction for serious AEs was not significant ($p > 0.1$),[20] but the treatment-by-MDD stratum interaction was significant for "treatment-emergent" AEs, with higher incidence of 10 nonserious AEs in treated patients with MDD relative to treated adults without MDD. The three most common of these "treatment-emergent" AEs in treated patients were nausea (31.6%), headache (19.6%), and dry mouth (19.1%) in the duloxetine-MDD group, which were 0.4 to 3.3 percent higher than the rates in the treated group without MDD. AEs were reported only by treatment group, not by subgroup, in two pooled milnacipran studies[49,50] and in one duloxetine study.[48] AEs were not reported in the three pooled pregabalin studies.[33,51,52] Only one of four observational studies reported adverse treatment effects: a crossover study of 10 patients treated with naltrexone (off label).[54]

Strength of Evidence

Table B summarizes the major findings and associated strength of evidence for subgroup analyses with at least two studies. The strength of evidence for assessing differential treatment effects in subgroups of adults with fibromyalgia is low or insufficient for pharmacologic interventions and insufficient for physical, psychological, and mixed interventions. Higher quality studies could change the conclusions of this review. All but one comparison for which we could assign strength of evidence involved duloxetine effects. Most compared those with and without major depression.

Table B. Key Question 1: Benefits of treatment—summary and strength of evidence of effectiveness and comparative effectiveness of treatments for fibromyalgia in adult subgroups[a]

Population (FM Subgroup)	Intervention Vs. Placebo	Outcome: Change From Baseline	Conclusion	Number of Studies	Strength of Evidence
With MDD/ depression	Duloxetine	BPI average pain severity score	No evidence that treatment effects differ in subgroup	6: 5 RCTs; 1 pooled analysis[b]	Low (high risk of bias/many study limitations; consistent direction of effect)
	Duloxetine	PGI-I	No evidence that treatment effects differ in subgroup	3: 2 RCTs; 1 pooled analysis[b]	Low (high risk of bias/many study limitations; consistent direction of effect)

Table B. Key Question 1: Benefits of treatment—summary and strength of evidence of effectiveness and comparative effectiveness of treatments for fibromyalgia in adult subgroups[a] (continued)

Population (FM Subgroup)	Intervention Vs. Placebo	Outcome: Change From Baseline	Conclusion	Number of Studies	Strength of Evidence
With MDD/ Depression (continued)	Duloxetine	FIQ total score	No evidence that treatment effects differ in subgroup	2: 1 RCT; 1 pooled analysis [b]	Low (high risk of bias/many study limitations)
	Duloxetine	HAMD	Unable to determine impact of duloxetine on HAMD in adults with MDD and FM	2: 1 RCT; 1 pooled analysis [b]	Insufficient (pooled interaction NS; RCT within stratum only)
	Milnacipran	VAS for pain	Unable to determine whether milnacipran effects on VAS pain differ in adults with MDD and FM	2: 1 RCT (NR); 1 post hoc RCT analysis	Insufficient (outcomes reporting issues: 1 indirect, 1 incomplete)
Age	Duloxetine	BPI average pain severity score	No evidence that treatment effects differ in subgroup	3 RCTs	Low (high risk of bias/many study limitations)
	Duloxetine	PGI-I	No evidence that treatment effects differ in subgroup	2 RCTs	Low (high risk of bias/many study limitations)
Sex	Duloxetine	BPI average pain severity score	Weak evidence that treatment effects may differ in subgroup (3 NS; in 1study females improved more than males))	4 RCTs	Insufficient (high risk of bias/many study limitations, inconsistent)
	Duloxetine	PGI-I	No evidence that treatment effects differ in subgroup	2 RCTs	Low (high risk of bias/many study limitations)
Race	Duloxetine	BPI average pain severity score	Weak evidence that treatment effects may differ in subgroup (2 NS; in 1 study nonwhites improved more than whites)	3 RCTs	Insufficient (high risk of bias/many study limitations, inconsistent)
	Duloxetine	PGI-I	No evidence that treatment effects differ in subgroup	2 RCTs	Low (high risk of bias/many study limitations)

[a]Table shows strength of evidence for subgroup-treatment-outcome combinations with at least 2 relevant studies. Other comparisons that had insufficient evidence (addressed by single studies that had high risk of bias and small sample sizes) are not shown.
[b]Arnold (2009)[20] pooled analysis of patient-level data from 4 RCTs is partially redundant, with 3 of 4 RCTs included in this report. Nonoverlapping outcomes information was included for the pooled analysis in this review.
Notes: BPI = Brief Pain Inventory; FIQ = Fibromyalgia Impact Questionnaire; FM = fibromyalgia; HAMD = Hamilton Rating Scale for Depression; MDD = major depressive disorder; NR = not reported; NS = not significant; PGI-I = Patient Global Impression of Improvement; RCT = randomized controlled trial; VAS = visual analog scale.

Discussion

Key Findings

Despite the clinical belief that the treatment effects for fibromyalgia may vary in adult subgroups,[20-22] there is little information to support this hypothesis. Evidence is largely insufficient to determine subgroup effects, with the exception of the drug duloxetine. We were

unable to conduct a meta-analysis because relatively few studies examined subgroups, as well as because of the variety of subgroup-treatment-outcome combinations we encountered.

Limited low-strength evidence, mostly for duloxetine effects on pain in adults with fibromyalgia and MDD, suggests that treatment effects do not differ in this subgroup. Sparse low-strength evidence suggests that duloxetine effects on global improvement (PGI-I) and fibromyalgia impact (FIQ) do not differ in the MDD patient subgroup. Evidence was insufficient regarding duloxetine effects on depression (Hamilton Rating Scale for Depression) and milnacipran effects on VAS pain scores for adults with MDD and fibromyalgia.

Low-strength limited RCT evidence for duloxetine effects by age (on BPI average pain and PGI-I), sex (on PGI-I), and race (on PGI-I) suggest that treatment effects do not differ in these subgroups.

For all other subgroup-treatment-outcome comparisons, evidence was insufficient to draw conclusions about subgroup treatment effects.

Few studies have examined subgroup treatment outcomes in fibromyalgia. We found little evidence to inform treatment decisions for adults with fibromyalgia and nondepression psychological or medical comorbidities, as these individuals were often excluded from clinical trials. Uniformly excluded were those with rheumatologic conditions, serious medical conditions, and psychological disorders other than depression or anxiety. Little information was reported on individuals over age 55, and extensive medical exclusion criteria likely impacted the participation of older individuals in clinical trials.

In general, overall treatment benefits were small, and even smaller when substantial placebo-group improvements were considered relative to treatment effects. Subgroup effects paralleled the magnitude and direction of overall treatment and placebo effects in mixed-sample studies. Reporting of overall interaction results was inconsistent across and within studies, and most interaction results were reported in text only.

The fibromyalgia subgroup outcomes evidence is overwhelmingly pharmaceutical, and drug trials were based on the most highly selective sampling criteria of all the studies we reviewed. The pharmaceutical industry was heavily involved in all study aspects, including reporting. Nonsignificant subgroup effects were often difficult to find and sometimes indeterminable within selective article text. When reported, data tables most often presented p-values for individual comparisons within strata rather than overall negative subgroup interaction results.

In general, sample selection criteria were restrictive, and the extent to which such select patient samples reflect average patients in subgroups of adults with fibromyalgia is unknown. Despite this careful patient selection, attrition by 3-month followup was high (25% to 40% in most studies; range, 4% to 47%). Dropouts were typically reported only in aggregate; the effects of attrition on initially small subgroups or treatment group sample sizes were usually indeterminable.

AEs were rarely reported for subgroups and appear not to differ within them.

Applicability and Limitations of the Evidence Base

Several important characteristics limit the generalizability and applicability of these review results.

Study patients were largely middle-aged white females with moderate to severe fibromyalgia symptoms at baseline as measured by the FIQ, which is generally representative of the fibromyalgia patient population seen in clinical practice in the United States.[77,78] Few men were included in clinical trials. Sample selection criteria were most restrictive for pharmaceutical

studies that excluded adults with mental health conditions other than depression or anxiety and those with higher medical comorbidity burden.

Subgroup outcomes evidence is mostly pharmaceutical, especially for duloxetine. Fewer studies assessed the effects of physical interventions (such as exercise or weight loss) or psychological interventions (such as CBT, psychotherapy, or biofeedback), and very few assessed combination treatments.

Most drug trials were placebo-controlled RCTs. Other comparators included standard care, standard care plus adjunctive therapy, normal activities, or education and information sessions.

Several issues affect the subgroup outcomes reported in this review. Overwhelmingly, only short-term outcomes were reported, even though long-term outcomes are of greatest interest in the management of chronic fibromyalgia syndrome. Reporting issues were particularly prominent in drug studies. Pooled analyses failed to acknowledge that unacceptably high attrition during input RCTs greatly diminished the reported amount of pooled patient data available for short-term analysis. The text on the magnitude of drug treatment effects for specific outcomes rarely acknowledged placebo-group improvements that would have better contextualized the magnitude of treatment benefits had the difference been directly reported. We noted inconsistencies within and across studies in which subgroup interaction effects were reported. Selective reporting of subgroup outcomes was often noted in results tables, where individual within-stratum comparisons were identified but the overall interaction term was either not reported or reported only in text. The effect of attrition within subgroups was missing. Therefore, we could not determine the extent to which studies could detect a difference, even if one existed. Power calculations, when reported, were conducted to detect main, not subgroup, effects. Finally, although numerous outcomes measures were used, which impeded our ability to aggregate across studies, the range of type of outcomes assessed was not particularly broad. Multiple measures for pain were used. We found that pain, perceptions of global improvement, and changes in the overall impact of fibromyalgia were most commonly reported; physical and social functioning were infrequently reported.

Given this contextual information, the extent to which the fibromyalgia subgroup literature from clinical studies to date reflects the breadth and severity of the broader population of adult subgroups with fibromyalgia is unknown. Patients with both fibromyalgia and multiple physical and/or mental health comorbidities were most often excluded, limiting the applicability of these findings.

Limitations of the Comparative Effectiveness Review Process

This review's focus on subgroups required us to modify the systematic review processes used to assess overall benefits and harms of treatments in average adults. In assessing risk of bias, we assessed typical risk-of-bias domains for RCTs and added subgroup questions that were supported by the literature, which reflected common-sense statistical practices for subgroup evaluation. We created a quality assessment form for observational studies and added similar subgroup items. We created quality assessment forms for pooled RCT IPD analyses that included quality assessments of the methods and reporting used for the summary analysis, and risk-of-bias assessments of the individual input RCTs. Although risk-of-bias/study quality assessment is inherently subjective, we tried to evaluate quality as objectively as possible using prespecified forms that were uniformly used and rated by two reviewers.

In assessing subgroup prespecification for included studies, we relied on information in each article, which may overstate the actual number of subgroups that were determined a priori in RCTs.[79]

This review was limited to English-language publications. The possibility of missing clinical trials with subgroup reporting for treatments that were FDA approved and/or available in the United States with this restriction is remote, especially for conventional medical therapies.[80-82]

We did not find evidence on all a priori subgroups. Fibromyalgia duration and especially baseline severity as assessed with the FIQ were often part of the sample selection criteria for clinical trials, thereby excluding individuals with mild symptoms or impairment and/or shorter syndrome duration. Adults with rheumatologic conditions were routinely excluded.

Research Gaps

Many of the subgroups identified by experts as clinically important were never investigated or were studied for only a few therapies. For the few studies that examined subgroups, the strength of evidence was low or insufficient, suggesting that future studies with higher quality could change the conclusions of this review.

There is a clear need for more evidence for interventions other than duloxetine, and for adults with fibromyalgia and multiple comorbid conditions. Information on patients with concurrent pain conditions is particularly lacking. Fibromyalgia patients with conditions such as headache, gastroesophageal reflux disease, irritable bowel syndrome, back pain, and/or osteoarthritis[4,57,77,83,84] may require treatment modifications or mixed treatment approaches, which could not be determined from the literature to date. Also, individuals with comorbid mental health conditions other than depression or anxiety and/or those with higher medical comorbidity burden were excluded from most clinical trials, especially drug trials. The extent to which such multimorbidity affects treatment needs, feasible treatment options, and AEs requires further investigation to provide useful treatment information on multimorbid adults. Individuals with comorbid rheumatologic and other autoimmune disorders are virtually missing from the general literature on fibromyalgia treatment outcomes and may require varied treatment approaches to successfully manage and accommodate both conditions. The use of observational methods to examine existing electronic health data (e.g., health plan, integrated health care systems) could supplement clinical trial data for individuals with fibromyalgia and other conditions.

Despite purportedly high use of multicomponent treatments for adults with fibromyalgia, few studies of multicomponent treatment reported on subgroup effects. Drug studies dominated the studies that assessed subgroup effects; far fewer studies assessed the effects of nondrug interventions that showed potential benefits.

The vast majority of studies are short term (3 months), leaving many questions about the durability of treatment effects in the management of this chronic condition. Only one study reported that short-term overall improvements were not sustained when duloxetine was taken for 6 months.[63] For clinicians, short-term studies provide very little information about how best to treat adults with fibromyalgia.

Little is reported on functional outcomes in subgroups of patients with fibromyalgia, including physical, cognitive, and social functioning. Changes in work attendance, work performance, and participation in avocational activities were rarely reported but could benefit the evidence base.

Potential differences in AEs in adult subgroups warrant more attention. Although most treatment harms were not serious, potentially differential effects in subgroups were reported in only one pooled IPD RCT analysis.

Study reporting needs improvement to make research information usable for clinicians, particularly in drug studies. Transparently reported, sufficiently powered clinical studies with a priori subgroup and hypothesis specifications were lacking, making subgroup treatment effect conclusions tenuous and limited. Efforts to reduce knowledge gaps from research involving fibromyalgia adult subgroups should aim to present findings that are clear and concise for clinicians to interpret. Reporting of the impact of very high attrition on the strength of study conclusions is critical but is currently inadequate. Placebo effects, which are prominent in this patient population, should be openly reported to enable clinicians and readers to better assess the magnitude of treatment effects.

Conclusions

The fibromyalgia evidence is largely insufficient to determine subgroup effects for interventions other than duloxetine. The limitations of the primary literature preclude any change of policy or practice based on these findings.

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Introduction

Background

Fibromyalgia is a chronic, diffuse musculoskeletal pain syndrome that has no clearly identified etiology.[1-4] It affects mostly adults[5] and is characterized by chronic widespread pain, abnormal processing of and heightened sensitivity to pain, chronic fatigue, sleep disorders, and emotional distress or depression.[5,6] Fibromyalgia reduces quality of life and productivity and is associated with functional disability, lost work time, and increased use of health care services.[5,7-9] Based on diagnostic criteria developed in 1990 by the American College of Rheumatology (ACR), fibromyalgia affects more than 5 million Americans,[10] most of whom are middle-aged women; men are less likely to be diagnosed with fibromyalgia even if they meet diagnostic criteria (3.4% women vs. 0.5% men).[1,10,11]

Although fibromyalgia can occur in children, diagnosis is typically made in middle age, and prevalence increases with age until age 65, then declines in women.[5,12]

Diagnosis

The diagnostic criteria for fibromyalgia have evolved[13,14] since the first publication by the ACR in 1990. The original criteria included palpation of myofascial "tender points" during physical examination and the presence of widespread pain for at least 3 months.[15] In 2010 the ACR eliminated the tender point examination and added (1) physician-rated severity in two scales, the Widespread Pain Index and the Symptom Severity Scale, and (2) a requirement of symptoms for at least 3 months and the absence of another disorder that would account for the symptoms.[13,16] A survey version of the 2010 ACR criteria was also released for research purposes in 2011; it replaced physician estimates of somatic symptom severity with a patient-generated summary score derived from three self-reported symptom domains.[14] Compared with the 1990 criteria, the 2010 ACR preliminary diagnostic criteria capture a broader population of fibromyalgia patients, which affects prevalence estimates and patient heterogeneity in more recent studies.[16-18] Alternative diagnostic criteria are under consideration.[19]

Treatment Strategies

Treatments for fibromyalgia syndrome include drugs and nonpharmacologic therapies to help mitigate symptoms and improve function.[5] Treatment goals are to mitigate diffuse musculoskeletal pain, maximize physical and cognitive function, optimize patient self-management and self-efficacy, and manage comorbid medical and psychiatric disorders. Treatment components may include pharmaceutical therapy, exercise programs, cognitive behavioral therapy, patient education (self-management, sleep hygiene, importance of exercise, etc.), and the treatment of comorbid medical and mental health conditions.[5,20] Complementary and alternative medicine (CAM) approaches such as acupuncture and massage are also common.[20,21] Large-scale fibromyalgia clinics typically use multimodal treatment approaches, although many patients still receive uncoordinated care by seeking treatment from individual health care providers across multiple clinical settings.

Pharmacologic Treatments

Pharmacologic interventions include both Food and Drug Administration (FDA) approved medications specifically for the treatment of fibromyalgia and other FDA approved drugs not specifically approved for the management of fibromyalgia symptoms in the United States.

FDA-Approved Drugs for Fibromyalgia

Three oral medications have been FDA approved for fibromyalgia since 2007: duloxetine and milnacipran (serotonin-norepinephrine reuptake inhibitors [SNRIs]) and pregabalin (a gamma-aminobutyric acid agonist).

Pregabalin was the first FDA approved medication for fibromyalgia. Antiepileptic drugs, such as pregabalin, are commonly used to treat neuropathic pain.[22] Although its exact mechanism of action is unknown, pregabalin acts on neurons and results in analgesic, anxiolytic, and antiepileptic effects in animal studies.[22]

Newer SNRIs, such as duloxetine and milnacipran, differ from selective serotonin reuptake inhibitors (SSRIs) because of their reuptake inhibition of both norepinephrine and serotonin neurotransmitters.[23] SNRIs were designed to have superior efficacy in treating depression than SSRIs, and with fewer side effects than tricyclic antidepressants,[22] but evidence for this claim is not persuasive.[24] Duloxetine was the first SNRI that demonstrated efficacy for reducing pain in patients with fibromyalgia, although the exact mechanism of action on the perception of pain is unknown. Milnacipran was approved after demonstrating efficacy in concurrent improvements in pain, physical function, and global impression of disease. Additional information about these medications is listed in Table 1.

Table 1. FDA-approved drugs for the treatment of fibromyalgia

Trade Name	Generic Name	Manufacturer	Therapeutic Drug Class	Drug Subclass	Year FDA Approved
Lyrica	Pregabalin	Pfizer Inc.	Antiepileptics	Gamma-aminobutyric acid agonist	2007
Cymbalta	Duloxetine HCL	Eli Lilly and Co.	Antidepressants	SNRI	2008
Savella	Milnacipran	Forest Labs/Cypress Bioscience, Inc.	Antidepressants	SNRI	2009

Abbreviation: SNRI = serotonin and norepinephrine reuptake inhibitors.

Off-Label Use of FDA-Approved Drugs

Numerous drugs that are approved for other conditions are currently used off-label in patients with fibromyalgia, such as antidepressants, analgesics, opioid analgesics, anti-inflammatories, and skeletal muscle relaxants. A table of pharmacologic agents that are used off-label for the treatment of fibromyalgia in the United States is in Appendix A.

Nonpharmacologic Treatments for Fibromyalgia

A wide array of nondrug treatments is used to manage pain and other symptoms associated with fibromyalgia, often in combination. Treatment goals are to reduce pain, improve physical function and endurance, and foster self-efficacy in fibromyalgia management, both short and long-term. Common therapies are listed in Table 2.

Table 2. Nonpharmacologic treatments for fibromyalgia

Type	Category	Examples
Psychological	Cognitive behavioral therapy	Cognitive behavioral therapy sessions
	Other cognitive	Mindfulness training
Physical	Passive	Massage therapy, acupuncture, chiropractic; modalities (such as ultrasound, heat, electrical muscle stimulation, etc.); other (such as magnets)
	Active	Supervised or independent exercise (such as aerobic, strength training, stretching, water/pool-based, yoga)
	Multimodal physical	Combinations of active and/or passive physical interventions
Multicomponent	Various	Combinations of multiple intervention categories (such as pharmacologic + psychological + physical interventions simultaneously or in coordination)
Lifestyle modifications	Independent or with education, advice or support	Weight loss, dietary changes (such as vegetarian or gluten-free), smoking cessation, sleep habit improvement, etc.
Other therapies	Mind-body therapies	Meditation, hypnosis, tai chi, visualization
	Nutraceuticals	S-adenosyl-methionine (SAMe), coenzyme Q10, omega-3 fatty acids, algae
	Other	Transcranial direct current stimulation

Abbreviation: SAMe = S-adenosyl-methionine

Rationale for Review

Many clinical trials suggest a modest benefit from treatments for a general population of fibromyalgia patients.[1,20] Although clinicians believe that treatment effectiveness may vary in subgroups,[25-27] less is known about the efficacy and comparative effectiveness of these treatments for subgroups of adults (defined by number and type of coexisting syndromes or conditions, severity of pain or impairment at baseline,[13] presence of a mood or other mental health disorder, primary complaint at baseline, or demographic or other related factors). Understanding subgroup treatment effects might help to inform clinical decisions. For example, moderate to severe depression affects 20 to 40 percent of fibromyalgia patients in clinical trials,[3,27-29] and approximately 10 percent have anxiety disorders.[30]

This systematic review provides information for both patients and providers on treatment outcomes in fibromyalgia subgroups; such patients typically present with multiple, chronic symptoms and/or conditions and pose significant treatment dilemmas for providers.

Selection of Patient Subgroups

Certain subgroups of patients have a higher prevalence of fibromyalgia, are more clinically complex or challenging to treat, and/or have historically unsatisfactory treatment outcomes.[10,31] The patient subgroups were chosen a priori from the literature and with input from experts and other stakeholders, including: women,[32-36] older[37,38] or obese[39] adults, individuals with coexisting mental health conditions,[5,10,29,40,41] those with high severity[41-44] or longer fibromyalgia duration,[45] multiple medical comorbidities,[5,45,46] or other chronic pain conditions.[5,10,20,29,47]

- Women: Population-based prevalence estimates of fibromyalgia in women are two to seven times higher than those of males.[11,48] Women comprise the majority of fibromyalgia patients seen in clinical practice[49] and many studies were conducted exclusively in women. Women with fibromyalgia tend to have higher tender point counts, lower pain thresholds (per dolorimeter), and report more fibromyalgia symptoms (such as all-over pain, sleep disturbance, fatigue, and irritable bowel syndrome) than men.[50] Recent studies also identified differences by sex in depression, somatic symptoms, modes

of treatment used, and patterns of health care service use.[32-36] More information is needed about how outcomes differ between men and women for the same modes and intensities of treatment and which treatment modes best benefit men or women.

- Individuals with coexisting mental health conditions: Coexisting mental health disorders are particularly common in fibromyalgia patients, especially depression and/or anxiety (which occurs in more than one-third of fibromyalgia patients) and substance abuse.[5,10,29,40] Traumatic or stressful events and post-traumatic stress disorder may trigger or exacerbate fibromyalgia.[5,51] Simultaneous treatment of co-occurring mental health disorders has been advised, especially in severe cases.[41]
- Individuals with high fibromyalgia symptom severity (Fibromyalgia Impact Questionnaire (FIQ) 59-100):[42] Patients with high FIQ scores report greater functional limitations, higher overall impairment, and more severe symptoms; typical treatments may be less effective[43] or not feasible and may require adaptation to severity.[41,44] These highly-affected individuals present special treatment and management challenges for providers.
- Older adults: Older adults may have higher comorbidity burden, functional limitations, or altered renal clearance that require treatment modifications compared with middle-aged adults. More frequent and more severe medical comorbidities in older adults may increase the likelihood of adverse effects, drug interactions, and altered drug tolerance from pharmaceutical therapies for fibromyalgia, increasing the risk for falls, fractures, and other injuries from standard treatments. Recent information shows less impact of fibromyalgia on health-related quality of life (HRQoL) in older women[37] and less fibromyalgia symptomatology in older adults compared with middle-age adults.[38] However, feasible modes of treatment and outcomes may vary in this subgroup.
- Obese adults: Obese adults with fibromyalgia report greater fibromyalgia symptoms (pain, stiffness, depression) and poorer physical function[39] and may have differential treatment responses compared with nonobese adults with fibromyalgia.[52,53] High rates of obesity (45 percent) and overweight (27 percent) are reported in patients with fibromyalgia, and severe obesity is particularly associated with greater fibromyalgia symptoms and lower quality of life.[39]
- Individuals with multiple medical comorbidities:[45]
  - Concurrent rheumatic disease: rheumatoid arthritis (RA), lupus (SLE), ankylosing spondylitis (AS), etc., including osteoarthritis (OA). At least one-third of patients with rheumatic conditions also have fibromyalgia.[5,46]
  - Other comorbidities
- Persons with other significant chronic pain conditions: The presence of other somatic syndromes with fibromyalgia complicates treatment and compromises outcomes.[47]
  - Migraine or tension headaches affect up to than half of patients.[5,10,29]
  - Somatic syndromes (e.g., irritable bowel syndrome, chronic fatigue syndrome, temporomandibular joint dysfunction, low back pain, and others) are associated with fibromyalgia.[5,20]
- Individuals with longer duration of fibromyalgia symptoms: Longer duration of symptoms is associated with poorer outcomes. Initial assessment values are predictive of longer-term outcomes in fibromyalgia patients seen in rheumatology centers.[45]

Scope and Key Questions

Scope of the Review

This systematic review examined whether specific subgroups would benefit from being treated differently from the general fibromyalgia patient population.

Unlike most systematic reviews that compare average treatment effects for average patients with a specific condition, the goal of this report is to provide summary information on the evidence to date to support patient and provider treatment choices when comorbid or complex clinical situations are present in adults with fibromyalgia. The subgroups, chosen a priori, reflect medically and/or psychologically complex patients or those who reported greater impairment or less responsiveness to treatments. Additional subgroups were included as found in the literature.

We limited this systematic review to subgroup treatment effects because McMaster University in Canada is currently conducting a comprehensive systematic review of randomized controlled trials (RCTs) on interventions for fibromyalgia in adults.[54] Our systematic review complements the McMaster work by examining outcomes in fibromyalgia patient subgroups and by including observational literature.

Because fibromyalgia is largely a chronic condition in adults, we limited our analysis to studies of individuals age 18 or older that compared treatments for fibromyalgia in subgroups of adults and reported outcomes at least 3 months after treatment initiation.

Key Questions

The following two Key Questions were the focus of this systematic review:

Key Question 1 (KQ 1). What are the efficacy and comparative effectiveness of treatments for fibromyalgia in specific adult subpopulations?

- Women
- Individuals with coexisting mental health conditions
- Individuals with high fibromyalgia symptom severity (FIQ 59-100)
- Older adults
- Obese adults
- Persons with multiple medical comorbidities
  - Concurrent rheumatic disease: rheumatoid arthritis (RA), lupus (SLE), ankylosing spondylitis (AS) etc., including osteoarthritis (OA)
  - Other comorbidities
- Individuals with other significant chronic pain conditions (low back pain, headache, irritable bowel syndrome (IBS), etc.)
- Individuals with longer duration of fibromyalgia symptoms

Key Question 2 (KQ 2). What are the harms of treatments for fibromyalgia in specific adult subpopulations?

- Women
- Individuals with coexisting mental health conditions
- Individuals with high fibromyalgia symptom severity (FIQ 59-100)

- Older adults
- Obese adults
- Individuals with multiple medical comorbidities
  - Concurrent rheumatic disease: rheumatoid arthritis (RA), lupus (SLE), ankylosing spondylitis (AS) etc., including osteoarthritis (OA)
  - Other comorbidities
- Individuals with other significant chronic pain conditions (low back pain, headache, irritable bowel syndrome (IBS), etc.)
- Individuals with longer duration of fibromyalgia symptoms

Components of the PICOTS framework to answer the Key Questions on fibromyalgia for this review are described in Table 3.

Table 3. PICOTS framework

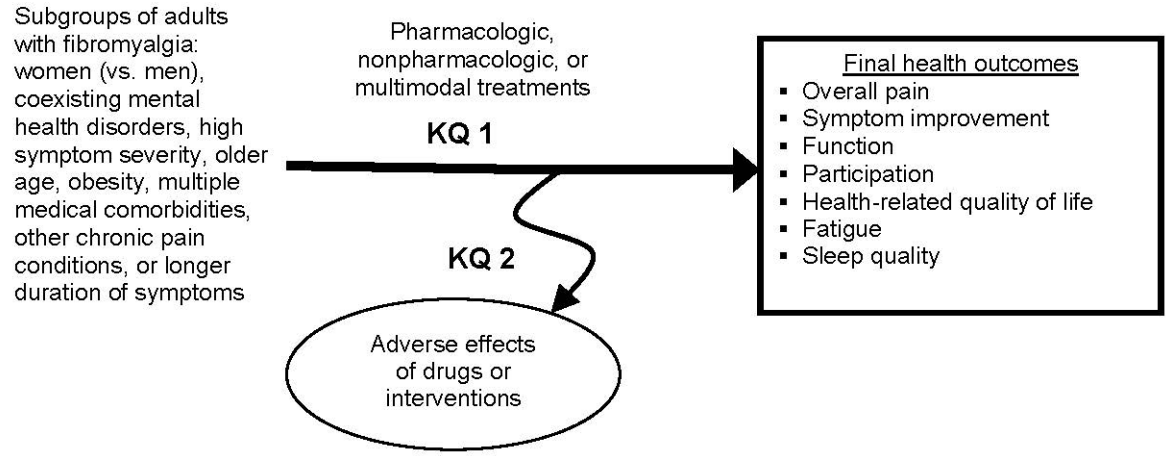
PICOTS Element	Inclusion Criteria
Population	Adults (age 18 and older) with fibromyalgia in studies that tested the effectiveness of treatments for fibromyalgia and reported outcomes in at least one of the adult subgroups of interest: sex differences, patients with high symptom severity (e.g., Fibromyalgia Impact Questionnaire (FIQ) scores ≥59 (severe) or severe on a related scale); patients with coexisting mental health disorders; older adults (age 65 or older), obese adults (body mass index [BMI] of 30 or higher or similar classification), patients with multiple medical comorbidities (rheumatic diseases/osteoarthritis, other), with other chronic pain conditions, or patients with longer duration of fibromyalgia symptoms (such as 1 year or more). Patients met either the 1990[15] or 2010[13] revised fibromyalgia diagnostic criteria from the American College of Rheumatology (ACR), or the Yunus criteria for fibrositis[55] for studies published from 1985-1990. Additional subgroups were included as found in the literature.
Interventions	Pharmacologic treatments that are or were FDA approved for use in the U.S. for fibromyalgia or other conditions (off-label use for fibromyalgia) were included. Nonpharmacologic interventions that are or were available for use in the U.S. were included.
Comparators	Placebo, sham, alternate dose or dosing regimen, or any active pharmacologic or nonpharmacologic treatment available for use in the U.S.
Outcomes	**KQ 1:** Change from baseline in any measures used to assess the status in fibromyalgia patients regarding: - Overall pain (such as a Visual Analog Scale [VAS],[56] Brief Pain Inventory,[57] or the McGill Pain Questionnaire[58]) - Symptom improvement (such as the Fibromyalgia Impact Questionnaire [FIQ],[59] Revised FIQ [FIQR],[60] Patient Global Impression of Change [PGI-C],[61] or Patient Global Impression of Improvement [PGI-I][61]) - Physical and/or emotional function (such as the FIQ, FIQR subscales) - Participation in work or social activities (such as the FIQ, FIQR subscales[42,62]) - Health-related quality of life [HRQoL] (such as the SF-36[63]) - Fatigue (such as the Multidimensional Assessment of Fatigue [MAF][64]) - Sleep quality (such as the Medical Outcomes Study [MOS] Sleep Scale[65]) **KQ 2:** Adverse effects or harms of intervention(s) - Drug-related side effects (such as dizziness, nausea, fatigue, dry mouth, weight gain, difficulty concentrating, hypertension, thoughts of suicide, peripheral edema, anxiety, tachycardia, constipation, etc.) - Adverse effects from nonpharmaceutical treatments (such as muscle aches, minor injuries or falls during or after exercise; soreness or aches from passive physical treatments such as massage, etc.)
Timing	A minimum of 3 months followup on interventions of any length. Since fibromyalgia is a chronic condition, outcomes improvements over time are more salient to patients and providers than temporary treatment effects.
Setting	Any outpatient setting

Abbreviations: ACR=American College of Rheumatology; BMI=body mass index; FIQ=Fibromyalgia Impact Questionnaire; FIQR=Revised Fibromyalgia Impact Questionnaire; HRQoL=health-related quality of life; MAF=Multidimensional Assessment of Fatigue; MOS=Medical Outcomes Study; PGI-C=Patient Global Impression of Change; PGI-I=Patient Global Impression of Improvement; VAS=Visual Analog Scale.

Analytic Framework

Figure 1 depicts the two Key Questions within the context of the PICOTS described in Table 3. The figure illustrates how the use of pharmacologic, nonpharmacologic, or multimodal treatments for fibromyalgia may improve outcomes for adults with fibromyalgia. The patients for this study are subgroups of individuals with fibromyalgia who are identified by at least one of the following characteristics: sex, coexisting mental health disorders, high symptom severity, older age, obesity, multiple medical comorbidities, other chronic pain conditions, or longer duration of fibromyalgia symptoms. The Key Question 1 outcome categories include overall pain, symptom improvement, function, participation (work or social), health-related quality of life (HRQoL), fatigue, and sleep quality. Adverse effects of drugs or interventions may also occur at any point after the treatment is initiated; these will be examined in Key Question 2.

Figure 1. Analytic framework for treatments for fibromyalgia in adult subgroups



Note: KQ = Key Question

Methods

We followed the methods suggested in the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" for this comparative effectiveness review (CER) follow (available at wwweffectivehealthcare.ahrq.gov/methodsguide.cfm). The main sections below reflect the elements of the protocol established for this CER; certain methods map to the PRISMA checklist.

Topic Refinement and Review Protocol

The topic of this report and preliminary Key Questions arose through a public process that involved a topic nomination by a consumer, followed by refinement of the research questions with input from various stakeholder groups, including professionals from the disciplines of rheumatology, psychology, psychiatry, physical therapy, nursing, gerontology, chiropractic, and outcomes research. We used a preliminary literature scan and expert input to determine which subgroups to address a priori in this review.

The draft Key Questions were posted for public comment on AHRQ's Effective Health Care website from October 25, 2013, through November 14, 2013. Based on that feedback, minor revisions were made to the analytic framework (added symptom improvement as a final outcome, deleted intermediate outcomes as not salient to this topic), and PICOTS (limited treatment to noninpatient settings). We then drafted a protocol for the review and recruited a panel of technical experts to provide high-level content and methodological expertise during the development of the review. The Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts. Any potential conflicts of interest were balanced or mitigated. Neither Key Informants nor members of the TEP performed analysis of any kind, nor did any of them contribute to the writing of this report. Members of the TEP were invited to provide feedback on an initial draft of the review protocol which was then refined based on their input, reviewed by AHRQ, and posted for public access on the AHRQ Effective Health Care Website.

Literature Search Strategies

We searched Ovid MEDLINE®, Embase®, Ovid PsycINFO®, AMED (Allied and Complementary Medicine) and the Cochrane Central Register of Controlled Trials (CENTRAL) bibliographic databases to identify randomized controlled trials, systematic reviews, and observational studies with control groups published from 1985 to August 2014 on treatments for adults with fibromyalgia. CINAHL was excluded from our search; it was unlikely to provide additional subgroup studies beyond the five databases we searched.[66,67]

Our search strategies are included in Appendix B. An experienced librarian in the Minnesota EPC developed the MEDLINE search strategy; we modified the search for other databases. The search strategy used relevant Medical Subject Headings (MeSH®) and natural language terms to identify two fibromyalgia concepts: (1) fibromyalgia, fibrositis and myofascial pain syndrome, and (2) specific filters to identify study designs. We supplemented bibliographic database searches with backward citation searches of highly relevant systematic reviews.

Inclusion and Exclusion Criteria

Included

Since fibromyalgia is a chronic condition in adults, we limited our analysis to studies of individuals age 18 or older that compared treatments for fibromyalgia in subgroups of adults who were followed 3 months or longer after treatment initiation. We included randomized controlled trials (RCTs), pooled analyses of individual patient-level RCT data, and observational studies that examined one or more treatments for fibromyalgia in adults, utilized a comparator group, and reported treatment outcomes in at least one subgroup 12 or more weeks after the initiation of treatment. RCTs of mixed samples (not pure subgroups) provided direct outcome comparisons. Pure subgroup populations (the study was designed to sample from the subgroup) were also included for indirect evidence. We included clinical studies that were published from 1985 to August 2014 in the English language. The possibility that non-English language studies would have tested treatments that were FDA approved or used in the United States, and reported on subgroups is remote.[68-70]

Excluded

We excluded studies: of drugs not FDA approved in the United States for any condition; that included patients with different health conditions and did not separately report baseline and outcomes in fibromyalgia patients; that did not use established fibromyalgia diagnostic criteria for subject selection (American College of Rheumatology [ACR][13-15] or Yunus[55] criteria for fibrositis from 1985–1990); or pharmacologic RCTs where patients were unblinded to treatment for any part of the study. Studies that did not examine patient-important outcomes (such as brain imaging or lab studies) were excluded. For drug trials, we excluded randomized controlled trials where patients were unblinded to treatment for any part of the clinical study or followup or where the blinding status of patients to treatment was unclear or conflicted in the article text.

Study Selection

Two independent investigators reviewed titles and abstracts that resulted from the bibliographic database searches to identify studies that examined interventions for fibromyalgia in adults. Citations deemed as potentially eligible by either investigator underwent full text screening for possible subgroup reporting. Study selection involved an extensive full text review process to identify adult subgroups, since subgroup reporting was usually not evident in titles and abstracts. Full text articles were initially reviewed to identify outcomes reporting for at least one adult subgroup. Differences in screening decisions were resolved through discussions; when needed, a third investigator was consulted until consensus was achieved.

We conducted additional grey literature searches to identify relevant completed and ongoing clinical studies. Grey literature search results were also used to identify studies, outcomes, and analyses not reported in the published literature. We searched ClinicalTrials.gov and the International Controlled Trials Registry Platform (ICTRP) for studies that specified a fibromyalgia subgroup analysis in their study protocol. We also reviewed Scientific Information Packets sent by manufacturers to AHRQ for recent information on relevant pharmaceuticals and other interventions.

Data Extraction

One investigator trained in research methodology extracted relevant study, population, risk of bias, and outcomes data. Initial data abstraction was quality checked by a second trained investigator. Data fields were determined based upon the proposed summary analysis. These fields included author, year of publication, setting, fibromyalgia diagnostic and severity criteria used, subject inclusion and exclusion criteria, subgroup, intervention(s), allowed and disallowed co-interventions, control characteristics (intervention delivery, timing, frequency, duration), treatment and followup duration, participant baseline demographics, comorbidities, descriptions and results of primary outcomes and adverse effects, results of treatment-by-subgroup interactions, within-stratum primary outcomes when subgroup interaction results were lacking for a given comparison, and study funding source. Data were entered into Excel spreadsheets by one trained investigator and checked for accuracy by a second.

For pooled RCT analyses of drug trial data, we examined the pooled study and the input RCTs that comprised the pooled sample to assure nonoverlap of our subsequent reporting of subgroup-treatment-outcomes in this review.

Quality (Risk-of-Bias) Assessment of Individual Studies

The risk of bias of eligible studies was assessed by two independent investigators using instruments specific to each study design (Appendix C). The two investigators consulted to reconcile any discrepancies in overall risk of bias assessments and, when needed, a third investigator was consulted to reconcile the summary judgment.

For RCTs, we assessed the risk of bias using a modified Cochrane Risk of Bias tool.[71] The seven domains of the tool are sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias (i.e., problems not covered by other domains). We also evaluated potential risk of bias associated with treatment definition. We included additional items to assess the credibility of subgroup analyses of individual RCTs with mixed patient samples based on Sun et al.[72] These guidelines were: if the subgroup variable was measured at baseline, if the subgroup hypothesis was a priori, if the study included only a small number of subgroup hypotheses, if the interaction test suggests a low likelihood of chance explanation, among other contextual issues.[72]

Overall summary risk of bias assessments for each study were classified as low, moderate, or high based upon the collective risk of bias inherent in each domain and confidence that the results are believable given the study's limitations.[71] A consolidating algorithm was not used. Elements that contributed to a low risk of bias assessment included whether a study used a random sequence generation, concealed allocation of treatment assignments, blinded outcomes assessors, demonstrated treatment fidelity, had minimal to modest missing outcomes data or balanced missing data across groups with similar reasons for missing data, and credible subgroup analysis methods.[71] High risk of bias elements include nonrandom sequence generation, lack of blinding of outcomes assessors when the outcome was likely to be affected by the lack of blinding, or high and/or differential losses to followup across treatment groups when missing outcomes data may have been related to real outcomes. Moderate risk of bias was assigned to studies that were challenged across several of the domains but the study was blinded or, if blinding was not possible, outcome assessors were blinded to treatment assignment. The

potential for placebo effects in fibromyalgia treatments is high, thus special weight was given to the blinding domain.

We developed an instrument to assess risk of bias for observational studies using the RTI Observational Studies Risk of Bias and Precision Item Bank[73] because concerns about selection bias and blinding make the use of observational studies debatable in comparative effectiveness reviews. We selected items most relevant in assessing risk of bias from observational studies of fibromyalgia and to foster consistency with the risk of bias instrument for randomized controlled trials[71] Bias issues common to observational studies involve the nonrandom selection of subjects, the completeness and validity of the recording of baseline patient information, attrition, and the ascertainment of outcomes. Items included from the RTI Item Bank addressed participant selection, group membership, efforts to address selection bias, identification of baseline effect modifiers and confounders, and appropriateness of analytic methods for observational studies. We classified the overall summary risk of bias assessments for each individual study as low, moderate, or high based on the collective risk of bias inherent in each outcome domain and confidence that the results are believable given the study's limitations. Similar to risk of bias for RCTs, the overall summary risk of bias was weighted towards low for studies that demonstrated comparability across groups. Moderate risk of bias would have been assigned to large cohort studies with a sample size for adequate power to detect differences, moderate to large effect sizes, and strong evidence of attempting to control for plausible confounders.

We paid special attention to risk of bias assessment for observational studies that pooled patient-level data from randomized controlled trials. Risk of bias of pooled analyses depended in part on the risk of bias of the inputs (RCTs) and the risk of bias in how the pooled analysis was conducted and reported. The risk of bias of the individual RCTs that comprise each pooled analysis was assessed per the Cochrane tool as described above.[71,72] The additional risk of bias in how the pooled analysis was conducted was assessed using the critical appraisal by Fisher et al.[74] of the principal methods for pooling individual-level RCT data to determine treatment-covariate interactions in the literature. Only within-trial patient-level interactions were considered as across-trial information has a higher risk of bias.[74]

The risk of bias and quality assessment forms are included in Appendix C.

Data Synthesis

We summarized the results into evidence tables and qualitatively synthesized evidence by the type of study (RCT, observational, pooled individual patient data [IPD] RCT analyses) for each unique population, comparison, and outcome combination within specific followup time periods. Because of the high probability of placebo effects in fibromyalgia treatments, if subgroup analysis was available through an RCT or pooled RCT literature for a given subgroup-treatment-outcome comparison, the observational literature was not included in the analytic set for that comparison. Studies were grouped by study design, intervention category and then subgroup.

We summarized patient-centered subgroup outcomes comparisons[72] for pain, global improvement, function, fatigue, and quality of life. Pooling was planned for measures that assessed the same outcome and had comparable scoring characteristics (such as the FIQ[59] and FIQR[60] tools). However, quantitative meta-analysis with pooling of data was not possible due to differences in subgroup-treatment-outcome combinations.

Wherever possible, we report data and/or interaction results that assessed whether treatment effects varied in subgroups. If interaction results were not reported and data were presented for within-stratum results (such as stratum-specific change from baseline in pain in those with MDD

(treated vs. control) and for those without MDD (treated vs. control), we identify and report within-stratum information.

When available in the literature, we identified minimal clinically important outcomes differences for measures specific to fibromyalgia patients. Additionally, when subgroup data were provided, we calculated the difference in mean change from baseline between treated and control groups by subgroup strata as a general measure of magnitude of the treatment effect relative to the placebo (control) group.

Strength of the Body of Evidence

We evaluated the overall strength of evidence for select clinical outcomes within each comparison based on four domains: (1) study limitations (internal validity); (2) directness (single, direct link between the intervention and outcome); (3) consistency (similarity of effect direction and size); and (4) precision (degree of certainty around an estimate), with the study limitations domain having considerable importance.[75] Study limitations were rated as low, moderate, or high according to study design and conduct. Consistency was rated as consistent, inconsistent, or unknown/not applicable (e.g., single study), based on direction and magnitude of effect. Directness was rated as either direct or indirect based on outcome and study design. Precision was rated as precise or imprecise based on the number of patients needed for an evidence base to be adequately powered. We required the existence of at least two studies (which could be high risk of bias) to assign low rather than insufficient strength of evidence. We required at least one low risk of bias study for moderate strength of evidence and two low risk of bias studies for high strength of evidence. In addition, to be considered moderate or higher, intervention-outcome pairs need a positive response on two out of the three domains other than risk of bias. Based on these factors, the possible SOE grades were:[75]

- **High.** Very confident that the estimate of effect lies close to the true effect. Few or no deficiencies in body of evidence; findings believed to be stable.
- **Moderate.** Moderately confident that the estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings likely to be stable but some doubt.
- **Low.** Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence necessary before concluding that findings are stable or that estimate of effect is close to true effect.
- **Insufficient.** No evidence, unable to estimate and effect, or no confidence in estimate of effect. No evidence is available or the body of evidence precludes judgment.

Applicability

Applicability of studies was determined according to the PICOTS (populations, interventions, comparators, outcomes, timing, settings) framework. Study characteristics that could affect applicability include, but are not limited to, changes in the diagnostic criteria over time (1990 vs. 2010), narrow inclusion criteria, or patient and intervention characteristics different than those described by population studies of fibromyalgia treatments. Importantly, adults in clinical trials of fibromyalgia treatments may be higher functioning, less impaired, and have fewer or less severe concomitant medical or mental health conditions than the fibromyalgia patient population as a whole, which impacts the generalizability of clinical trial results to the broader fibromyalgia population.

Results

Organization of Results

The Results are broadly organized by the Key Questions. The Key Questions are further subdivided by class of treatment (pharmacologic, physical, psychological, or mixed) and within that, by subgroups. We first examine the effects of drugs on various subgroups and then address the effects of other treatments. Within each class of treatment, subgroup/intervention/outcome comparisons with at least low strength of evidence are provided first. Brief details for the subgroups with insufficient evidence are provided second.

A complete list of abbreviations and acronyms can be found at the end of this report.

Type and Labeling of Included Studies

We included several types of studies. RCTs with mixed patient samples refer to studies that identified a patient subgroup after randomization (such as adults with fibromyalgia, a proportion of whom had depression). RCTs that selected within particular subgroups (such as postmenopausal women) comprised another group of included studies; we refer to these as pure subgroup RCTs. A third type of study was a pooled analysis of individual patient data from several RCTs to report subgroup outcomes. We refer to these as pooled analyses of individual patient data (IPD) from RCTs, or pooled IPD RCT analyses, which were pooled within-study comparisons. All such studies investigated drug interventions. Finally, observational studies with comparator groups were included.

Results of Literature Searches

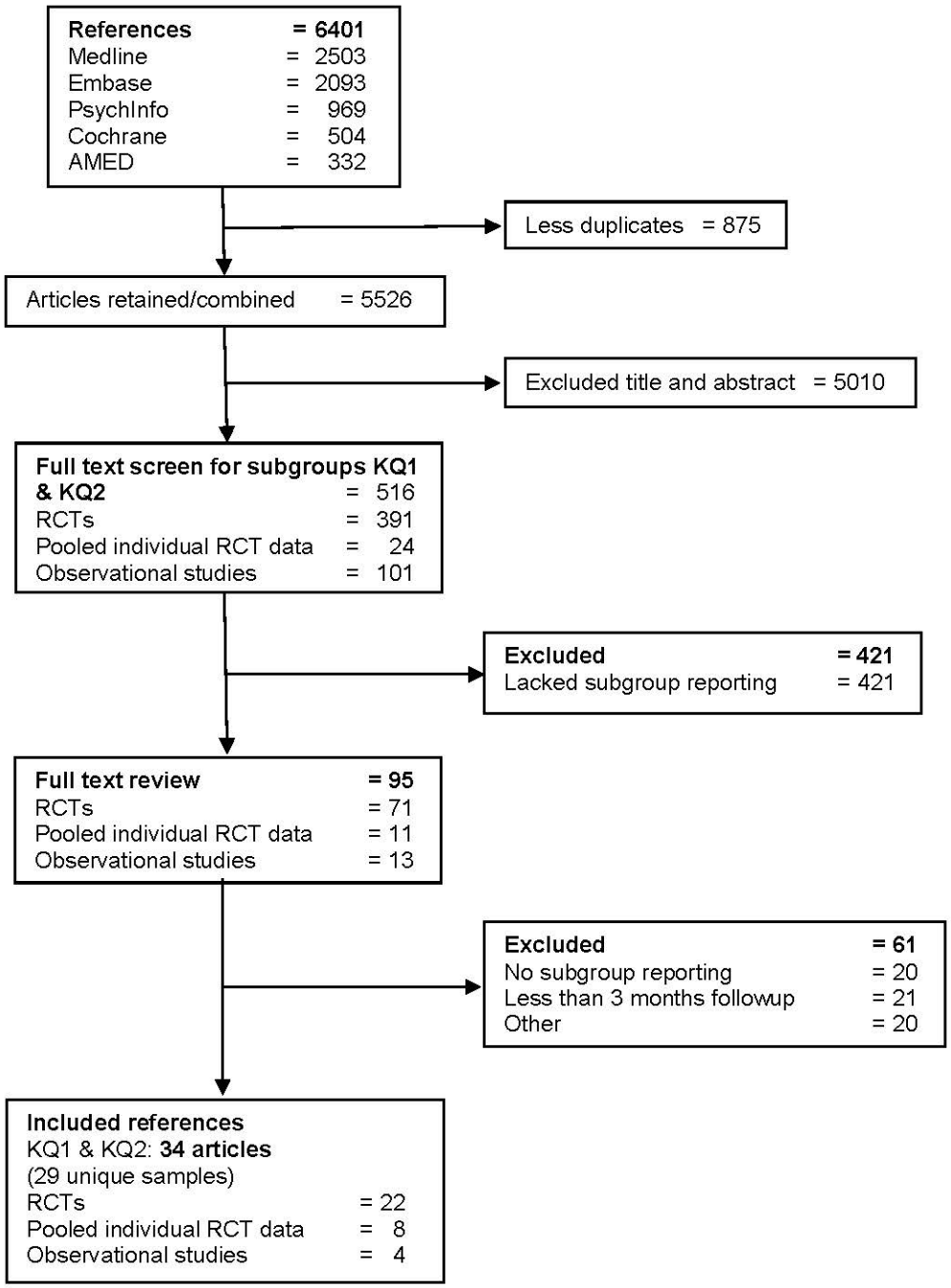
We identified 6401 citations from all databases combined. We examined the full text of 516 articles (391 RCTs, 24 pooled analyses of patient-level RCT data, and 101 observational studies) to assess for subgroup reporting. Of those, 34 studies were included in the analysis (Table 4 and Figure 2): 22 RCTs, eight analyses that pooled IPD from RCTs,[25,26,29,76-80] and four observational studies.[81-84] The two types of RCTs included ten studies with mixed patient samples[3,4,27,28,30,85-89] and 12 RCTs of pure subgroup samples.[52,53,90-99] Of the 22 RCTs, ten were placebo-controlled trials (eight mixed samples and two pure subgroup RCTs). Twenty studies were drug trials (59 percent). All included studies were published in 2001 or later, with the eight pooled IPD RCT analyses all published since 2009. Appendix D contains a list of studies that were excluded after the initial full text screen for subgroup reporting, with rationale for exclusion.

Table 4. Included fibromyalgia subgroup studies, by study design

Study Design	Count
Randomized controlled trials	10
Randomized controlled trials of pure subgroups	12
Pooled analyses of individual patient data from randomized controlled trials	8
Observational studies	4
Total of included studies for report	**34**

Figure 2 shows the QUORUM diagram for the study selection process beginning with the total number of citations retrieved from the literature searches and ending with the number of studies that satisfied the inclusion criteria for this report. Of the 516 references that underwent initial full-text screening, the majority were excluded for lack of subgroup outcomes reporting.

Figure 2. Disposition of fibromyalgia studies identified for this review



Abbreviations: AMED = Allied and Complementary Medicine Database; KQ1 = Key Question 1; KQ2 = Key Question 2; RCT = randomized controlled trial

Key Question 1. Treatment Effectiveness in Fibromyalgia Subgroups

Overview

Table 5 provides a basic map of the included studies to assess treatment effectiveness in fibromyalgia subgroups. It is readily apparent that little evidence is available for any given treatment-subgroup-outcome combination regarding potential differential treatment effects in subgroups of adults with fibromyalgia. With the exception of studies on duloxetine, there are few areas where more than one study has examined a treatment-outcome combination for a given subgroup. Persons with depression have been most commonly studied. Pain was the most frequently studied outcome, followed by the measure of Patient Global Impression Improvement (PGI-I).

Sample selection criteria were highly selective, particularly in drug trials. Study specific selection criteria are shown in Appendix Tables E1-E3. Thirty-three of 34 included studies (97 percent) used the 1990 ACR preliminary diagnostic criteria for fibromyalgia; one study did not specify the fibromyalgia diagnostic criteria used.

Basic study information for all included studies is provided in Appendix Tables E4-E7.

Given the sparse evidence for specific treatment-subgroup-outcome combinations, we were unable to conduct meta-analyses (Appendix Tables E8 and E9). Instead, we present subgroup results in tables in the few instances where data for subgroup outcomes were reported (two RCTs[3,89] and five pooled IPD analyses[25,26,76,79,81]), provide summary tables of results from articles with text-only reporting of interaction effects, and add qualitative summary information on other comparisons in the text below.

Key Points

- Evidence is largely insufficient to determine subgroup effects for interventions other than duloxetine in adults with fibromyalgia.
- For duloxetine, patient subgroups do not experience significantly different fibromyalgia treatment effects relative to other adults with fibromyalgia (low strength evidence).
- The most commonly addressed subgroup was adults with fibromyalgia and major depressive disorder, especially for the effects of duloxetine on pain. Less information is available on treatment effects for other subgroups (such as age, sex, race, anxiety), other outcomes or for other (nondrug) interventions.
- All but two individual RCTs had high risk of bias; all RCTs used in pooled IPD analyses had high risk of bias.
- Evidence is overwhelmingly short-term (3 months)

Pharmacologic Therapies

The strength of evidence was low or insufficient for the effectiveness of all pharmacologic interventions in alleviating symptoms of fibromyalgia in subgroups. Individual clinical trials all had high risk of bias (Appendix Tables E10-E12).

The majority of included studies reported the effects of pharmacologic therapies on pain and other outcomes in subgroups of adults with fibromyalgia. All eight pooled analyses of patient-level RCT data were drug studies. Duloxetine effects were studied most often (six mixed-sample

RCTs[3,4,27,28,30,89] and three pooled IPD RCT analyses[25,26,76]). Subgroups that we determined a priori that were found in drug studies included depression (12 studies), age (seven studies), sex (six studies), anxiety (four studies), obesity/Body Mass Index (BMI) (two studies), and medical comorbidities (one study). Additional subgroups found in drug studies were race (four studies), baseline fatigue level (one study), prior antidepressant use (one study), postmenopausal women (two studies), and one study that used baseline Visual Analog Scale (VAS) pain ratings for subgroup definition.

The literature set for drug treatment consists exclusively of high risk of bias studies due to very high attrition, lack of attrition reporting for subgroups or treatment groups, and small subgroup sample sizes in nonpooled analyses (Appendix C). Overall attrition in drug trials ranged from 4 percent in one off-label international trial[91] to at least 47 percent,[3] with most studies having 30 to 40 percent attrition. Only two off-label international drug trials reported overall attrition of less than 25 percent.[90,91]

Industry funded 85 percent of the 17 drug trials that reported the source of study funding (Appendix Tables E4-E7). Industry involvement in studies included data management, statistical support, manuscript drafting, construction of figures and tables, and study management. Corresponding authors in pharmaceutical trials were often industry employees.

Subgroup Outcomes

In this section, we first examine the effect of drugs on various subgroups and then address the effects of other treatments. Those subgroup-intervention-outcome comparisons with at least low strength of evidence are provided first. Brief details for the subgroups with insufficient evidence are provided second.

Comorbid Mental Health Conditions

Depression

Adults with fibromyalgia and major depressive disorder (MDD) or history thereof were the most frequently assessed subgroup for potential differential treatment effects in patients with MDD (treatment interactions) in pharmaceutical studies, and across all other types of treatments. Eleven drug studies (eight RCTs, seven FDA approved, one off-label), two pooled IPD RCT analyses, and one observational study) assessed treatment-by-MDD interactions on the outcomes of pain, global improvement, fibromyalgia impact, and depression. One additional pooled IPD RCT analysis reported stratum-specific (differences in outcomes in treated vs. controls, but only among patients with depression) changes from baseline in a weekly average pain diary rating rather than an interaction effect (Table 6).[79]

Drug treatments did not appear to have differential effects in adults with fibromyalgia and depression. Low-strength evidence from six RCTs of duloxetine and one pooled IPD analysis[25] suggest that pain outcomes for adults with fibromyalgia and depression do not differ.[3,4,25,27,28,30,89] Pain was the most common outcome assessed in adults with fibromyalgia and comorbid depression, including six RCTs (five of duloxetine[3,4,27,28,89] and one of milnacipran,[85]) and two pooled RCT analyses,[25,26] both of duloxetine. All treatment-by-MDD interactions on pain as an outcome in the pharmacologic studies we examined were either not significant or not reported. Five different measures were used to assess pain in the MDD subgroup; the Beck Depression Inventory (BPI) average pain severity score was used most often (Appendix Tables E8 and E9). Two high risk of bias RCTs[3,89] and one pooled IPD RCT analysis of four high risk

of bias RCTs[25] of duloxetine trials presented data on MDD subgroup BPI average pain severity scores (Tables 7 and 8). Two MDD subgroup interactions were not significant;[25,89] one was not explicitly reported but the text implies that it was not significant.[3] Irrespective of MDD status, when placebo group improvements are examined alongside treatment effects (Table 7), differences in improvements from baseline between treated and control group patients in BPI average pain severity were small.(0.45-1.23 points).

For the MDD subgroup, two studies (one RCT[4] and one pooled IPD[25]) showed no difference on the Fibromyalgia Impact Questionnaire (FIQ) total score with duloxetine.[4,86] Two RCTs (one of duloxetine[72] and one of fluoxetine[86]) examined the FIQ and FIQ pain subscales as primary outcomes; both treatment-by-MDD interactions on the FIQ pain subscales[4,86] and FIQ total scores[4] were not significant.

Low-strength evidence from three studies of duloxetine (two RCTs[3,30] and one pooled analysis[25]) showed no difference among subgroups on the Patient Global Impression of Improvement (PGI-I), a 7 point scale ranging from 1 (very much better) to 7 (very much worse).[61] For the PGI-I, the duloxetine-by-MDD interaction in was not statistically significant,[25,30] or not reported.[3] The RCT by Russell et al. 2008[3] displayed MDD subgroup data for the PGI-I. Study authors noted similar improvements in PGI-I in treated versus controls regardless of MDD status but did not report the interaction result. However, dropouts were assigned a PGI-I score of 4 (corresponding to no change) for the analysis, which assumed no treatment benefit or decrement for patients who did not complete the 3- or 6-month treatment phases[3] (Table 7).

Treatment-by-MDD interaction results for all other outcomes were found in article text only, with or without p-values; these were either not significant or results were not specifically reported (Tables 9 and 10).

Insufficient information on duloxetine effects on the Hamilton Rating Scale for Depression[3,25] (Table 11) and the Beck Depression Inventory[28] was available for analysis for the MDD subgroup.

One observational study of milnacipran was a post-hoc analysis of RCT data that stratified by baseline Beck Depression Inventory score to assess improvement in VAS pain scores. No formal statistical analysis was conducted for subgroup effects.[81]

These reported results should be considered along with issues common to this set of studies. At baseline, MDD subgroup sample sizes were small in all RCTs, and difficult to determine in pooled analyses that reported only the number of patients randomized to the input RCTs, excluding attrition information. The number of patients with MDD at final followup in both treatment and control groups was usually not determinable due to incomplete reporting of denominator values and dropouts per subgroup or by treatment groups after baseline. The lack of denominator values after baseline was common in both RCT and pooled analyses.

Anxiety

Three RCTs provided insufficient evidence for duloxetine effects in patients with generalized anxiety disorder (GAD) on the BPI average pain severity score[28,89] and PGI-I[28,30] (Table 9). One pooled IPD RCT analysis provided insufficient evidence for pregabalin in stratum-specific changes from baseline in a weekly average pain diary rating, rather than an interaction[79] (Table 6).

Other Subgroups

Age

Six drug studies examined potential age-related differences in treatment effectiveness in adults with fibromyalgia.[21,24,2576,80,89] Five of the six studies tested duloxetine effects (four RCTs[3,28,30,89] and one pooled IPD RCT analysis[76]) and one pooled IPD analysis examined pregabalin.[80] Five studies reported 3-month outcomes; two RCTs reported 6 month outcomes.[3,89]

Of these, three RCTs with low-strength evidence found no differences by age for duloxetine effects on the BPI average pain severity score at 3 or 6 months[21,2489] (Tables 7 and 9).

Two low-strength evidence RCTs found no differences by age in duloxetine effects on the PGI-I[24,25] (Tables 7 and 9).

One pooled IPD analysis by Bennett et al.[76] provided pooled data for nonsignificant differences in the effect of duloxetine on FIQ stiffness by age, dichotomized at age 55 (Table 8). One pregabalin study was a statistical modeling paper that provided insufficient evidence for the effect of pregabalin on weekly pain by age[80] (Table 10).

Sex

For the BPI average pain severity score, four RCTs that assessed duloxetine effects by sex offered insufficient evidence of a mixed pattern; in three there was no difference by sex[3,28,89] at 3[3,28] or 6 months,[2489] but in one study, females improved more than males at 3 months ($p=0.046$)[72] (Tables 9 and 10).

When PGI-I was the outcome, low-strength evidence from two duloxetine studies showed no differences by sex in 3 and 6 month treatment effects.[3,30]

Three studies reported outcomes for other pain measures; all evidence was insufficient. One pooled analysis/statistical modeling paper of four RCTs with 8-14 weeks of followup reported greater weekly pain reduction in females versus males in text but did not provide useable interaction results[80] (Table 10). Two high risk of bias pure subgroup RCTs provided insufficient evidence for off-label drug treatment effects in postmenopausal women with fibromyalgia. One underpowered study examined the effects of transdermal estrogen versus placebo on pain and found no difference between groups.[90] The second study of 100 women found that women treated with raloxifen had greater mean reduction in pain, sleep disturbance, and tender points but no effect on anxiety and depression relative to women treated with placebo.[91]

One RCT offered insufficient interaction evidence that women improved more than men in the Sheehan Disability Scale ($p=0.007$).[4]

Race

Although not listed as an a priori subgroup due to the expected small number of nonwhite race patients in fibromyalgia trials, treatment-by-race interactions were assessed in four RCTs, all of duloxetine[3,28,30,89] (Table 9). The outcomes included BPI average pain severity[3,28,89] and global improvement (PGI-I).[3,30]

There was insufficient evidence of mixed effects by race for duloxetine on the BPI average pain severity from three RCTs; two RCTs found no difference in BPI average pain severity by race[3,89] but in one underpowered RCT, nonwhites improved more than whites.[28] The sample size for the nonwhite subgroup was small at baseline (22 treated, 17 placebo) and was not reported for the 3-month followup.[28]

Two RCTs with low-strength evidence reported no difference by race when PGI-I was the outcome.[3,30]

Obesity

Two pooled IPD analyses, one of duloxetine[76] and one of milnacipran[77] provided insufficient evidence for the outcomes of stiffness[76] (FIQ subscale) and weight loss[77] for subgroups determined by BMI at baseline. All input RCTs for these pooled IPD analyses were high risk of bias studies. The duloxetine pooled IPD analysis[76] assessed whether treatment effects on stiffness associated with fibromyalgia, measured by the FIQ stiffness subscale (one item), varied by BMI. The 3-month outcomes data were reported, stratified by BMI (normal, overweight, obese, and morbidly obese) (Table 8). The treatment-by-BMI interaction was not significant. However, the small differences between treated and placebo-controlled patients in changes in FIQ stiffness from baseline decreased with increasing levels of BMI. No interaction result was reported in a pooled milnacipran study that reported that overweight and obese patients had greater mean weight loss than normal or underweight patients at 3 months.[77]

Other Subgroup Outcomes

One high risk of bias duloxetine RCT reported 6-month changes in BPI average pain severity for patients stratified by prior antidepressant use at baseline (Table 7).[89] The interaction was significant, whereby treated patients with previous antidepressant use had greater improvements in BPI average pain then those without prior antidepressant use (p=0.028).

Bradley et al.[26] conducted a pooled analysis of IPD RCT data to determine if duloxetine effects on the BPI average pain score varied by baseline level of fatigue using the FIQ tiredness subscale. The interaction term was not significant; data are shown in Table 8.

Within-subgroup changes from baseline in pain in fibromyalgia patients with any of ten different concomitant conditions (such as headache, irritable bowel syndrome, or gastrointestinal reflux) were reported by Bhadra et al.[79] in a study of varying doses of pregabalin. No interaction effects were assessed (Table 6).

No other subgroups were separately reported in included studies.

Physical Treatments

Due to the sparse literature on physical treatment effects in subgroups of adults with fibromyalgia, this section is organized by the type of study design, and subsequently, by specific type of intervention. All physical interventions were assessed in pure subgroup RCTs. Study duration ranged from 3 months to 6 months (Appendix Table E5).

Five pure subgroup RCTs examined the effects of exercise interventions[92-94,98] and one assessed the impact of dietary changes[53] on outcomes in subgroups of adults with fibromyalgia. Two studies of physical interventions had moderate risk of bias;[52,92] all others were high risk of bias. Sample sizes ranged from 21 to 83 adults at enrollment, for a total of 311 subjects across all five studies.

One moderate risk of bias RCT exclusively of sedentary women with fibromyalgia[92] compared the aerobic exercise interventions of deep water running versus land-based exercise (control) on the outcomes of fibromyalgia impact (FIQ), pain (VAS), depression (BDI), health status (SF-36), and Patients Global Assessment of response to treatment (PGART). Both groups improved significantly with 15 weeks of three times per week exercise, with greater

improvements in the FIQ in the deep water running group. There were no differences in improvement from baseline between groups in all other measures.

Gusi et al.[52] assessed the effects of whole body vibration on dynamic balance in a post hoc analysis of RCT data by baseline body weight. This moderate risk of bias studies found that participants with the heaviest weight and worst balance at baseline improved more than others ($p<0.001$).

Two exercise interventions were evaluated in females with fibromyalgia based on their menopausal status;[93,94] both studies had a high risk of bias. Hakkinen et al.[93] evaluated the isometric knee strength and serum hormone effects of 21 weeks of supervised strength training in premenopausal women. Only isometric knee strength increased significantly in the strength-trained versus normal activities group. The high risk of bias Valkeinen study[94] of strength and aerobic training versus no training in postmenopausal women age 50 and older reported a 2 percent improvement in strength and significant improvements in pain, walking, and stair climbing ability in the trained versus no strength or aerobic training group, with no differences in fatigue, well-being, or sleep quality reported.

The strength of evidence was insufficient to compare treatment outcomes by physical interventions in these pure subgroup RCTs. All studies tested unique treatments in unique subgroups and had small sample sizes; four of six were high risk of bias studies (Appendix Table E10).

Psychological Therapies

Four studies examined the effects of psychological therapies in subgroups of adults with fibromyalgia: one mixed-sample RCT,[87] two pure subgroup RCTs,[95,96] and one observational study.[83] Study duration ranged from 3 months to 1 year, which was the longest followup of any studies included in this report. Sample sizes were small; the total number of adults included across these psychological studies was 210. All assessed unique outcomes in disparate subgroups and all were high risk of bias studies.

Junghaenel et al.[87] compared outcomes in fibromyalgia patients by their level of education and dominant pain coping strategy at baseline to assess the effects of a written emotional disclosure intervention on pain, fatigue, and psychological wellbeing in a mixed-sample RCT. Outcomes from the writing intervention did not differ by level of education or baseline pain coping strategy for pain or fatigue, but adults with the pain coping strategy called "interpersonally-distressed" improved more in the psychological wellbeing outcome than did the "adaptive" pain coping group. Also, only graduate-educated adults had significant improvements in psychological well-being with the intervention compared to less educated individuals.

The longest of all included studies was a year-long study of the effects of psychotherapy versus four primary care consultations with advice on medication and exercise on multiple outcomes. This high risk of bias pure subgroup RCT included women with fibromyalgia, all of whom had concomitant psychological comorbidity, including MDD, dysthymia, anxiety, and double depression.[96] Both interventions were deemed to be equally effective; there were no significant outcomes differences from psychotherapy versus primary care interventions by type of baseline psychological comorbidity. This was the only study that included patients with mental health conditions other than major depressive disorder or anxiety.

One high risk of bias pure subgroup RCT compared CBT versus other behavioral therapy versus usual care on sleep patterns in adults with fibromyalgia and insomnia. Both treatment

groups improved, with the CBT group showing the greatest improvements in polysomnography assessed wake times.

One high risk of bias observational biofeedback study examined the benefits of using EMG-reduction training of visual and auditory feedback to teach two groups of subjects the same muscle relaxation techniques.[83] Subjects were stratified by baseline Minnesota Multiphasic Personality Inventory (MMPI) scores to assess outcomes of pain perception, tender point scores, and the SF-36. Although the group with "psychologically abnormal" MMPI scores was worse off than "psychologically normal" women in all measures at baseline, the *psychologically abnormal* group had improvements in all outcomes measures, including pain and fibromyalgia symptoms, which were not experienced in the comparator group of women.

The strength of evidence was insufficient to compare subgroup treatment effects for psychological interventions in these four studies due to their high risk of bias and small sample sizes (Appendix Table E10 and E11).

Mixed Types of Treatments

Four studies assessed combination therapies, and each study had a high risk of bias; one RCT, two pure subgroup RCTs and one observational study.[84,88,97,99]

A mixed sample RCT included a subgroup of 16 patients with fatigue.[88] Multidisciplinary treatment with CBT showed greater improvements in the FIQ total score and SF-36 emotional well-being in fatigue patients than with multidisciplinary treatment alone. The study was not powered to assess subgroup effects.

In a pure subgroup RCT, Fontaine et al.[97] assessed the effects of a cognitive behavioral physical activity promotion program on multiple outcomes in adults with fibromyalgia who had suboptimal physical activity in the prior 6 months per U.S. Surgeon General's recommendations. The treated group increased daily walking (count of steps) by 54 percent, and had a significant reduction in mean total FIQ (-16 percent; MCID (minimum clinically important difference) is 14 percent[42]) and reduction in the FIQ pain subscore. No differences were noted in the 6 minute walk test, BMI, fatigue, depression, or number of tender points between groups. Martinez et al.[99] found that adults treated with CBT for insomnia improved total FIQ and sleep measures after 6 weeks of treatment compared with sleep education in a pure subgroup study. Most adults also took medication; the effect of CBT was not sustained at 3 or 6 months.

One observational study evaluated the effects of supervised multifaceted exercise and relaxation (exercise plus relaxation) versus amitriptyline for subgroups determined by socioeconomic status and FIQ pain score.[84] Both strategies equally reduced disability.

The strength of evidence was insufficient to compare treatment outcomes for mixed types of fibromyalgia treatments. All four studies assessed unique treatment-subgroup-outcomes combinations, and all had a high risk of bias (Appendix Tables E10 and E11).

Key Question 2. Adverse Treatment Effects in Fibromyalgia Subgroups

The clinical trial literature on adults with fibromyalgia that reported on subgroup treatment effects was nearly devoid of adverse effect (harms) reporting for subgroups. Therefore, this section is organized by the type of study design, under which we report summary information on harms only.

Key Points

- Adverse effects (AEs) were rarely reported by subgroup
- Evidence was insufficient to determine whether or not AEs of treatments for adults with fibromyalgia vary in adult subgroups or whether subgroups experience atypical AEs for a given treatment
- When reported, AEs did not markedly differ in subgroups

RCTs

None of the ten mixed sample RCTs with adverse effect reporting and subgroup treatment outcomes separately reported AEs by subgroups.[3,4,27,28,30,85-89]

Pure Subgroup RCTs

Of the 12 RCTs that sampled within at least one subgroup, only three reported any information on adverse treatment effects: two off-label pharmacologic studies[90,91] and one test of an exercise intervention.[92] The most common side effect in the deep water running versus land-based exercise intervention was muscle pain, which was more common in the land-based exercise control group.[92] The raloxifen versus placebo study[91] reported one serious AE (deep vein thrombosis) affecting 2 percent of the treated group with less severe issues of leg cramps, anxiety, and flushing affecting 10-15 percent of the treated group. The second small RCT tested transdermal 17B-estradiol on pain in 29 women.[90] The study was halted at half the planned sample size due to new information that emerged with concerns for the health effects of hormone replacement therapy.

Pooled IPD RCT Analyses

Adverse effects were reported for subgroups in one pooled analysis of duloxetine clinical trials.[25] In a pooled analysis of patients with fibromyalgia and major depressive disorder, the treatment-by-MDD interaction for serious adverse events was not significant ($p>0.1$).[25] However, the treatment-by-MDD stratum interaction was significant for "treatment-emergent adverse events," with higher rates of 10 adverse effects in treated patients with MDD relative to treated adults without MDD. The three most common of the "treatment-emergent adverse effects" in treated patients were nausea (31.6 percent), headache (19.6 percent), and dry mouth (19.1 percent) in the duloxetine-MDD group, which was 0.4-3.3 percent higher than the rates in the group treated without MDD. The lower proportion of placebo-treated patients with MDD that experienced these adverse effects was similar to those experienced by placebo-treated adults without MDD.

AEs were reported only by treatment group, not by subgroup, in two pooled milnacipran studies[77,78] and in one duloxetine study.[76] AEs were not reported in the three pooled pregabalin studies.[29,79,80]

Observational Studies

Only one of four observational studies reported adverse treatment effects in a crossover study of 10 patients treated with naltrexone (off-label) versus placebo that were grouped by baseline erythrocyte sedimentation rate (ESR).[82] The most common AEs were vivid dreams, nausea, and insomnia.

Table 5. Number of studies by subgroup-treatment-outcome combinations in adults with fibromyalgia

Subgroup-by Treatment	Brief Pain Inventory Average Pain Score	Patient Global Impression of Improvement (PGI-I)	Fibromyalgia Impact Questionnaire (FIQ) Total Score	FIQ Subscale	Visual Analog Scale (VAS) for Pain	Patient Global Impression of Change (PGI-C)	HAMD	Other Pain Measure	Other Nonpain Measures
Drugs									
Duloxetine									
Depression/MDD	6 Arnold, 2012[28] Russell, 2008[3] Chappell, 2008[89] Arnold, 2005[27] Arnold, 2004[4] Arnold, 2009[25]*	3 Arnold, 2010[30] Russell, 2008[3] Arnold, 2009[25]*	2 Arnold, 2004[4] Arnold, 2009[25]*	1 (pain) Arnold, 2004[4]			2 Russell, 2008[3] (within strata) Arnold, 2009[25]		1 each outcome: SF-36 Arnold, 2009[25] SDS, CGI-S, MFI; Arnold, 2009[25]
Anxiety/GAD	2 Arnold, 2012[28] Chappell, 2008[89]	1 Arnold, 2010[30]							
Age	3 Arnold, 2012[28] Russell, 2008[3] Chappell, 2008[89]	2 Arnold, 2010[30] Russell, 2008[3]		1 (stiffness) Bennett, 2012[76]					
Sex	4 Arnold, 2012[28] Russell, 2008[3] Arnold, 2004[4] Chappell, 2008[89]	2 Arnold, 2010[30] Russell, 2008[3]	1 Arnold, 2004[4]	1 (pain) Arnold, 2004[4]					1:SDS Arnold, 2004[4]

Table 5. Number of studies by subgroup-treatment-outcome combinations in adults with fibromyalgia (continued)

Subgroup-by Treatment	Brief Pain Inventory Average Pain Score	Patient Global Impression of Improvement (PGI-I)	Fibromyalgia Impact Questionnaire (FIQ) Total Score	FIQ Subscale	Visual Analog Scale (VAS) for Pain	Patient Global Impression of Change (PGI-C)	HAMD	Other Pain Measure	Other Nonpain Measures
Race	3 Arnold, 2012[28] Russell, 2008[3] Chappell, 2008[89]	2 Arnold, 2010[30] Russell, 2008}[3]							
Obesity/BMI				1 (stiffness) Bennett, 2012[76]					
Fatigue/Tiredness	1 Bradley, 2010[26]	1 Bradley, 2010[26]	1 Bradley, 2010[26]	1 (multiple) Bradley, 2010[26]					1 (SF-36) Bradley, 2010[26]
Prior antidepressant use	1 Chappell, 2008[89]								
Milnacipran									
Depression					2 Gendreau, 2005[85] Arnold, 2012[81]	1 Arnold, 2012[81]		1 (3 different pain scores) Gendreau, 2005[85]	1 (Beck Depression) Arnold, 2012[81]
Obesity/BMI									1 (weight loss) Arnold, 2012[77]
Baseline VAS pain					1 Geisser, 2011[78]	1 Geisser, 2011[78]			1 (SF-36 PCS) Geisser, 2011[78]
Pregabalin									
Age						1 (NR) Byon, 2010[80]		1 (NR) Byon, 2010[80]	
Sex						1 (NR) Byon, 2010[80]		1 (NR) Byon, 2010[80]	

Table 5. Number of studies by subgroup-treatment-outcome combinations in adults with fibromyalgia (continued)

Subgroup-by Treatment	Brief Pain Inventory Average Pain Score	Patient Global Impression of Improvement (PGI-I)	Fibromyalgia Impact Questionnaire (FIQ) Total Score	FIQ Subscale	Visual Analog Scale (VAS) for Pain	Patient Global Impression of Change (PGI-C)	HAMD	Other Pain Measure	Other Nonpain Measures
Depression						1 (within stratum) Bhadra, 2010[79]		1 (within stratum) Bhadra, 2010[79]	1 (HADS-D) Arnold, 2010[29]
Anxiety						1 (within stratum) Bhadra, 2010[79]		1 (within stratum) Bhadra, 2010[79]	1 (HADS-A) Arnold, 2010[29]
Immune/allergies						1 (within stratum) Bhadra, 2010[79]		1 (within stratum) Bhadra, 2010[79]	
GI reflux						1 (within stratum) Bhadra, 2010[79]		1 (within stratum) Bhadra, 2010[79]	
Insomnia						1 (within stratum) Bhadra, 2010[79]		1 (within stratum) Bhadra, 2010[79]	
IBS						1 (within stratum) Bhadra, 2010[79]		1 (within stratum) Bhadra, 2010[79]	
Neurological						1 (within stratum) Bhadra, 2010[79]		1 (within stratum) Bhadra, 2010[79]	
Asthma						1 (within stratum) Bhadra, 2010[79]		1 (within stratum) Bhadra, 2010[79]	
Restless legs/RLS						1 (within stratum) Bhadra, 2010[79]		1 (within stratum) Bhadra, 2010[79]	

Table 5. Number of studies by subgroup-treatment-outcome combinations in adults with fibromyalgia (continued)

Subgroup-by Treatment	Brief Pain Inventory Average Pain Score	Patient Global Impression of Improvement (PGI-I)	Fibromyalgia Impact Questionnaire (FIQ) Total Score	FIQ Subscale	Visual Analog Scale (VAS) for Pain	Patient Global Impression of Change (PGI-C)	HAMD	Other Pain Measure	Other Nonpain Measures
Off-label									
Depression (Fluoxetine)			1 Arnold, 2002[86]	1 (pain) Arnold, 2002[86]					
Postmenopausal women (17B-estradiol)								1 Stening, 2011[90]	
Postmenopausal women (Raloxifen)								1 Sadreddini, 2008[91]	1 (4 other measures) Sadreddini, 2008[91]
ESR level at baseline (Naltrexone)									1 (FM symptom severity) Younger, 2009[82]
Physical									
Sedentary women (deep water vs. land based exercise)			1 Assis, 2006[92]		1 Assis, 2006[92]				1 (BDI, SF-36, PGART) Assis, 2006[92]
Sedentary women (strengthening vs. flexibility exercise)			1 Gavi, 2014[98]		1 Gavi, 2014[98]				1 (HRV, fitness, IDATE, SF-36) Gavi, 2014[98]
Body weight (whole body vibration)									1 (dynamic balance) Gusi, 2010[52]
Premenopausal women(strength training)									1 (knee strength, hormones) Hakkinen, 2001[100]
Obese adults (weight reduction)			1 Senna, 2012[53]						1 (BDI, Sleep quality index, TPs) Senna, 2012[53]
Postmenopausal (strength and aerobic training)									1 (5 measures) Valkeinen, 2008[94]
Psychological									
Baseline MMPI (EMG-biofeedback)								1 Drexler, 2002[83]	1 (SF-36 and 3 other measures) Drexler, 2002[83]

Table 5. Number of studies by subgroup-treatment-outcome combinations in adults with fibromyalgia (continued)

Subgroup-by Treatment	Brief Pain Inventory Average Pain Score	Patient Global Impression of Improvement (PGI-I)	Fibromyalgia Impact Questionnaire (FIQ) Total Score	FIQ Subscale	Visual Analog Scale (VAS) for Pain	Patient Global Impression of Change (PGI-C)	HAMD	Other Pain Measure	Other Nonpain Measures
Insomnia (CBT)									1 (polysomnography) Edinger, 2005[95]
Women–all with psychological comorbidity (psychotherapy)			1 Scheidt, 2013[96]					1 Scheidt, 2013[96]	1 (2 other measures) Scheidt, 2013[96]
Coping style (Written emotional disclosure)								1 Junghaenel, 2008[87]	1 (fatigue, psychological well-being) Junghaenel, 2008[87]
Educational status (Written emotional disclosure)								1 Junghaenel, 2008[87]	1 (fatigue, psychological well-being) Junghaenel, 2008[87]
Mixed									
Fatigue (Multidisciplinary plus CBT or medications)			1 Lera, 2009[88]						1 (SF-36, SCL-90-R) Lera, 2009[88]
Females with insomnia (CBT for insomnia vs education)			1 Martinez, 2014[99]					1 Martinez, 2014[99]	1 (PSQI, MFI, SCL-90-R) Martinez, 2014[99]
Sedentary adults (cognitive-behavioral physical activity promotion program vs. information)			1 Fontaine, 2010[97]	1 Fontaine, 2010[97]	1 Fontaine, 2010[97]				1 (4 other measures) Fontaine, 2010[97]

Table 5. Number of studies by subgroup-treatment-outcome combinations in adults with fibromyalgia (continued)

Subgroup-by Treatment	Brief Pain Inventory Average Pain Score	Patient Global Impression of Improvement (PGI-I)	Fibromyalgia Impact Questionnaire (FIQ) Total Score	FIQ Subscale	Visual Analog Scale (VAS) for Pain	Patient Global Impression of Change (PGI-C)	HAMD	Other Pain Measure	Other Nonpain Measures
Severe fibromyalgia (exercise and relaxation vs. drug)			1 Joshi, 2009[84]						
Socioeconomic status (exercise and relaxation vs. drug)			1 Joshi, 2009[84]						

Abbreviations: BDI = Beck Depression Inventory; BMI = Body Mass Index; BPI = Brief Pain Inventory; CBT = Cognitive Behavioral Therapy; CGI-S = Clinical Global Impression of Severity Scale; EMG = Electromyography; EQ-5D = EuroQol health outcomes assessment; FIQ = Fibromyalgia Impact Questionnaire; FM = fibromyalgia; GAD = Generalized Anxiety Disorder; GI = gastrointestinal; HADS-A = Hospital Anxiety and Depression Scale, anxiety subscale score; HADS-D = Hospital Anxiety and Depression Scale, depression subscale score; HAMD = Hamilton Rating Scale for Depression; HRV = Heart Rate Variability; IBS = Irritable Bowel Syndrome; MDD = Major Depressive Disorder; MFI = Multidimensional Fatigue Inventory; NR = not reported; PGART = Patient Global Assessment of Response to Therapy; PGI-C = Patient Global Impression of Change Scale; PGI-I = Patient Global Impression of Improvement Scale; PSQI = Pittsburg Sleep Quality Index; RLS = Restless legs syndrome; SDS = Sheehan Disability Scale; SCL-90-R = Symptom Checklist-90-Revised; SF-36 = MOS Short-Form 36-item Health Survey; SF-36 PCS = SF-36 Physical component score; TPs = Tender Points; VAS = Visual Analog Scale.

*Arnold 2009[25] pooled analysis of patient-level data from 4 RCTs is partially redundant with included RCTs (3 of 4 RCTs included in this report. Rationale for inclusion is provided in the report text

Table 6. Pregabalin results from pooled patient-level RCT study: mean change from baseline in Weekly Mean Pain Diary Score (11-point scale) by comorbid condition

Author, Year	Followup Duration	Comorbid Condition at Baseline*	Placebo	Pregabalin 300 mg/Day	Pregabalin 450 mg/Day	Pregabalin 600 mg/Day
Bhadra, 2010[79]	8-12 weeks	Headache	-1.0	-1.7	-1.7	-1.5
		Immune/allergies	-1.1	-1.8	-1.9	-2.0
		GI reflux	-1.1	-1.9	-1.9	-1.8
		Insomnia	-1.3	-2.0	-2.0	-2.0
		Depression	-1.0	-1.6	-1.9	-2.1
		IBS	-1.1	-1.6	-2.1	-1.7
		Neurological	-1.1	-2.0	-1.9	-1.9
		Asthma	-1.0	-2.1	-1.9	-2.1
		Anxiety	-1.1	-1.8	-1.4	-2.0
		RLS	-1.6	-1.6	-1.7	-2.0

Abbreviations: GI = gastrointestinal; IBS = irritable bowel syndrome; RLS = restless legs syndrome

* Comorbid conditions not mutually exclusive

Table 7. Duloxetine randomized controlled trials with subgroup data showing 6-month outcomes in adults with fibromyalgia, with or without major depressive disorder

Author, Year Time	Outcome Measure	Subgroup	N-tx*	Dose, Mean BPI Change in Treated (SE)	N-c*	Mean BPI Change in Placebo (SE)	Interaction p Value	Difference in Mean Effect (tx-c)
Chappell, 2008[89]	Brief Pain Inventory (BPI) average pain severity	Previous antidepressant use	162	60mg/d, titrated to 120mg/d at week 8	168		0.028	
		Yes (43% of patients)	71	-1.85 (0.29)	72	-0.65 (0.27)		-1.20
		No	91	-1.56 (0.29)	96	-1.51 (0.29)		-0.05
Russell, 2008[3] 6 months	Brief Pain Inventory (BPI) average pain severity**	Major depressive disorder (MDD) (24% of patients)	**79**†	**20 mg/day**‡	144		NR	
		With MDD	22	-2.58 (0.53)	35	-1.35 (0.45)		-1.23
		Without MDD	57§	-2.16 (0.34)	109§	-1.48 (0.25)		-0.68
			150†	**60 mg/day**				
		With MDD	35	-2.35 (0.46)	35	-1.35 (0.45)		-1.00
		Without MDD	115§	-1.93 (0.25)	109§	-1.48 (0.25)		-0.45
			147†	**120 mg/day**				
		With MDD	34	-2.56 (0.48)	35	-1.35 (0.45)		-1.21
		Without MDD	113§	-2.20 (0.25)	109§	-1.48 (0.25)		-0.72
				Dose, PGI-I				
	Patient Global Impression of Improvement (PGI-I)††		**79**†	**20 mg/day**‡			NR	
		With MDD	22	2.85 (0.33)		3.28 (0.28)		-0.43
		Without MDD	57§	2.76 (0.22)		3.37 (0.16)		-0.61
			150†	**60 mg/day**				
		With MDD	35	2.96 (0.29)		3.28 (0.28)		-0.32
		Without MDD	115§	3.07 (0.16)		3.37 (0.16)		-0.30
			147†	**120 mg/d**				
		With MDD	34	2.41 (0.30)		3.28 (0.28)		-0.87
		Without MDD	113§	3.04 (0.16)		3.37 (0.16)		-0.33

Abbreviations: BPI = Brief Pain inventory; MDD = major depressive disorder; N-tx = number randomized to treatment group; N-c = number randomized ton control group; PGI-I= patient global impression of improvement scale; SE = standard error; tx-c = difference in mean outcome between treated and control groups (treated minus control)

BPI: Treatment by subgroup interactions not significant for age, sex and race at 3 or 6 months (p-values reported but no data).

* Number of patients randomized to each group-does not account for attrition

†Denominators for both 3 and 6 month followup in Table 2 of the article report baseline enrollment totals by treatment group that do not reflect dropouts. Of the 520 randomized patients, 325 (62.5%*) completed the study for 3 months, and 278 for 6 months. Denominators for the number of patients per dose at 3 and 6 month followups were not reported in tables or text.

‡Duloxetine patients on the 20mg dose during the first 3 months had their dose blindly increased to 60 mg/day for months 4 through 6 (n=49†).

§Calculated by the MN EPC, not article authors

**Minimum clinically important difference (MCID) for the BPI average pain severity score in fibromyalgia patients is 2.1 points[101]

†† PGI-I: 7 point scale ranging from 1 (very much better) to 7 (very much worse). Dropouts were assigned a PGI-I score of 4 (corresponding to no change); the analyses assume no treatment benefit or decrement for patients who did not complete the 3- or 6-month treatment phases.[3]

Table 8. Results from pooled patient-level RCT data: primary outcome with subgroup changes from baseline in pooled studies that reported subgroup data

Drug Author, Year	Time	Outcome	Subgroup	N-tx Baseline	Treatment, Dose	N-c Baseline	Control	Difference in Effect (tx-c)*	Interaction p Value	MCID for Fibromyalgia
Duloxetine										
Bennett, 2012[76]	3 months	FIQ stiffness change (0-10 scale)	**Age** (years)		**Duloxetine 60 and 120 mg/day**		**Placebo**		0.246	13% change in FIQ stiffness[42]
			<55	485	-2.43(0.12)	345	-1.50 (0.12)	-0.93		
			≥55	275	-2.14(0.17)	172	-1.50 (0.12)	-0.67		
			BMI						0.102	
			Normal	208	-2.40(0.18)	157	-1.36 (0.21)	-1.04		
			Overweight	230	-2.08(0.17)	149	-1.31 (0.21)	-0.77		
			Obese	253	-2.51(0.17)	164	-1.80 (0.20)	-0.71		
			Extreme obesity	62	-2.01(0.34)	41	-1.53 (0.41)	-0.48		
Bradley, 2010[26]	3 months	BPI average pain score	**FIQ Tiredness**		**Duloxetine 60 and 120 mg/day**				>0.1	2.1 points for BPI average pain severity[101]
			mild	9**	-1.3(0.5)	20	-1.8 (0.5)	0.5		
			moderate	50**	-1.6(0.2)	83	-1.1 (0.2)	-0.5		
			severe	204**	-2.0(0.1)	430	-1.1 (0.1)	-0.9		
Arnold, 2009[25]	3 months	BPI average pain score	**Major Depressive Disorder (MDD**)		**Duloxetine 60 and 120 mg/day**				0.48	2.1 points for BPI average pain severity[101]
			Without MDD	594	-1.9(0.1)	388	-1.2 (0.1)	-0.07		
			With MDD	203	-2.0(0.2)	147	-1.2 (0.2)	-0.08		
Milnacipran										
Arnold, 2012[77] 2 doses	3 months	Mean weight change (kg)	**BMI** n/group		***Milnacipran 100 mg/day***				NR	NA
			<25 711	NR	-0.33(0.21)	NR	0.06 (0.20)	-0.39		
			25-30 886	NR	-1.39(0.23)	NR	0.03 (0.24)	-1.42		
			≥30 1507	NR	-1.48(0.21)	NR	-0.17 (0.19)	-1.31		
			BMI		***Milnacipran 200 mg/day***				NR	
			<25 711	NR	-0.44(0.25)	NR	0.06 (0.20)	-0.50		
			25-30 886	NR	-0.91(0.28)	NR	0.03 (0.24)	-0.94		
			≥30 1507	NR	-1.13(0.26)	NR	-0.17 (0.19)	-0.96		

Abbreviations: 1 kg = 1 kilogram = 2.2 pounds; BMI = Body Mass Index; BPI = Brief Pain Inventory; c = controls; d = day; FIQ = stiffness-Fibromyalgia Impact Questionnaire stiffness subscale; MCID = minimum clinically important difference; MDD = Major depressive disorder; mg = milligrams; mo = month; NA = not assessed; N-c = number in control group; NR = not reported; N-tx = number in treatment group; tx=treated.

*difference = change in outcome of (treated – control) per row Calculated by the MN EPC, not article authors. Positive difference indicates that placebo improved more than treated.

**calculated by the MN EPC from article text. Not directly reported by authors.

Table 9. Fibromyalgia mixed-sample RCT treatment-by-subgroup interaction outcomes reported in the text,* by outcome measure

Treatment	Author, Year	FIQ Total	FIQ Subscale	BPI Average Pain Severity	VAS Pain	PGI-I	HAMD	Other
Mixed sample RCTs (not pure subgroups)								
Pharmacologic								
Duloxetine	Arnold, 2012[28]			a: NS s: NS r: Nonwhite $^{+}$> White p=0.017 d: NS g: NS				
	Arnold, 2010[30]					a: NS s: NS r: NS d: NS g: NS		
	Chappell, 2008[89]			a: NS s: NS r: NS d: NS g: NS				
	Russell, 2008[3]**			a: NS s: NS r: NS d: NR		a: NS s: NS r: NS d: NR	d:NS within MDD strata	
	Arnold, 2005[27]			d: NS				
	Arnold, 2004[4] Primary: FIQ pain subscale	s: NS, p=0.101 d: NS, p=0.862	pain s: NS, p=0.121 d: NS, p=0.677	s: F $^{+}$> M, p=0.046 d: NR				s: F $^{+}$> M in Sheehan disability (p=0.007)
Milnacipran	Gendreau, 2005[85]				d: NR			d: Mean pain scores on e-diary, Gracely or McGill pain questionnaires, NR
Fluoxetine	Arnold, 2002[86]	d: NS	d: NS					

Table 9. Fibromyalgia mixed-sample RCT treatment-by-subgroup interaction outcomes reported in the text,* by outcome measure (continued)

Treatment	Author, Year	FIQ Total	FIQ Sub-scale	BPI Average Pain Severity	VAS Pain	PGI-I	HAMD	Other
Psychological								
Written emotional disclosure	Junghaenel, 2008[87]							3 composite measures for: c: pain, NS; c: fatigue, NS; c:psychological well-being: interpersonally distressed $^{+}$> adaptive coping, p=0.08. e: psychological well-being: graduate educated $^{+}$> college or less educated
Mixed								
Multidisciplinary (MT) with/without CBT	Lera, 2009[88]	f:MTCBT^{+} >MT in fatigued p=0.21 NS						f: MTCBT^{+}> MT on SF-36 emotional well-being in fatigued p=0.21 NS

Abbreviations: a = age; s = sex; r = race; d = depression, major depressive disorder (MDD) or history of MDD; e = education[87]; f = fatigue; g = generalized anxiety disorder (GAD); c = coping style[87]; w = SF-36 emotional well-being[88] o = other subgroup

CBT = cognitive behavioral therapy; MTCBT = multidisciplinary (MT) with CBT; NR = interaction significance was not reported; NS = Treatment by subgroup interaction not statistically significant; SF-36 = Medical Outcomes Study short form 36 item health survey

+ the study reported statistically positive treatment effect in the subgroup for the outcome

> improved more than

* no additional subgroup data provided in any articles except in Russell 2008

** Russell 2008 included text and table reporting of subgroup data

Table 10. Summary of pooled RCT outcomes in fibromyalgia subgroups: significance of overall treatment-by-subgroup interaction terms where interaction results were reported (in text with/without p-values but without supporting data)

Treatment and Subgroup	Author, Year	Followup	FIQ	FIQ Subscales	BPI	VAS Pain	PGI-I	PGI-C	SF-36	Other
Pharmacologic										
Duloxetine										
Age (<55, ≥55)	Bennett, 2012[76]	3 months		**NS** p=0.246						
BMI (normal, overweight, obese, extreme obesity)	Bennett, 2012[76]	3 months		**NS** p=0.102						
FIQ Tiredness (mild, moderate, severe)	Bradley, 2010[26]	3 months	**NS** p=0.74	**NS** p>0.1	**NS** p>0.1		**NS** p=0.908		**NS** p>0.1	
MDD: Major depressive disorder	Arnold, 2009[25]	3 months	**NS** p=0.46		**NS** p=0.48 primary outcome		**NS** p=0.45		**NS** p=NR	**NS** (all) HAMD p=0.14 CGI-S p=0.98 SDS p=0.18 MFI p= NR
Milnacipran										
BMI (<25, 25-30, ≥30)	Arnold, 2012[77]	3 months								Weight loss **NR**
Baseline VAS Pain (≤64.7, >64.7)	Geisser, 2011[78]	3 months and 6 months				Reported % (n) with ≥30% improvement only **NR**		Reported % (n) with PGI-C ≤2 only **NR**	6 pt better in SF-36 PCS **NR**	≥30% better on PGI-C and VAS pain **NR**
Pregabalin										
Anxiety	Arnold, 2010[29]	Pooled 8, 13, and 14 weeks				**I**				HADS-A (≥2 pts, <2 pts) **I**
Depression	Arnold, 2010[29]	*Pooled 8, 13, and 14 weeks				**I**				HADS-D **I**
10 Comorbid Conditions	Bhadra, 2010[79]	*8-12 weeks						**NR**		Weekly pain rating of 0-10 **NR** all subgroups

Table 10. Summary of pooled RCT outcomes in fibromyalgia subgroups: significance of overall treatment-by-subgroup interaction terms where interaction results were reported (in text with/without p-values but without supporting data) (continued)

Treatment and Subgroup	Author, Year	Followup	FIQ	FIQ Subscales	BPI	VAS Pain	PGI-I	PGI-C	SF-36	Other
Age (<40, 40-60, >60)	Byon, 2010[80]	* 8-14 weeks						**NR**		Weekly mean pain rating: greater pain reduction in older vs. younger patients **NR**
Sex	Byon, 2010[80]	* 8-14 weeks						**NR**		Weekly mean pain rating: greater pain reduction in females vs. males **NR**

Abbreviations: BPI = Brief Pain Inventory; CGI-S = Clinical Global Impression of Severity Scale; FIQ = Fibromyalgia Impact Questionnaire; HADS-A = Hospital Anxiety and Depression Scale, anxiety subscale score; HADS-D = Hospital Anxiety and Depression Scale, depression subscale score; HAMD = Hamilton Rating Scale for Depression; I = indeterminable as reported (figures, lack n's, etc.); MFI = Multidimensional Fatigue Inventory; N = not significant; NR = significance of interaction not reported; NA = not assessed; PGI-C = Patient Global Impression of Change Scale; PGI-I = Patient Global Impression of Improvement Scale; SDS = Sheehan Disability Scale; SF-36 = MOS Short-Form 36-item Health Survey; VAS = Visual Analog Scale

* At least 1 of the pooled studies reported longest followup outcomes at less than 12 weeks.

Table 11. Change in depression as measured by the Hamilton Depression Scale (HAMD) in one randomized controlled trial of duloxetine among fibromyalgia patients with MDD at baseline*

Author, Year	Group	Baseline HAMD With MDD	6-Month Change in HAMD With MDD
Russell, 2008[3]	Placebo	15.3 (4.58)	-4.8 (n=30)
	20 mg/day‡	15.1 (4.9)	-5.2 (n=22) 20→60 mg
	60 mg/day	15.4 (5.8)	-6.9 (n=30)
	120 mg/day	16.3 (4.4)	-7.2 (n=29)

* Authors reported baseline HAMD in patients without MDD, but did not report 6 month followup for those without MDD
†Denominators for both 3 and 6 month followup in Table 2 of the article report baseline enrollment totals by treatment group that do not reflect dropouts. Of the 520 randomized patients, 325 (62.5%*) completed the study for 3 months, and 278 for 6 months. Denominators for the number of patients per dose at 3 and 6 month followups were not reported in tables or text.
‡Duloxetine patients on the 20 mg dose during the first 3 months had their dose blindly increased to 60 mg/day for months 4 through 6 (n=49†)

Discussion

Key Findings and Strength of Evidence

Despite the clinical belief that the treatment effects for fibromyalgia may vary in adult subgroups,[25-27] there is little information to support this hypothesis. Evidence is largely insufficient to determine subgroup effects, with the exception of the drug duloxetine. We were unable to conduct a meta-analysis because relatively few studies examined subgroups as well as the variety of subgroup-treatment-outcome combinations we encountered.

Table 12 summarizes the major findings and associated strength of evidence for subgroup analyses with at least two studies. All but one comparison for which we could assign strength of evidence involved duloxetine.

Limited, low-strength evidence, mostly for duloxetine effects on pain in adults with fibromyalgia and major depressive disorder, suggests that treatment effects do not differ in this subgroup. Sparse, low-strength evidence suggests that duloxetine effects on global improvement (PGI-I) and fibromyalgia impact (FIQ) do not differ in the MDD patient subgroup. Evidence was insufficient regarding duloxetine effects on depression (HAMD) and milnacipran effects on VAS pain scores for adults with MDD and fibromyalgia.

Low-strength, limited RCT evidence for duloxetine effects by age (on BPI average pain and PGI-I), sex (on PGI-I) and race (on PGI-I) suggest that treatment effects do not differ in these subgroups.

For all other subgroup-treatment-outcome comparisons, evidence was insufficient to draw conclusions about subgroup treatment effects.

Few studies have examined subgroup treatment outcomes in fibromyalgia. We found little evidence to inform treatment decisions for adults with fibromyalgia and nondepression psychological or medical comorbidities, as these individuals were often excluded from clinical trials. Uniformly excluded were those with rheumatologic conditions, serious medical conditions, and psychological disorders other than depression or anxiety. Little information was reported on individuals over age 55, and extensive medical exclusion criteria likely impacted the participation of older individuals in clinical trials.

Clinicians and patients are thus left with little to guide their treatment decisions. Multimorbid fibromyalgia patients are the clinical reality.[40,76,79,102-105] Yet, clinical trial results from restricted patient samples offer little information to assist in clinical decisionmaking when multiple comorbid conditions are present. Although the prevalence of single subgroup membership is estimated for some individual conditions (such as depression), the prevalence of subgroups with simultaneous (multiple) comorbid conditions within this population is incompletely identified.

In general, overall treatment effects were small and even less when substantial placebo-group improvements were considered relative to treatment effects. Subgroup effects paralleled the magnitude and direction of overall treatment and placebo effects in mixed-sample studies. Reporting of overall interaction results, or assessment for differential treatment effects based on subgroup membership, was inconsistent across and within studies, and most interaction results were reported in text only.

The fibromyalgia subgroup outcomes evidence is overwhelmingly pharmaceutical and all but one comparison for which we could assign strength of evidence involved duloxetine. Drug trials were based on the most highly selective sampling criteria of all the studies we reviewed. The pharmaceutical industry was heavily involved in all study aspects, including funding, study management, data analysis, and results reporting. It was common to find the corresponding and

other authors located in industry (Appendix Tables E13-E17). Nonsignificant subgroup effects in drug studies were often difficult to find and sometimes indeterminable within selective article text. When subgroup interactions were assessed, data tables often presented p-values for individual comparisons within strata, rather than overall negative subgroup interaction results.

In general, sample selection criteria were restrictive, and the extent to which such select patient samples reflect average patients in subgroups of adults with fibromyalgia is unknown. Despite this careful patient selection, attrition by 3-month followup was high (25 to 40 percent in most studies; range 4 percent to 47 percent). Dropouts were typically reported only in aggregate; the effects of attrition on initially small subgroup or treatment group sample sizes were usually indeterminable. All but one study used the 1990 ACR preliminary diagnostic criteria for fibromyalgia.

Adverse effects were rarely reported for subgroups and appear not to differ within them.

Subgroup samples were small except in pooled drug RCT analyses. However, drug studies, including pooled analyses, routinely reported only baseline enrollment sample sizes; the tables and text did not account for attrition. Other common methodological limitations were insufficient power to detect subgroup effects and lack of correction for multiple outcomes testing. Also, it was often not possible to determine whether or not subgroups were decided a priori or post hoc (Appendix tables E4-E7).

Applicability and Limitations of the Evidence Base

Several important characteristics limit the generalizability and applicability of these review results.

Study patients were largely middle-aged white females with moderate to severe fibromyalgia symptoms at baseline as measured by the FIQ, which is generally representative of the fibromyalgia patient population seen in clinical practice in the United States.[11,102] Few men were included in clinical trials. Sample selection criteria were most restrictive for pharmaceutical studies so that adults with mental health conditions other than depression or anxiety, or those with higher medical comorbidity burden, were excluded.

Subgroup outcomes evidence is mostly pharmaceutical, especially for duloxetine. Fewer studies assessed the effects of physical interventions (such as exercise or weight loss), psychological interventions (such as CBT, psychotherapy, or biofeedback), and very few assessed combination treatments.

Most drug trials were placebo-controlled RCTs. Other comparators included standard care, standard care plus adjunctive therapy, normal activities or education and information sessions.

We included four RCTs of duloxetine that are contained in three pooled IPD RCT analyses that are also included in this review. Appendix Table E17 shows differentiating study features that allowed inclusion of this literature set in our review. On careful examination, differences in outcomes timing, drug dosages (single dose vs. aggregated doses for pooled analysis), outcome measures, and an omitted treatment group in the pooled analyses were sufficient to include the four RCTs and three pooled analyses in the review.

Several issues affect the subgroup outcomes reported in this review. Outcomes are overwhelmingly reported for short-term outcomes despite that long term outcomes are of greatest interest in the management of chronic fibromyalgia syndrome. Reporting issues were particularly prominent in drug studies. The effect of attrition within subgroups was missing so the extent to which studies could detect a difference even if one existed was not determinable, particularly since power calculations, when reported, were conducted to detect main not subgroup effects.

Pooled analyses failed to acknowledge that unacceptably high attrition during input RCTs greatly diminished the reported amount of pooled patient data available for short-term analysis (more than 40 percent in some cases, see Appendix table E17). The text on the magnitude of drug treatment effects for specific outcomes rarely acknowledged placebo group improvements that would have better contextualized the magnitude of treatment benefits had the difference been directly reported. We noted inconsistencies within and across studies in which subgroup interaction effects were reported, even when methods sections identified that subgroup-treatment interactions were assessed. Selective reporting of subgroup outcomes was most often noted in results tables where individual within-stratum comparisons were identified, but the overall interaction term was either not reported or reported only in text that was distant from the table.

Additionally, statistical corrections for multiple comparisons were either not conducted or not reported in most studies, raising the chance that significant differences in outcomes across groups, if present, may have been detected by chance alone. Although numerous outcomes measures were utilized, which impeded our ability to aggregate across studies, the range of outcomes assessed was not particularly broad. Multiple measures for pain were used. Pain, perceptions of global improvement, and changes in the overall impact of fibromyalgia were most commonly reported; physical and social functioning were infrequently reported. Finally, industry funding and study involvement were considerable across all aspects of pharmaceutical trials, including manuscript construction. Careful consideration for potential reporting biases cannot be overlooked in the context of outcomes interpretation from the included drug trials.

Given this contextual information, the extent to which the fibromyalgia subgroup literature from clinical studies to date reflects the breadth and severity of the broader population of adult subgroups with fibromyalgia is unknown. Patients with both fibromyalgia and multiple physical and/or mental health comorbidities were most often excluded, which limits the applicability of these findings.

Limitations of the Comparative Effectiveness Review Process

This review's focus on subgroups required us to modify the systematic review processes used to assess overall benefits and harms of treatments in average adults. In assessing risk of bias, we assessed typical risk of bias domains for RCTs and added subgroup questions that were supported by the literature, which reflected common sense statistical practices for subgroup evaluation. We created a quality assessment form for observational studies and added similar subgroup items. We created quality assessment forms for pooled RCT IPD analyses that included quality assessments of the methods and reporting used for the summary analysis, and risk of bias assessments of the individual input RCTs. Although risk of bias/study quality assessment is inherently subjective, we tried to evaluate quality as objectively as possible using pre-specified forms that were uniformly used and rated by two reviewers.

In assessing subgroup pre-specification for included studies, we relied on information in each article, which may overstate the actual number of subgroups that were determined a priori in randomized controlled trials.[106]

This review was limited to English-language publications. The possibility of missing clinical trials with subgroup reporting with this restriction for treatments that were FDA approved and/or available in the United States is remote, especially for conventional medical therapies.[68-70]

We did not find evidence on all a priori subgroups, such as individuals with higher severity or longer duration of fibromyalgia, or rheumatologic conditions. Fibromyalgia duration and

especially baseline severity as assessed with the FIQ were often part of the sample selection criteria for clinical trials, thereby excluding individuals with mild symptoms or impairment and/or shorter syndrome duration. Adults with rheumatologic conditions were routinely excluded.

Research Gaps

Many of the subgroups identified by experts as clinically important were never investigated or were studied for only a few therapies. For the few studies that have examined subgroups, the strength of evidence was low or insufficient, suggesting that future studies with higher quality could change the conclusions of this review.

There is a clear need for more evidence for interventions other than duloxetine, and for adults with fibromyalgia and multiple comorbid conditions. Information on patients with concurrent pain conditions is particularly lacking. For example, fibromyalgia patients with conditions such as headache, gastroesophageal reflux disease, irritable bowel syndrome, back pain, and/or osteoarthritis,[4,28,102,105,107] may require treatment modifications or mixed treatment approaches, which could not be determined from the literature to date. Also, individuals with comorbid mental health conditions, other than depression or anxiety, and/or those with higher medical comorbidity burden, have been excluded from most clinical trials, especially drug trials. The extent to which such multimorbidity affects treatment needs, feasible treatment options and adverse effects requires further investigation to provide useful treatment information on multimorbid adults. Individuals with comorbid rheumatologic and other autoimmune disorders are virtually missing from the general fibromyalgia treatment outcomes literature, and may require varied treatment approaches to successfully manage and accommodate both conditions. The use of observational methods to examine existing electronic health data (e.g., health plan, integrated health care systems) could supplement clinical trial data for individuals with fibromyalgia and other conditions.

Despite purportedly high utilization of multicomponent treatments for adults with fibromyalgia, few such studies reported on subgroup effects. Drug studies dominated the studies that assessed subgroup effects; far fewer studies assessed the effects of nondrug interventions that showed potential benefits.

The vast majority of studies are short term (3 months), leaving many questions about the durability of treatment effects in the management of this chronic condition. Only one study reported that short term overall improvements were not sustained when duloxetine was taken for 6 months.[89] For clinicians, short-term studies provide very little information about how best to treat adults with fibromyalgia.

Little is reported on functional outcomes in subgroups of patients with fibromyalgia, including physical, cognitive, and social functioning. Changes in work attendance, work performance, and participation in avocational activities were rarely reported but could benefit the evidence base.

Potential differences in adverse effects in adult subgroups warrant more attention. Although most treatment harms were not serious, potentially differential effects in subgroups were reported in only one pooled IPD RCT analysis.

Study reporting needs improvement to make research information useable for clinicians, particularly in drug studies. Transparently reported, sufficiently powered clinical studies with a priori subgroup and hypothesis specifications were lacking, making subgroup treatment effect conclusions tenuous and limited. Efforts to reduce knowledge gaps from research involving

fibromyalgia adult subgroups should aim to present findings that are clear and concise for clinicians to interpret. Reporting of the impact of very high attrition on the strength of study conclusions is critical but is currently inadequate. Placebo effects, which are prominent in this patient population, should be openly reported to enable clinicians and readers to better assess the magnitude of treatment effects.

Conclusions

The fibromyalgia evidence is largely insufficient to determine subgroup effects for interventions other than duloxetine. The limitations of the primary literature preclude any change of policy or practice based on these findings.

Table 12. Key Question 1: Benefits of treatment—summary and strength of evidence of effectiveness and comparative effectiveness of treatments for fibromyalgia in adult subgroups*

Population (FM subgroup)	Intervention vs. Placebo	Outcome: Change from Baseline	Conclusion	Number of Studies	Strength of Evidence
With major depressive disorder (MDD)/ depression	Duloxetine	Brief Pain Inventory (BPI) average pain severity score	No evidence that treatment effects differ in subgroup	6: 5 RCTs; 1 pooled analysis**	Low (high risk of bias/many study limitations; consistent direction of effect)
	Duloxetine	Patient Global Impression of Improvement (PGI-I)	No evidence that treatment effects differ in subgroup	3: 2 RCTs; 1 pooled analysis**	Low (high risk of bias/many study limitations; consistent direction of effect)
	Duloxetine	Fibromyalgia Impact Questionnaire (FIQ) total score	No evidence that treatment effects differ in subgroup	2: 1 RCT; 1 pooled analysis**	Low (high risk of bias/many study limitations)
	Duloxetine	Hamilton Rating Scale for Depression (HAMD)	Unable to determine (impact of duloxetine on HAMD in adults with MDD and FM)	2: 1 RCT; 1 pooled analysis**	Insufficient (pooled interaction NS; RCT within stratum only)
	Milnacipran	Visual Analog Scale (VAS) for pain	Unable to determine (whether milnacipran effects on VAS pain differ in adults with MDD and FM)	2: 1 RCT (NR), 1 post hoc RCT analysis	Insufficient (outcomes reporting issues: 1 indirect, 1 incomplete)
Age	Duloxetine	BPI average pain severity score	No evidence that treatment effects differ in subgroup	3 RCTs	Low (high risk of bias/many study limitations)
	Duloxetine	PGI-I	No evidence that treatment effects differ in subgroup	2 RCTs	Low (high risk of bias/many study limitations)
Sex	Duloxetine	BPI average pain severity score	Weak evidence that treatment effects may differ in subgroup (3 NS; in 1 study females improved more than males)	4 RCTs	Insufficient (high risk of bias/many study limitations, inconsistent)
	Duloxetine	PGI-I	No evidence that treatment effects differ in subgroup	2 RCTs	Low (high risk of bias/many study limitations)
Race	Duloxetine	BPI average pain severity score	Weak evidence that treatment effects may differ in subgroup (2 NS; in 1 study nonwhites improved more than whites)	3 RCTs	Insufficient (high risk of bias/many study limitations, inconsistent)
	Duloxetine	PGI-I	No evidence that treatment effects differ in subgroup	2 RCTs	Low (high risk of bias/many study limitations)

Abbreviations: F = female; FM = fibromyalgia; HAMD = Hamilton Rating Scale for Depression; M = male; MDD = major depressive disorder; NR = not reported; NS = not significant; NW = nonwhite; RCT = randomized controlled trial; W = white

*Table shows strength of evidence for subgroup-treatment-outcomes combinations with at least two relevant studies. Other comparisons that had insufficient evidence (addressed by single studies that had high risk of bias and small sample sizes) are not shown.

**Arnold 2009[25] is a pooled analysis of patient-level data from four RCTs that are also included in this report. Rationale for the inclusion of non-overlapping information from these studies is provided in the Discussion and Appendix Table E17.

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Abbreviations

ACR	American College of Rheumatology
AE	Adverse effects
AMED	Allied and Complementary Medicine
AS	Ankylosing spondylitis
BDI	Beck Depression Inventory
BPI	Brief Pain Inventory
BMI	Body Mass Index
CAM	Complementary and alternative medicine
CENTRAL	Cochrane Central Register of Controlled Trials
CER	Comparative effectiveness review
CGI-S	Clinical Global Impression of Severity Scale
EMG	Electromyography
EQ-5D	EuroQol health outcomes assessment
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
FIQ	Fibromyalgia Impact Questionnaire
FIQR	Revised FIQ
FM	Fibromyalgia
GAD	Generalized Anxiety Disorder
GI	Gastrointestinal
HAMD	Hamilton Rating Scale for Depression
HRQoL	Health-related quality of life
IBS	Irritable Bowel Syndrome
IPD	Individual patient data
ICTRP	International Controlled Trial Registry Platform
MAF	Multidimensional Assessment of Fatigue
MCID	Minimum Clinically Important Difference
MDD	Major Depressive Disease
MeSH	Medical subject headings
MOS	Medical Outcomes Study sleep scale
MFI	Multidimensional Fatigue Inventory
MMPI	Minnesota Multiphasic Personality Inventory
MT	Multidisciplinary Treatment
NR	Not Reported
NW	Non White
OA	Osteoarthritis
PGART	Patient's Global Assessment of Response to Therapy
PGIC	Patient Global Impression of Change Score
PGI-I	Patient Global Impression of Improvement Scale
PICOTS	Population, Intervention, Comparator, Outcomes, Timing, Setting
PSQI	Pittsburgh Sleep Quality Index
QoL	Quality of Life
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
SCL-90-R	Symptom Checklist-90-Revised

SDS	Sheehan Disability Scale
SF-36	MOS Short-Form 36-item Health Survey
SLE	Lupus
SSRI	Selective Serotonin Reuptake Inhibitors
SNRI	Serotonin Nor-epinephrine Reuptake Inhibitors
W	White
VAS	Visual Analogue Scale

Appendix A. Medications Used Off Label for Fibromyalgia Syndrome in the United States

Trade Name	Generic Name	Manufacturer	Therapeutic Class	FDA-Fibro	Subclass
Prozac	Fluoxetine	Eli Lilly and Co	Antidepressants	Off label	SNRI
Elavil	Amitriptyline	AstraZeneca	Antidepressants	Off label	Tricyclic anti-depressant
Paxil CR	Paroxetine	GlaxoSmithKline	Antidepressants	Off label	SNRI
Mirapex	Pramepixole	Boehringer Ingelheim	Anti-Dyskinetic	Off label	Nonergot Dopamine Agonist
Amrix	Cyclobenzapine	Cephalon, Inc	Muscle relaxant	Off label	Centally-acting skeletal muscle relaxant
Ultracet	Tramadol	Janssen Pharmaceuticals	Analgesic	Off label	Synthetic opioid analgesic, SNRI
Ultram	Tramadol	Janssen Pharmaceuticals	Analgesic	Approved for chronic pain	Synthetic opioid analgesic, SNRI
ConZip	Tramadol	Vertical Pharmaceuticals	Analgesic	Off label	Synthetic opioid analgesic, SNRI
Neurontin	Gabapentin	Pfizer	Anti-convulsant	Off label	GABA (gamma amino-butyric acid) analog
Deptran	Doxepin	Generic	Antidepressant, Anxiolytic, Antipruritic	Off label	Tricyclic antidepressant
Tizanadine	Xanaflex	Cephalon, Inc	Muscle relaxant	Off label	Central alpha-2 Adrenergic Agonist
Flexeril	Cyclobenzapine	McNeil Consumer and Specialty	Muscle relaxant	Off label	Centrally-acting skeletal muscle relaxant
Ambien	Zolpidem	Sanofi Aventis	Sedative-Hypnotic(Non-Barbiturate)	Off label	Imidazopyridine
Lunesta	Eszipoclone	Sunovion Pharms Inc	Non-barbiturate hypnotic	Off label	Non-benzodoazepine
Klonopin	Clonazepam	Roche	Anxiolytic	Off label	Benzodiazepine
Lexapro	Escitalopram	Forest Labs	Antidepressants	Off label	SSRI
Zoloft	Sertraline	Pfizer	Antidepressants	Off label	SSRI
Motrin	Ibuprofen	Pfizer	Analgesic/Anti-inflammatory	Off label	NSAID
Advil	Ibuprofen	Pfizer	Analgesic/Anti-inflammatory	Off label	NSAID
Aleve	Naproxen	Bayer	Analgesic/Anti-inflammatory	Off label	NSAID
Celebrex	Celecoxib	Pfizer	Analgesic/Anti-inflammatory	Off label	NSAID
Aspirin	Acetylsalicyclic acid	Bayer	Analgesic/Anti-inflammatory	Off label	NSAID
Tylenol	Acetaminophen	McNeil Consumer Healthcare	Analgesics	Off label	Non-opioid Analgesics
Desyrel	Trazadone	Generic	Antidepressants	Off label	serotonin antagonist reuptake inhibitor
Oxycontin	Oxycodone	Purdue	Analgesics	Off label	Opioid Analgesics
Percocet	Oxycodone	Endo	Analgesics	Off label	Opioid Analgesics
Vicodin	Hydrocodone	AbbVie	Analgesics	Off label	Opioid Analgesics
Dilaudid	Hydromorphine	Purdue	Analgesics	Off label	Opioid Analgesics
MsContin	Morphine	Purdue	Analgesics	Off label	Opioid Analgesics
Duragesic	Fentanyl	Generic	Analgesics	Off label	Opioid Analgesics
Valium	Diazepam	Roche	Anxiolytic	Off label	Benzodiazepine
Clinoxan	Tetrazapem	Generic	Anxiolytic	Off label	Benzodiazepine
Millipred	Prednisolone	Generic	Anti-inflammatory-Immunosuppressant	Off label	Corticosteroid, Glucocorticosteroid

Trade Name	Generic Name	Manufacturer	Therapeutic Class	FDA-Fibro	Subclass
Xyrem	Sodium Oxybate	Jazz Pharmaceuticals	CNS depressant	Off label	Narcotic sedative: FDA rejected for FM

Abbreviations: FDA-Food and Drug Administration; FM-Fibromyalgia; NSAID-Non-Steroidal Anti-Inflammatory Drugs; SNRI-Serotonin Norepinephrine Re-uptake Inhibitors; SSRI-Selective Serotonin Reuptake Inhibitors

Appendix B. Fibromyalgia Search Strings

Database: Ovid MEDLINE® Search Strategy:

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1 meta analysis as topic/ (14174)
2 meta-analy$.tw. (58094)
3 metaanaly$.tw. (1283)
4 meta-analysis/ (51865)
5 (systematic adj (review$1 or overview$1)).tw. (47251)
6 exp Review Literature as Topic/ (7718)
7 or/1-6 (115989)
8 cochrane.ab. (33481)
9 embase.ab. (29939)
10 (psychlit or psyclit).ab. (1190)
11 (psychinfor or psycinfo).ab. (8325)
12 or/8-11 (48550)
13 reference list$.ab. (11704)
14 bibliograph$.ab. (11806)
15 hand search.ab. (876)
16 relevant journals.ab. (904)
17 manual search$.ab. (2248)
18 or/13-17 (25683)
19 selection criteria.ab. (26165)
20 data extraction.ab. (10119)
21 19 or 20 (33811)
22 review/ (1921415)
23 21 and 22 (26055)
24 comment/ (537610)
25 letter/ (807565)
26 editorial/ (337037)
27 animal/ (5506319)
28 human/ (13689930)
29 27 not (28 and 27) (3970292)
30 or/24-26,29 (5167730)
31 7 or 12 or 18 or 23 (144954)
32 31 not 30 (135948)
33 randomized controlled trials as topic/ (102691)
34 randomized controlled trial/ (390224)
35 random allocation/ (81795)
36 double blind method/ (131905)
37 single blind method/ (19625)
38 clinical trial/ (504861)
39 clinical trial, phase i.pt. (16220)
40 clinical trial, phase ii.pt. (26918)
41 clinical trial, phase iii.pt. (10181)
42 clinical trial, phase iv.pt. (997)

43 controlled clinical trial.pt. (89925)
44 randomized controlled trial.pt. (390224)
45 multicenter study.pt. (182851)
46 clinical trial.pt. (504861)
47 exp Clinical trials as topic/ (296596)
48 or/33-46 (959756)
49 (clinical adj trial$).tw. (211765)
50 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (129589)
51 placebos/ (33783)
52 placebo$.tw. (161799)
53 randomly allocated.tw. (16078)
54 (allocated adj2 random$).tw. (18581)
55 49 or 50 or 51 or 52 or 53 or 54 (418203)
56 48 or 55 (1126654)
57 case report.tw. (184302)
58 case report.tw. (184302)
59 letter/ (807565)
60 historical article/ (300466)
61 57 or 58 or 59 or 60 (1281048)
62 56 not 61 (1102751)
63 exp cohort studies/ (1371088)
64 cohort$.tw. (263920)
65 controlled clinical trial.pt. (89925)
66 epidemiologic methods/ (30994)
67 limit 66 to yr=1971-1983 (5365)
68 63 or 64 or 65 or 67 (1546297)
69 exp case-control study/ (666622)
70 (case$ and control$).tw. (314550)
71 69 or 70 (892406)
72 exp Fibromyalgia/ (6360)
73 fibromyalgia.ti,ab. (6304)
74 myofascial pain syndrome*.ti,ab. (387)
75 32 or 62 or 68 or 71 (2692964)
76 72 or 73 or 74 (7791)
77 75 and 76 (2584)
78 limit 77 to “all adult (19 plus years)” (1910)
79 limit 78 to “all child (0 to 18 years)” (309)
80 77 not 79 (2275)
81 78 or 80 (2584)

Database: Embase Classic+Embase Search Strategy:

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1 fibromyalgia/ (13099)
2 fibromyalgia.ti,ab. (10216)
3 exp myofascial pain/ (6786)
4 myofacial pain syndrome*.ti,ab. (27)
5 1 or 2 or 3 or 4 (20091)
6 retracted article/ (7252)
7 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab. (1017703)
8 (animal$ not human$).sh,hw. (3953097)
9 (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/ (4100517)
10 6 or 7 (1024797)
11 10 not (8 or 9) (836009)
12 exp cohort analysis/ (170749)
13 exp longitudinal study/ (69111)
14 exp prospective study/ (264902)
15 exp follow up/ (816417)
16 cohort$.tw. (389844)
17 12 or 13 or 14 or 15 or 16 (1380858)
18 exp case-control study/ (94713)
19 (case$ and control$).tw. (472185)
20 18 or 19 (507755)
21 (case$ and series).tw. (193606)
22 exp review/ (2091689)
23 (literature adj3 review$).ti,ab. (234902)
24 exp meta analysis/ (80432)
25 exp “Systematic Review”/ (70130)
26 22 or 23 or 24 or 25 (2301941)
27 (medline or embase or pubmed or cinahl or amed or psychlit or psychinfo or scisearch or cochrane).ti,ab. (106533)
28 retracted article/ (7252)
29 27 or 28 (113736)
30 26 and 29 (84397)
31 (systematic$ adj2 (review$ or overview)).ti,ab. (72028)
32 (meta?anal$ or meta anal$ or metaanal$ or metanal$).ti,ab. (80995)
33 30 or 31 or 32 (170495)
34 11 or 17 or 20 or 21 or 33 (2715453)
35 5 and 34 (4204)
36 limit 35 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) (379)
37 limit 36 to (adult <18 to 64 years> or aged <65+ years>) (289)
38 35 not 36 (3825)
39 37 or 38 (4114)
40 limit 39 to (book or book series or conference abstract or conference paper or conference proceeding or “conference review” or editorial or letter or note or report or short survey or trade journal) (887)
41 39 not 40 (3227)

Database: PsycINFO® Search Strategy:

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1 fibromyalgia/ (1194)
2 myofacial pain syndrome*.ti,ab. (2)
3 fibromyalgia.ti. (1331)
4 1 or 2 or 3 (1594)
5 limit 4 to (“0200 book” or “0240 authored book” or “0280 edited book” or “0300 encyclopedia” or “0400 dissertation abstract”) (168)
6 4 not 5 (1426)
7 limit 6 to (abstract collection or bibliography or chapter or “column/opinion” or “comment/reply” or dissertation or editorial or encyclopedia entry or letter or obituary or poetry or publication information or reprint or review-book or review-media or review-software & other) (126)
8 6 not 7 (1300)
9 limit 8 to (childhood <birth to 12 years> or adolescence <13 to 17 years>) (34)
10 limit 9 to adulthood <18+ years> (23)
11 8 not 9 (1266)
12 10 or 11 (1289)

Database: Cochrane Library Search Strategy:

Fibromyalgia’ in title, abstract, keyword

AMED (Allied and Complementary Medicine)

Set	Search
001	meta analysis.af.
002	meta-analy$.tw.
003	metaanaly$.tw.
004	meta-analysis/
005	(systematic adj (review$1 or overview$1)).tw.
006	literature review.af.
007	1 or 2 or 3 or 4 or 5 or 6
008	cochrane.ab.
009	embase.ab.
010	(psychlit or psyclit).ab.
011	(psychinfor or psycinfo).ab.
012	8 or 9 or 10 or 11
013	reference list$.ab.
014	bibliograph$.ab.
015	hand search.ab.
016	relevant journals.ab.
017	manual search$.ab.
018	13 or 14 or 15 or 16 or 17
019	selection criteria.ab.
020	data extraction.ab.
021	19 or 20
022	review.af.
023	21 and 22
024	letter.pt.
025	comment.pt.
026	editorial.pt.
027	animal.af.
028	human.af.
029	(animal not (human and animal)).af.
030	24 or 25 or 26 or 29
031	7 or 12 or 18 or 23
032	((meta analysis or meta-analy$ or metaanaly$ or meta-analysis or (systematic adj (review$1 or overview$1)) or literature review or (cochrane or embase or (psychlit or psyclit) or (psychinfor or psycinfo)) or (reference list$ or bibliograph$ or hand search or relevant journals or manual search$) or ((selection criteria or data extraction) and review)) not (letter or comment or editorial or (animal not (human and animal)))).af.
033	randomized controlled trials/
034	randomized controlled trial/
035	random allocation/
036	double blind method/
037	single blind method/
038	clinical trial/
039	clinical trial.pt.

040 controlled clinical trial.pt.
041 randomized controlled trial.pt.
042 multicenter study.pt.
043 clinical trial.pt.
044 clinical trial.af.
045 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
046 (clinical adj trial$).tw.
047 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$ 3)).tw.
048 placebos/
049 placebo$.tw.
050 randomly allocated.tw.
051 (allocated adj2 random$).tw.
052 46 or 47 or 48 or 49 or 50 or 51
053 45 or 52
054 case report.tw.
055 case report.tw.
056 letter.pt.
057 historical article.af.
058 54 or 56 or 57
059 53 not 58
060 exp cohort studies/
061 cohort$.tw.
062 controlled clinical trial.pt.
063 epidemiologic methods/
064 60 or 61 or 62
065 exp Case Control Studies.
066 (case$ and control$).tw.
067 65 or 66
068 exp FIbromyalgia/
069 fibromyalgia.ti,ab.
070 myofascial pain syndrome*.ti,ab
071 32 or 59 or 64 or 67
072 68 or 69 or 70
073 71 and 72
074 adult/ or aged/ or middle aged/
075 child/ or infant/
076 73 and 74
077 76 not 75
078 (adult or aged or middle aged).af
079 (child or infant).af.
080 73 and 78
081 (73 and 78) not 79

Appendix C. Treatments for Fibromyalgia in Adult Subgroups Risk of Bias Assessment for Observational Studies

Question	Response	Criteria	Justification
		Internal Validity	
1. Study design: prospective, retrospective or mixed?	Prospective ☐	Outcome had not occurred when study was initiated; information was collected over time	
	Mixed ☐	One group was studied prospectively; other(s) retrospectively	
	Retrospective ☐	Analyzed data from past records, claims	
2. Were inclusion/exclusion criteria clearly stated?	Yes ☐	Clearly stated	
	Partially ☐	Some, but not all criteria stated or some not clearly stated.	
	No ☐	Unclear	
3. Were baseline characteristics measured using valid and reliable measures and are they equivalent in both groups?	Yes ☐	Valid measures, groups ~equivalent	
	No ☐	Non-validated measures or nonequivalent groups	
	Uncertain ☐	Could not be ascertained	
4. Were important variables known to impact the outcome(s) assessed at baseline?	Yes ☐	Yes, most or all known factors were assessed	
	No ☐	Critical factors are missing	
	Uncertain ☐		
5. Is the level of detail describing the intervention adequate?	Yes ☐	Intervention sufficiently described	
	Partially ☐	Some of the above features.	
	No ☐	Intervention poorly described	
6. Is the selection of the comparison group appropriate?	Yes ☐	Other fibromyalgia patients with similar patient characteristics, severity and comorbid features	
7. Was the impact of a concurrent intervention or an unintended exposure that might bias results isolated?	Yes ☐	By inclusion criteria, protocol or other means	
	Partially ☐	Some were isolated, others were not	
	No ☐	Important concurrent interventions were not isolated or prohibited	
8. Were there attempts to balance the allocation across groups? (e.g., stratification, matching or propensity scores)	Yes ☐	(*If yes, what method was used?)*	
	No ☐		
	Uncertain ☐	Could not be ascertained	
9. Were outcomes assessors blinded?	Yes ☐	Who assessed outcomes?	
	No ☐		
	Uncertain ☐	Not reported	
10. Were outcomes assessed using valid and reliable measures, and used consistently across all study participants?	Yes ☐	Measures were valid and reliable (i.e., objective measure, validated scale/tool); consistent across groups	
	Partially ☐	Some of the above features	
	No ☐	None of the above features	
	Uncertain ☐	Could not be ascertained.	
11. Was length of followup the same for all groups?	Yes ☐		
	No ☐		
	Uncertain ☐	Could not be ascertained	
12. Did attrition result in	Yes ☐	*(If yes, for which followup period(s)?)*	

Question	Response	Criteria	Justification
	Internal Validity		
differences in group characteristics between baseline and followup?	No ☐		
	Uncertain ☐	Could not be ascertained	
13. If dissimilar baseline characteristics, does the analysis control for baseline differences between groups?	Yes ☐	What method?	
	No ☐		
	Uncertain ☐	Could not be ascertained	
14. Were confounding and/or effect modifying variables assessed using valid and reliable measures across all study participants?	Yes ☐		
	No ☐		
	Uncertain ☐	Could not be ascertained (i.e., retrospective designs where eligible at baseline could not be determined)	
	NA ☐	No confounders or effect modifiers included in the study.	
15. Were important confounding and effect modifying variables taken into account in design and/or analysis? (e.g., matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment)	Yes ☐		
	Partially ☐	Some variables taken into account or adjustment achieved to some extent.	
	No ☐	Not accounted for or not identified.	
	Uncertain ☐	Could not be ascertained	
16. Are statistical methods used to assess the primary outcome appropriate to the data?	Yes ☐	Statistical techniques used must be appropriate to the data.	
	Partially ☐		
	No ☐		
	Uncertain ☐	Could not be ascertained	
17. Is there suggestion of selective outcome reporting?	Yes ☐	Not all prespecified outcomes reported, subscales not prespecified reported, outcomes reported incompletely	
	No ☐		
	Uncertain ☐	Could not be ascertained	
18. Was the funding source identified?	No ☐		
	Yes ☐	Who provided funding?	
	Uncertain ☐		

Additional subgroup items[1]	
Was subgroup variable measured at baseline?	
Were subgroups pre-specified (a priori)?	
Was direction of subgroup effect on each/main outcome specified a priori? If so, was result consistent with it?	
Is subgroup effect significant? Skeptical p>0.01; Maybe (0.01<p<0.1) vs p<0.001 believable)	
Is subgroup effect large?	
Is subgroup effect independent? (is another interaction significant that is a related variable?)	
Is the interaction effect consistent across similar outcomes in the study?	

Question	Response	Criteria	Justification
	Internal Validity		
Overall Assessment			
Overall Risk of Bias assessment	Low ☐	Results are believable taking study limitations into consideration	
	Moderate ☐	Results are probably believable taking study limitations into consideration	

Question	Response	Criteria	Justification
	Internal Validity		
	High ☐	Results are uncertain taking study limitations into consideration	

Reference

1. Sun X, Briel M, Walter SD, et al. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ. 2010;340:c117. PMID 2035401.

RCT Risk of bias assessment: Fibromyalgia subgroup studies

Selection Bias	
Was method of randomization used to generate the sequence described in sufficient detail to assess whether it should produce comparable groups? (inadequate randomization?)	
Were all randomized participants analyzed in the group to which they were allocated?	
Were the groups similar at baseline regarding the most important prognostic indicators?	
Was method of treatment allocation adequate to keep treatment concealed until desired time?(inadequate allocation concealment)	
Risk of selection bias (inadequate randomization or allocation concealment):	**[Low, Unclear, High]**
Performance Bias	
Was the care provider blinded to the intervention?	Yes, no, NR
Were the participants blinded to the intervention?	Yes, no, NR
Nondrug interventions: Were interventions adequately defined so they could be replicated?	
Was the intended blinding effective?	
Risk of performance bias due to lack of participant and personnel blinding, intervention definition & fidelity to treatment?	**[Low, Unclear, High]**
Detection Bias	
Were the outcome assessors blinded to the intervention?	Yes, no, NR, NA
Was the scale/tool used to measure outcomes validated, reliable?	
Were co-interventions avoided?	
Was the timing of the outcome assessment similar in all groups?	
Were significance estimates for results appropriately corrected for multiple comparisons?	
Was study adequately powered – To detect main effects? To detect differences in subgroups?	
Risk of detection bias due to lack of outcome assessor blinding, measurement of outcomes, statistical analysis, low study power	**[Low, Unclear, High]**
Attrition Bias	
Was attrition lower than 20%? -overall -in subgroups	Y, N, NR, NR for SG %
Were reasons for incomplete/missing data adequately explained? (# assessed, # dropped out, # lost to follow-up)	
Were losses to followup also reported for subgroups?	
Was incomplete data handled appropriately?	

Risk of attrition bias due to amount, nature, or handling of incomplete outcome data?	**[Low, Unclear, High]**
Reporting Bias	
Were all outcomes reported in Results or were only select outcomes reported?	
Were results (in tables and/or text) reported for all randomized patients -for main outcomes? -for all outcomes? -for subgroups?	
What is the risk of reporting bias due to selective outcome reporting?	**[Low, Unclear, High]**
Other Sources of Bias	
Are there other risks of bias? If yes, describe them	
Additional subgroup items	
Was subgroup variable measured at baseline or after randomization?	
Were subgroups pre-specified (a priori)?	
Was direction of subgroup effect on each/main outcome specified a priori? If so, was result consistent with it?	
Is subgroup effect significant? (skeptical: p>0.01 vs maybe (0.01<p<0.1) vs p<0.001 believable)	S-M-B vs NR -or text of "NS"
Is subgroup effect large?	
Is subgroup effect independent?	
Is the interaction effect consistent across similar outcomes in the study?	
Overall Risk of Bias Assessment by outcome(s)	**[Low, Moderate or High] and explanation (1-2 sentences)**

References:

1. Sun X, Briel M, Walter SD, et al. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ. 2010;340:c117. PMID 2035401
2. Viswanathan M, Ansari M, Berkman N, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. AHRQ. 2012.
3. Higgins JPT, Altman D, Sterne J. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions: Version 5.1.0. The Cochrane Collaboration; 2011.

Pooled individual patient data RCTs risk of bias assessment: Fibromyalgia subgroup studies

Study Inputs	
Overall risk of bias summary – input study #1	
Overall risk of bias summary – input study #2	
Overall risk of bias summary – input study #3	
Overall risk of bias summary – input study #4	
Considerations for subgroup interaction in IPD pooled RCT analysis	
Did authors consider inclusion of "across-trial" information? [Fisher, 2011]	
Analytic technique selected, ordered from most to least optimal:[Fisher, 2011] 1. OSM: "one-stage" model with covariate interaction (do authors include a term for trial membership, if this method was chosen?) 2. PWT: pooling of within-trial covariate interaction 3. CWA: "manually" combining separately calculated within- and across-trial effects 4. TCDS: testing for treatment effect differences across covariate subgroups	
Was heterogeneity in interaction effects discussed? (E.g., large I^2 or obvious outlier, or confounding)	
Optimal presentation: were results of interaction effect presented graphically for reader to see (similar to "default presentation style" suggested by Fisher 2011[Fisher, 2011 #4632])?	
Risk of analytic bias based on IPD method for pooled analysis:	[Low, Unclear, High]
Reporting Bias- pooled IPD analysis	
Were all outcomes reported in Results or were only select outcomes reported? (compare to methods section)	
Were results (in tables and/or text) reported for all randomized patients -for main outcomes? -for all outcomes? -for subgroups?	
What is the risk of reporting bias due to selective outcome reporting in pooled analysis?	[Low, Unclear, High]
Additional subgroup items- pooled IPD analysis (adapted from Sun et al.[Sun, 2010 #4677])	
Were subgroups pre-specified (a priori in RCTs) or only for pooled analysis?	
Was direction of subgroup effect on each/main outcome specified a priori? If so, was result consistent with it?	
Is subgroup effect significant? (Skeptical: p>0.01 vs Maybe (0.01<p<0.1) vs p<0.001 Believable)	S-M-B vs NR -or text of "NS"
Is subgroup effect large?	
Is subgroup effect independent? (is another interaction significant for a related variable?)	
Is the interaction effect consistent across similar outcomes in the study?	
Risk of Bias Assessment for pooled IPD methods and reporting	[Low, Moderate or High] and brief rationale (transfer to bottom of this assessment form)

RCT inputs for pooled analysis	
Selection Bias-input RCTs	
Was method of randomization used to generate the sequence described in sufficient detail to assess whether it should produce comparable groups? (inadequate randomization)?	
Were all randomized participants analyzed in the group to which they were allocated? (Intention to treat (ITT))	
Were the groups similar at baseline regarding the most important prognostic indicators?	
Was method of treatment allocation adequate to keep treatment concealed until desired time?(inadequate allocation concealment)	
Risk of selection bias (inadequate randomization or allocation concealment):	[Low, Unclear, High]
Performance Bias-input RCTs	
Was the care provider blinded to the intervention?	Yes, no, NR
Were the participants blinded to the intervention?	Yes, no, NR
Nondrug interventions: Were interventions adequately defined so they could be replicated?	
Was the intended blinding effective?	
Risk of performance bias due to lack of participant and personnel blinding, intervention definition & fidelity to treatment?	[Low, Unclear, High]
Detection Bias-input RCTs	
Were the outcome assessors blinded to the intervention?	Yes, no, NR, NA
Was the scale/tool used to measure outcomes validated, reliable?	
Were co-interventions avoided?	
Was the timing of the outcome assessment similar in all groups?	
Were significance estimates for results appropriately corrected for multiple comparisons?	
Was study adequately powered – To detect main effects? To detect differences in subgroups?	
Risk of detection bias due to lack of outcome assessor blinding, measurement of outcomes, statistical analysis, low study power	[Low, Unclear, High]
Attrition Bias-input RCTs	
Was attrition lower than 20%? -overall -in subgroups	Y, N, NR, NR for SG %
Were reasons for incomplete/missing data adequately explained? -# assessed, -# dropped out, # lost to follow-up, # died	
Were losses to follow-up also reported for subgroups?	
Incomplete data handled appropriately?	
Risk of attrition bias due to amount, nature, or handling of incomplete outcome data?	[Low, Unclear, High]
Reporting Bias-input RCTs	
Were all outcomes reported in Results or were only select outcomes reported (compared to methods section)?	
Were results (in tables and/or text) reported for all randomized patients (vs. only treatment completers) -for main outcomes? -for all outcomes? -for subgroups?	
What is the risk of reporting bias due to selective outcome reporting?	[Low, Unclear, High]

Other Sources of Bias	
Are there other risks of bias? If yes, describe	
Additional subgroup items-input RCTs	
Was subgroup variable measured at baseline or after randomization?	
Were subgroups pre-specified (a priori)?	
Was direction of subgroup effect on each/main outcome specified a priori? If so, was result consistent with it?	
Is subgroup effect significant? Skeptical: p>0.01 vs Maybe (0.01<p<0.1) vs p<0.001 Believable [Sun, 2010 #4677]	S-M-B vs NR -or text of "NS"
Is subgroup effect large?	
Is subgroup effect independent?	
Is the interaction effect consistent across similar outcomes in the study?	
Risk of Bias Assessment for RCT inputs (by outcome)	[Low, Moderate or High] and explanation (1-2 sentences)
Risk of Bias Assessment for pooled IPD methods and reporting (from above)	[Low, Moderate or High] and explanation (1-2 sentences)
Overall Risk of Bias Assessment (by outcome)	[Low, Moderate or High] and brief explanation

Abbreviations: CWA: manually-combining separately calculated within- and across-trial effects; OSM: One-stage model with covariate interaction; PWT: pooling of within-trial covariate interactions; RCT: randomized clinical trial; TCDS: Testing for treatment effect differences across covariate subgroups

References

1. Higgins JPT, Altman D, Sterne J. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions: Version 5.1.0: The Cochrane Collaboration; 2011.
2. Viswanathan M, Ansari M, Berkman N, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions: AHRQ. 2012.
3. Sun X, Briel M, Walter SD, et al. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ 2010; 340:c117. 20354011.
4. Fisher DJ, Copas AJ, Tierney JF, et al. A critical review of methods for the assessment of patient-level interactions in individual participant data meta-analysis of randomized trials, and guidance for practitioners. J Clin Epidemiol 2011; Sep;64(9):949-67. 21411280

Appendix D. Excluded Studies

No Subgroup (n=20)

1. Huuhka MJ, Haanpaa ML, Leinonen EV. Electroconvulsive therapy in patients with depression and fibromyalgia. European Journal of Pain 2004 Aug;8(4):371-6. PMID: 15207518.
2. Jones KD, Sherman CA, Mist SD, et al. A randomized controlled trial of 8-form Tai chi improves symptoms and functional mobility in fibromyalgia patients. Clinical Rheumatology 2012 Aug;31(8):1205-14. PMID: 22581278.
3. Toussaint LL, Whipple MO, Abboud LL, et al. A mind-body technique for symptoms related to fibromyalgia and chronic fatigue. Explore: The Journal of Science & Healing 2012 Mar-Apr;8(2):92-8. PMID: 22385563.
4. Castel A, Cascon R, Padrol A, et al. Multicomponent cognitive-behavioral group therapy with hypnosis for the treatment of fibromyalgia: long-term outcome. Journal of Pain 2012 Mar;13(3):255-65. PMID: 22285609.
5. Ang DC, Kaleth AS, Bigatti S, et al. Research to encourage exercise for fibromyalgia (REEF): use of motivational interviewing, outcomes from a randomized-controlled trial. Clinical Journal of Pain 2013 Apr;29(4):296-304. PMID: 23042474.
6. Fontaine KR, Conn L, Clauw DJ. Effects of lifestyle physical activity in adults with fibromyalgia: results at follow-up. JCR: Journal of Clinical Rheumatology 2011 Mar;17(2):64-8. PMID: 21325963.
7. Alfano AP, Taylor AG, Foresman PA, et al. Static magnetic fields for treatment of fibromyalgia: a randomized controlled trial. Journal of Alternative & Complementary Medicine 2001 Feb;7(1):53-64. PMID: 11246937.
8. van Koulil S, van Lankveld W, Kraaimaat FW, et al. Tailored cognitive-behavioral therapy and exercise training for high-risk patients with fibromyalgia. Arthritis care & research 2010 Oct;62(10):1377-85. PMID: 20521308.
9. McCain GA. Role of physical fitness training in the fibrositis/fibromyalgia syndrome. American Journal of Medicine 1986 Sep 29;81(3A):73-7. PMID: 3532784.
10. Vitton O, Gendreau M, Gendreau J, et al. A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. Human Psychopharmacology 2004 Oct;19 Suppl 1:S27-35. PMID: 15378666.
11. Goldenberg DL, Clauw DJ, Palmer RH, et al. Durability of therapeutic response to milnacipran treatment for fibromyalgia. Results of a randomized, double-blind, monotherapy 6-month extension study. Pain Medicine 2010 Feb;11(2):180-94. PMID: 20002596.
12. Castro-Sanchez AM, Mataran-Penarrocha GA, Arroyo-Morales M, et al. Effects of myofascial release techniques on pain, physical function, and postural stability in patients with fibromyalgia: a randomized controlled trial. Clinical Rehabilitation 2011 Sep;25(9):800-13. PMID: 21673013.

13. Alda M, Luciano JV, Andres E, et al. Effectiveness of cognitive behaviour therapy for the treatment of catastrophisation in patients with fibromyalgia: a randomised controlled trial. Arthritis Research & Therapy 2011;13(5):R173. PMID: 22018333.

14. Pauer L, Winkelmann A, Arsenault P, et al. An international, randomized, double-blind, placebo-controlled, phase III trial of pregabalin monotherapy in treatment of patients with fibromyalgia. Journal of Rheumatology 2011 Dec;38(12):2643-52. PMID: 21965636.

15. Arnold LM, Wang F, Ahl J, et al. Improvement in multiple dimensions of fatigue in patients with fibromyalgia treated with duloxetine: secondary analysis of a randomized, placebo-controlled trial. Arthritis Research & Therapy 2011;13(3):R86. PMID: 21668963.

16. Mease PJ, Clauw DJ, Gendreau RM, et al. The efficacy and safety of milnacipran for treatment of fibromyalgia. a randomized, double-blind, placebo-controlled trial.[Erratum appears in J Rheumatol. 2009 Mar;36(3):661]. Journal of Rheumatology 2009 Feb;36(2):398-409. PMID: 19132781.

17. Mease PJ, Russell IJ, Arnold LM, et al. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. Journal of Rheumatology 2008 Mar;35(3):502-14. PMID: 18278830.

18. Cuatrecasas G, Alegre C, Fernandez-Sola J, et al. Growth hormone treatment for sustained pain reduction and improvement in quality of life in severe fibromyalgia. Pain 2012 Jul;153(7):1382-9. PMID: 22465047.

19. Cuatrecasas G, Riudavets C, Guell MA, et al. Growth hormone as concomitant treatment in severe fibromyalgia associated with low IGF-1 serum levels. A pilot study. BMC Musculoskeletal Disorders 2007 8:119. PMID: 18053120.

20. Jones KD, Deodhar AA, Burckhardt CS, et al. A combination of 6 months of treatment with pyridostigmine and triweekly exercise fails to improve insulin-like growth factor-I levels in fibromyalgia, despite improvement in the acute growth hormone response to exercise. Journal of Rheumatology 2007 May;34(5):1103-11. PMID: 17407215.

Less Than 3 Months Followup (n=21)

1. Tavoni A, Vitali C, Bombardieri S, et al. Evaluation of S-adenosylmethionine in primary fibromyalgia. A double-blind crossover study. American Journal of Medicine 1987 Nov 20;83(5A):107-10. PMID: 3318438.

2. Bagis S, Karabiber M, As I, et al. Is magnesium citrate treatment effective on pain, clinical parameters and functional status in patients with fibromyalgia? Rheumatology International 2013 Jan;33(1):167-72. PMID: 22271372.

3. Scudds RA, McCain GA, Rollman GB, et al. Improvements in pain responsiveness in patients with fibrositis after successful treatment with amitriptyline. Journal of Rheumatology - Supplement 1989 Nov;19:98-103. PMID: 2481743.

4. Holton KF, Taren DL, Thomson CA, et al. The effect of dietary glutamate on fibromyalgia and irritable bowel symptoms. Clinical & Experimental Rheumatology 2012 Nov-Dec;30(6 Suppl 74):10-7. PMID: 22766026.

5. Goldenberg DL, Felson DT, Dinerman H. A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. Arthritis & Rheumatism 1986 Nov;29(11):1371-7. PMID: 3535811.

6. Kempenaers C, Simenon G, Vander Elst M, et al. Effect of an antidiencephalon immune serum on pain and sleep in primary fibromyalgia. Neuropsychobiology 1994;30(2-3):66-72. PMID: 7800166.

7. Ozerbil O, Okudan N, Gokbel H, et al. Comparison of the effects of two antidepressants on exercise performance of the female patients with fibromyalgia. Clinical Rheumatology 2006 Jul;25(4):495-7. PMID: 16267603.

8. Schwartz TL, Siddiqui UA, Raza S, et al. Armodafinil for fibromyalgia fatigue. Annals of Pharmacotherapy 2010 Jul-Aug;44(7-8):1347-8. PMID: 20551299.

9. Ware MA, Fitzcharles MA, Joseph L, et al. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesthesia & Analgesia 2010 Feb 1;110(2):604-10. PMID: 20007734.

10. Sanudo B, de Hoyo M, Carrasco L, et al. Effect of whole-body vibration exercise on balance in women with fibromyalgia syndrome: a randomized controlled trial. Journal of Alternative & Complementary Medicine 2012 Feb;18(2):158-64. PMID: 22321155.

11. Cook DB, Stegner AJ, Nagelkirk PR, et al. Responses to exercise differ for chronic fatigue syndrome patients with fibromyalgia. Medicine & Science in Sports & Exercise 2012 Jun;44(6):1186-93. PMID: 22157881.

12. Passard A, Attal N, Benadhira R, et al. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. Brain 2007 Oct;130(Pt 10):2661-70. PMID: 17872930.

13. Roizenblatt S, Fregni F, Gimenez R, et al. Site-specific effects of transcranial direct current stimulation on sleep and pain in fibromyalgia: a randomized, sham-controlled study. Pain Practice 2007 Dec;7(4):297-306. PMID: 17986164.

14. Thomas AW, Graham K, Prato FS, et al. A randomized, double-blind, placebo-controlled clinical trial using a low-frequency magnetic field in the treatment of musculoskeletal chronic pain. Pain Research & Management 2007;12(4):249-58. PMID: 18080043.

15. Casanueva-Fernandez B, Llorca J, Rubio JB, et al. Efficacy of a multidisciplinary treatment program in patients with severe fibromyalgia. Rheumatology International 2012 Aug;32(8):2497-502. PMID: 21785956.

16. Miro E, Lupianez J, Martinez MP, et al. Cognitive-behavioral therapy for insomnia improves attentional function in fibromyalgia syndrome: a pilot, randomized controlled trial. Journal of Health Psychology 2011 Jul;16(5):770-82. PMID: 21346020.

17. Finset A, Wigers SH, Gotestam KG. Depressed mood impedes pain treatment response in patients with fibromyalgia. Journal of Rheumatology 2004 May;31(5):976-80. PMID: 15124260.

18. Affaitati G, Costantini R, Fabrizio A, et al. Effects of treatment of peripheral pain generators in fibromyalgia patients. European Journal of Pain 2011 Jan;15(1):61-9. PMID: 20889359.

19. Konuk N, Ortancil O, Bostanci B, et al. A comparison of reboxetine and amitryptilline in the treatment of fibromyalgia syndrome with co-morbid depressive symptoms: An open-label preliminary study. Klinik Psikofarmakoloji Bulteni 2010 20(1):29-37. PMID: 2010535038.

20. Vlaeyen JW, Teeken-Gruben NJ, Goossens ME, et al. Cognitive-educational treatment of fibromyalgia: a randomized clinical trial. I. Clinical effects. Journal of Rheumatology 1996 Jul;23(7):1237-45. PMID: 8823699.

21. Hoeger Bement MK, Weyer A, Hartley S, et al. Pain perception after isometric exercise in women with fibromyalgia. Archives of Physical Medicine & Rehabilitation 2011 Jan;92(1):89-95. PMID: 21187210.

Other

Post Hoc Subgroup/Exploratory (n=6)

1. Moore RA, Straube S, Paine J, et al. Fibromyalgia: Moderate and substantial pain intensity reduction predicts improvement in other outcomes and substantial quality of life gain. Pain 2010 May;149(2):360-4. PMID: 20347225.

2. Pauer L, Atkinson G, Murphy TK, et al. Long-term maintenance of response across multiple fibromyalgia symptom domains in a randomized withdrawal study of pregabalin. Clinical Journal of Pain 2012 Sep;28(7):609-14. PMID: 22688598.

3. King SJ, Wessel J, Bhambhani Y, et al. The effects of exercise and education, individually or combined, in women with fibromyalgia. Journal of Rheumatology 2002 Dec;29(12):2620-7. PMID: 12465163.

4. Arnold LM, Palmer RH, Ma Y. A 3-Year, open-label, flexible-dosing study of milnacipran for the treatment of fibromyalgia. Clinical Journal of Pain 2013 Dec;29(12):1021-8. PMID: 2013722877.

5. Burckhardt CS, Clark SR, Bennett RM. Long-term follow-up of fibromyalgia patients who completed a structured treatment program versus patients in routine treatment. Journal of Musculoskeletal Pain 2005;13(1):5-14. PMID: 2006152042.

6. Sayar K, Aksu G, Ak I, et al. Venlafaxine treatment of fibromyalgia. Annals of Pharmacotherapy 2003 Nov;37(11):1561-5. PMID: 14565792.

Predictors of Treatment Response (n=3)

1. Thieme K, Turk DC, Flor H. Responder criteria for operant and cognitive-behavioral treatment of fibromyalgia syndrome. Arthritis & Rheumatism 2007 Jun 15;57(5):830-6. PMID: 17530683.

2. Pae CU, Masand PS, Marks DM, et al. History of early abuse as a predictor of treatment response in patients with fibromyalgia: a post-hoc analysis of a 12-week, randomized, double-blind, placebo-controlled trial of paroxetine controlled release. World Journal of Biological Psychiatry 2009;10(4 Pt 2):435-41. PMID: 19382010.

3. Pae CU, Masand PS, Marks DM, et al. History of depressive and/or anxiety disorders as a predictor of treatment response: a post hoc analysis of a 12-week, randomized, double-blind, placebo-controlled trial of paroxetine controlled release in patients with fibromyalgia. Progress in Neuro-Psychopharmacology & Biological Psychiatry 2009 Aug 31;33(6):996-1002. PMID: 19433129.

Duplicate Sample (n=2)

1. Marangell LB, Clauw DJ, Choy E, et al. Comparative pain and mood effects in patients with comorbid fibromyalgia and major depressive disorder: secondary analyses of four pooled randomized controlled trials of duloxetine. Pain 2011 Jan;152(1):31-7. PMID: 20598442.
2. Arnold LM, Pritchett YL, D'Souza DN, et al. Duloxetine for the treatment of fibromyalgia in women: pooled results from two randomized, placebo-controlled clinical trials. Journal of Women's Health 2007 Oct;16(8):1145-56. PMID: 17937567.

Not Fibromyalgia Per Criteria (n=2)

1. Spitzer AR, Broadman M. A retrospective review of the sleep characteristics in patients with chronic fatigue syndrome and fibromyalgia. Pain Practice 2010 Jul-Aug;10(4):294-300. PMID: 20230458.
2. Skouen JS, Grasdal A, Haldorsen EM. Return to work after comparing outpatient multidisciplinary treatment programs versus treatment in general practice for patients with chronic widespread pain. European Journal of Pain 2006 Feb;10(2):145-52. PMID: 16310718.

Non U.S. Drug or Treatment (n=2)

1. Drewes AM, Andreasen A, Jennum P, et al. Zopiclone in the treatment of sleep abnormalities in fibromyalgia. Scandinavian Journal of Rheumatology 1991;20(4):288-93. PMID: 1925417.
2. Distler O, Eich W, Dokoupilova E, et al. Evaluation of the efficacy and safety of terguride in patients with fibromyalgia syndrome: results of a twelve-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis & Rheumatism 2010 Jan;62(1):291-300. PMID: 20039417.

Review of Another Trial (n=2)

1. Williams DA. Utility of cognitive behavioral therapy as a treatment for insomnia in patients with fibromyalgia. Nature Clinical Practice Rheumatology 2006 Apr;2(4):190-1. PMID: 16932684.
2. Mohs R, Mease P, Arnold LM, et al. The effect of duloxetine treatment on cognition in patients with fibromyalgia. Psychosomatic Medicine 2012 Jul-Aug;74(6):628-34. PMID: 22753629.

Cannot Differentiate Outcomes (n=1)

1. Fjorback LO, Arendt M, Ornbol E, et al. Mindfulness therapy for somatization disorder and functional somatic syndromes: randomized trial with one-year follow-up. Journal of Psychosomatic Research 2013 Jan;74(1):31-40. PMID: 23272986.

Inappropriate Comparison Group (n=2)

1. Rasmussen LB, Mikkelsen K, Haugen M, et al. Treatment of fibromyalgia at the Maharishi Ayurveda Health Centre in Norway II--a 24-month follow-up pilot study. Clinical Rheumatology 2012 May;31(5):821-7. PMID: 22278161.

2. Rasmussen LB, Mikkelsen K, Haugen M, et al. Treatment of fibromyalgia at the Maharishi Ayurveda Health Centre in Norway. A six-month follow-up study. Clinical & Experimental Rheumatology 2009 Sep-Oct;27(5 Suppl 56):S46-50. PMID: 20074439.

Appendix E. Evidence Tables

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Appendix Table E1. Sample selection criteria and allowed co-interventions for included fibromyalgia randomized clinical trials

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Pharmacologic					
Duloxetine					
Arnold, 2012[1] *Efficacy & Safety 30mg duloxetine* US, Mexico, Israel, Argentina Industry-funded	1990 ACR criteria	-Male & Female - ≥18 years -Score ≥4 on average pain severity of BPI-Modified Short Form -Included patients with MDD or GAD, as defined by DSM-IV and confirmed by MINI	-Prior duloxetine treatment -Prior participation in duloxetine study -Substance abuse within past year -Primary psychiatric diagnosis other than MDD/GAD within past year -History of psychosis or bipolar -Clinically judged at risk of suicide -Pregnant or breast-feeding women -Pain symptoms unrelated to FM (could interfere with outcomes) -Regional pain syndromes -Failed back syndrome -Chronic localized pain from past surgery -Rheumatoid, Inflammatory, or infectious arthritis -Autoimmune disease -Patients judged by investigator to be treatment-refractory -Patients with unstable medical conditions or whose response might be compromised by disability compensation	-Medications or herbal agents with primarily CNS activity, regular use of analgesics other than acetaminophen and aspirin, topical lidocaine or capsaicin, antidepressants, anticonvulsants, barbituates, muscle relaxants, chronic use of anti-emetics, hypnotics, and sedatives - <3 months stable therapy of anti-hypertensives, anti-arrhythmics, diuretics, and hormones; steroids other than episodic treatment of symptoms unrelated to FM; benzodiazepine use for FM pain	-Episodic use of some analgesics, such as NSAIDS, was allowed for acute injury or surgery

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Arnold, 2010[2] *Flexible Dosed Duloxetine* USA, Puerto Rico Funder not stated: industry is acknowledged; corresponding author is industry-affiliated	1990 ACR criteria	-Male & Female - ≥18 years -Score ≥4 on average pain severity of BPI-Modified Short Form at visits 1 and 2 (screening) and visit -Judged to be reliable and had a level of understanding that allowed them to communicate intelligibly and provide informed consent	-Current or diagnosed within last year with any primary psychiatric disorder other than MDD/GAD, as defined by DSM-IV -Clinically judged at risk of suicide -Unstable medical illness likely to require intervention or hospitalization -Pain syndromes unrelated to FM -Rheumatoid inflammatory arthritis -Other autoimmune disease -Severe liver disease -Pregnant or breast-feeding	-Analgesics (with the exception of up to 325 mg/day of aspirin for cardiac prophylaxis and acetaminophen up to 2 g/day for pain) -Antidepressants, including tricyclics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs) and SRNI -Encouraged not to initiate or alter ongoing nonconventional/ alternative therapies such as acupuncture, biofeedback, or CBT for study duration	-Patients entering study on stable sleep medications allowed to continue during study -Episodic use (up to 3 nights/week) of chloral hydrate, zolpidem, zopiclone, or zaleplon for sleep
Chappell, 2008[3] *Six-month Duloxetine* USA, Germany, Spain, Sweden, UK Industry-funded	1990 ACR Criteria	-Male & Female - ≥18 years -With or without MDD	-Current or previous treatment with duloxetine -Current primary psychiatric diagnosis other than MDD -Pain symptoms related to traumatic injury, structural rheumatic disease, or regional rheumatic disease -Regional pain syndromes -Multiple surgeries or failed back syndrome -Rheumatoid/ Inflammatory/Infectious arthritis -Other autoimmune disease -Serious medical illness	Not reported	Not reported

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Russell, 2008[4] *Flexible Dosed Duloxetine* USA, Puerto Rico Industry-funded	1990 ACR criteria	-Male & Female - ≥18 years -Score ≥4 on average pain severity of BPI-Modified Short Form at both screening and baseline -Patients with or without current MDD, were also evaluated for presence of psychiatric disorders using MINI	-Current primary psychiatric diagnosis other than MDD -Pain syndromes unrelated to FM -Regional pain syndromes -Multiple surgeries or failed back syndrome -Rheumatoid/ Inflammatory arthritis -Other autoimmune disease -Unstable medical or psychiatric disorders -Severe liver disease -Pregnant or breast-feeding -Substance abuse within past year -Patients judged by investigator to be treatment-refractory, or whose response might be compromised by disability compensation	-Analgesics (with the exception of up to 325 mg/day of aspirin for cardiac prophylaxis and acetaminophen up to 2 g/day for pain) -Antidepressants, anticonvulsants, or other medications taken for FM or pain -Encouraged not to initiate or alter ongoing nonconventional/ alternative therapies such as acupuncture, biofeedback, or CBT for study duration	-Sedating antihistamines and episodic use (up to 40 total days of use during the 6 months of treatment) of chloral hydrate, zolpidem, zopiclone, and zaleplon were allowed for sleep
Arnold, 2005[5] *Women with or without MDD* USA Industry-funded	1990 ACR criteria	-Females - ≥18 years - Score ≥4 on average pain severity of BPI-Modified Short Form at both screening and baseline	-Pain from traumatic injury or structural or regional rheumatic disease -Rheumatoid or Inflammatory arthritis -Autoimmune disease -Unstable medical or psychiatric illness -Primary psychiatric diagnosis other than MDD -Primary anxiety disorder within the past year (specific phobias allowed) -Substance abuse within the past year -Serious suicide risk -Pregnancy or breast-feeding -Judged by investigator to be treatment-refractory, or involvement in disability reviews that might compromise response -Severe allergic reactions to multiple medications -Prior participation in duloxetine study	-Medications or herbal agents with primarily CNS activity -Regular use of analgesics with the exception of acetaminophen up to 2 g/day and aspirin for cardiac prophylaxis up to 325 mg/day -Chronic use of sedatives, antiemetics, or antispasmodics -Initiation of or change in unconventional or alternative therapies	Not reported

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Arnold, 2004[6] *With or without MDD* USA Industry-funded with industry-managed trial implementation and statistical programming support	1990 ACR criteria	-Male & Female - ≥18 years -Score 4 on pain intensity item of FIQ at visits 1 and 2 -Judged to be reliable and had an educational level and degree of understanding that allowed them to communicate intelligibly	-Pain from traumatic injury or structural or regional rheumatic disease -Rheumatoid/Inflammatory arthritis -Autoimmune disease -Unstable medical or psychiatric illness -Dysthymia (more treatment resistant than MDD) -Primary psychiatric diagnosis other than MDD -Substance abuse within the past year -History of psychosis -Pregnancy or breast-feeding -Unacceptable contraception in those of childbearing potential -Involvement in disability reviews that might compromise response -Use of an investigational drug within 30 days -Prior participation duloxetine study -Severe allergic reactions to multiple medications -Intolerance to >3 psychoactive drugs or >1 SSRI -Failure to respond to ≥2 adequate regimens of 2 different classes of antidepressants for depression or FM	-Medications or herbal agents with primarily CNS activity -Regular use of analgesics with the exception of acetaminophen up to 2 g/day and aspirin up to 325 mg/day -Chronic use of sedatives, antiemetics, or antispasmodics -Episodic use of anticoagulants - <3 months stable therapy of antihypertensives, hormones antiarrhythmics, antidiarrheals, antihistamines, cough/cold preparations (excluding dextromethorphan), or laxatives -Initiation or change in unconventional or alternative therapies	Not reported
Milnacipran					
Gendreau, 2005[7] USA Industry-supported	1990 ACR criteria	-Ages 18 to 70 -Pain score >10 on a 20-point Gracely scale at baseline -Willing to use a contraceptive, if female, and to withdraw from all central nervous system-active therapies	- Psychosis -Active suicidality -Alcohol or substance abuse -Concurrent auto-immune, inflammatory, infectious or malignant disorder -Known sleep apnea or prostatic hypertrophy -Abnormal baseline liver or kidney function tests	-Antidepressants -Antiepileptics -Centrally-acting muscle relaxants -Hypnotics -Opioids and their derivatives -Fluoxetine	-Stable dose of NSAIDS, Aspirin, and Acetaminophen

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Off-label					
Stening, 2011[8] Sweden Industry funded	1990 ACR criteria	-Ages 49 to 60 -BMI <30 -Post-menopausal state for at least 6 months and had normal mammography screening during preceding year	-History of thromboembolism -Diabetes Mellitus -Polyneuropathy -Chronic liver disease -Alcohol or substance abuse -Hemoglobinopathy -Endometrial adenomatous hyperplasia or malignancy -Presence of untreated hypertension (>160/95) -Undiagnosed vaginal bleeding	-Anti-psychotics -Pro re nata ("unforeseen need") medications 24 hours before sensory testing -Opiates	-Daily prescribed analgesics (except opiates) -Antidepressants
Sadreddini, 2008[9] Iran No funding information	1990 ACR criteria	Postmenopausal women within 6 months before the onset of the study	-Other significant problem that causes secondary FM -Severe osteoporosis based on radiographies or DEXA (Dual X-ray Absorptiometry) examination -Prior history of thrombotic events -Prior history of breast or genital neoplasm -Immobile patients	Antidepressants	No information
Arnold, 2002[10] *Flexible-dose Fuloxetine* USA Industry-funded	1990 ACR criteria	-Females only - ≥18 years	-Evidence of traumatic injury -Inflammatory rheumatic disease -Infections or endocrine-related arthopathy -Clinically unstable medical illness -History of seizure, head trauma, or stroke -Lifetime history of hypomania, mania, psychosis, or dementia -Alcohol/substance dependence in past 6 months -Substantial risk of suicide -Current Axis I diagnosis (per the DSM-IV) -Score of ≥10 Hamilton Depression Rating Scale	-Monoamine oxidase inhibitors, tricyclics, lithium, SSRIs, or other antidepressants within 2 weeks before randomization -Investigational medications within 3 months before randomization Previously received fluoxetine for FM	-Acetaminophen or nonsteroidal anti-inflammatory medications on their usual schedule

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Physical					
Gavi, 2014[11] Spain No funding information	1990 ACR Criteria	-Females -Ages 18-65	-Cardiovascular, respiratory, metabolic, and rheumatic diseases that could limit exercise -Diseases associated with autonomic dysfunction (e.g., arterial hypertension, diabetes) -Exercise within the past 3 months -Inability to understand the questionnaires -Positive treadmill test for myocardial ischemia -Receipt of the social security benefits	-Beta blockers, calcium channel blockers, and any other anti-hypertensive -Anticonvulsants -Nontricyclic antidepressants -Opioid analgesics, including tramadol, cyclobenzaprine >10mg/day, andamitriptyline >25mg/day	-Paracetamol, max dose 2g/day
Senna, 2012[12] (nonexercise) Egypt No funding information	1990 ACR criteria	No information	-Medical disorder that would affect body weight -Inflammatory arthritis -Autoimmune disease -Unstable medical or psychiatric illness -Regimen that has not been stable for at least 2 months prior to baseline -Pregnant women or attempting to conceive -Antidepressant medication or sleeping pills	-Antidepressants -Sleeping pills	Medications prescribed by physician
Gusi, 2010[13] Spain No funding information	1990 ACR criteria	Patients meeting 1990 ACR criteria	-History of severe trauma -Frequent migraines -Peripheral nerve entrapment -Inflammatory rheumatic disease -Severe psychiatric illness -Other diseases that prevent physical loading -Pregnancy -Participation in other physical or psychological therapy program more than once a week for ≥30 minutes during a 2week period in last 5 years -Participation in other therapies (manual and/or psychological treatment) that could influence the current intervention	No information	No information
Valkeinen, 2008[14] Finland Government and foundation support	Not reported	Women >50 years	-Severe cardiovascular disease -Diabetes -Severe osteoarthritis of the large joints -Thyroid gland disorders -Any disease that might confound results -Participation in regular and aerobic and strength training and predictable difficulties for attending training sessions	No information	Previous medications for FM and other diseases such as analgesics, antidepressants and hormonal-replacement therapy

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Assis, 2006[15] Brazil Government-funded	1990 ACR criteria	-Age 18-60 -Literate -Kept in an unchanged drug regimen for at least 4 weeks prior to study	-Symptomatic cardiac failure -Uncontrolled thyroid disturbances -BMI ≥40 -Infectious contagious skin disease -Coronary disease -Pulmonary disease -Neurologic disease -Rheumatic disease limiting ability to exercise -Those who performed regular physical activity in the 6 weeks before trial	No information	Acetaminophen as rescue medication
Hakkinen, 2002[16] Finland No funding information	1990 ACR criteria	No additional information except that subjects were habitually physically active, but had no background in strength training	No information	No information	No information
Psychological					
Scheidt, 2013[17] Germany Industry Funded	-1990 ACR Criteria -ICD-10	-Female -18-70 years -Patients meeting 1990 ACR criteria for FM -diagnosis of comorbid depression or anxiety disorder	-Severe or life threatening diseases -Psychiatric or neuropsychiatric conditions associated with cognitive impairment and/or suicidal ideation -Current psychotherapy or participation in other clinical trials	No information	-Antidepressants if patient has comorbid depression -Analgesics
Castel, 2012[18] Spain No funding information	1990 ACR criteria	-Age 18-65 -Patients meeting 1990 ACR criteria for FM	-1 or more additional severe chronic medical pain conditions -Significant suicidal ideation -Severe psycho-pathology -Moderate-to-severe cognitive impairment	No information	-Analgesics -Antidepressants -Anticonvulsants -Myorelaxants
Junghaenel, 2008[19] USA Foundation funded	Not reported	-Female -FM diagnosis	No information	No information	Not reported

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Edinger, 2005[20] USA Government funded (NIAMS)	1990 ACR criteria	-Age 21-65 -Patients meeting 1990 ACR criteria for FM -Structured interview criteria for insomnia -Have 60 minutes or more of total nocturnal wake time on average over 1 week of sleep log monitoring	-Currently pregnant, breastfeeding, or not practicing contraception -Comorbid sleep-disruptive medical condition -Meeting structured interview criteria for an Axis I depressive (other than dysthymia), anxiety, or substance abuse disorder -Severe hypnotic dependence, suggested by the use of a hypnotic agent in a higher than recommended dosage or repeated episodes of rebound insomnia on withdrawal -Symptoms of sleep apnea, restless legs syndrome, or circadian rhythm disorder -Apnea-hypopnea index or periodic limb movement (PLM)-related arousal index of 15 or more per hour on a screening polysomnogram	No information	-Anti-depressants -Analgesics
Mixed					
MartÍnez, 2014[21] Brazil Government funded	1990 ACR Criteria	-Female -Ages 25-60 -Diagnosis of FM for at least 6 months -If taking medication, stable intake of analgesics, antidepressants, or other drugs at least 1 month before study -Met diagnostic criteria for insomnia, using DSM-IV criteria	-Medical history of significant head injury or neurological disorder -Major concomitant medical conditions -MDD with suicide ideation, or other major Axis I diagnoses -Symptoms of sleep-disruptive comorbidities with insomnia -An apnea hypopnea index or periodic limb movement-related arousal index of 15 or more per hour of sleep -Severe hypnotic dependence -Pregnancy	-Treatment with another psychological or physical therapy	Noted in inclusion criteria
Fontaine, 2010[22] USA Government funded (NIAMS)	1990 ACR criteria	-Age 18 or older -Patients meeting 1990 ACR criteria for FM.	-Acute or chronic medical conditions -Intention to change medication that might affect mood -Intent to seek professional treatment for anxiety or depression	No information	No information

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Lera, 2009[23] Spain No funding information	1990 ACR criteria	-Female -Patients meeting 1990 ACR criteria for FM	-Litigation against government for disability pensions -Suffering from severe depression, psychosis, or delusional disorder	No information	Analgesics

Abbreviations: ACR=American College of Rheumatology BDI=Beck Depression Inventory BMI=Body Mass Index BPI=Brief Pain Inventory CBT=Cognitive Behavioral Therapy CNS-Central Nervous System DEXA=Dual X-ray Absorptiometry DVD=Digital Video Disk DSM-IV=Diagnostic and Statistical Manual of Mental Disorder-Fourth Edition FIQ=Fibromyalgia Impact Questionnaire FM=Fibromyalgia GAD=Generalized Anxiety Disorder ICD-10=International Classification of Diseases – version 10 MDD=Major Depressive Disease MINI=Mini International Neuropsychiatric Interview NIAMS=National Institute of Arthritis and Musculoskeletal and Skin Diseases NSAID=Non-steroidal Anti-inflammatory Drug PLM=Periodic Limb Movements SSRI=Selective Serotonin Reuptake Inhibitors SNRI=Serotonin-norepinephrine reuptake inhibitor

Appendix Table E2. Sample selection criteria and allowed co-interventions for included pooled studies of patient-level randomized clinical trial data

Author, Year, Country, Funder, Studies Pooled	Diagnostic Criteria	Additional Inclusion Criteria*	Exclusion Criteria*	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Pharmacologic					
Duloxetine					
Bennett, 2012[24] USA, Puerto Rico, Germany, Spain, Sweden, United Kingdom Industry funded **Pooled**: Chappell, 2008[3] Russell, 2008[4] Arnold, 2005[5] Arnold, 2004[6]	1990 ACR criteria	-Male & Female (Female only in Arnold, 2005[5]) - ≥18 years -With or without MDD as defined by DSM-IV -Score ≥4 on either pain intensity item of FIQ (Arnold, 2004[6]) or average pain severity of BPI-Modified Short Form (Arnold, 2005,[5] Russell, 2008,[4] and Chappell, 2008[3])	-Current or prior duloxetine treatment -Current primary psychiatric (Axis I) diagnosis other than MDD as defined by DSM-IV, including current or past diagnosis of dysthymia -History of psychosis, bipolar disorder, or schizoaffective disorder -Any anxiety disorder as primary diagnosis within past year -Pain symptoms related to traumatic injury, structural rheumatic disease, or regional rheumatic disease (e.g., osteoarthritis, tendinitis) -Regional pain syndrome -Multiple surgeries or failed back syndrome -Current or previous rheumatoid arthritis, inflammatory arthritis, or autoimmune disease -Any serious medical illness	Not reported (in pooled manuscript)	Not reported (in pooled manuscript)

Author, Year, Country, Funder, Studies Pooled	Diagnostic Criteria	Additional Inclusion Criteria*	Exclusion Criteria*	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Bradley, 2010[25] USA, Puerto Rico, Germany, Spain, Sweden, United Kingdom Industry funded **Pooled**: Chappell, 2008[3] Russell, 2008[4] Arnold ,2005[5] Arnold, 2004[6]	1990 ACR criteria	-Male & Female (Female only in Arnold, 2005[5]) - ≥18 years -Score ≥4 on either pain intensity item of FIQ (Arnold, 2004[6]) or average pain severity of BPI-Modified Short Form (Arnold, 2005,[5] Russell, 2008,[4] and Chappell, 2008[3])	-Serious or unstable medical or psychiatric illness -Current primary psychiatric diagnosis other than MDD -Primary diagnosis of anxiety within past year -Pain from traumatic injury -Rheumatologic illness	Not reported (in pooled manuscript)	Not reported (in pooled manuscript)
Arnold, 2009[26] USA, Puerto Rico, Germany, Spain, Sweden, United Kingdom Industry funded **Pooled**: Chappell, 2008[3] Russell, 2008[4] Arnold, 2005[5] Arnold, 2004[6]	1990 ACR criteria	-Male & Female - ≥18 years -With or without MDD, diagnosed by MINI -Score ≥4 on average pain severity of BPI-Modified Short Form	-Pain from traumatic injury or structural or regional rheumatic disease -Rheumatoid arthritis, inflammatory arthritis, or autoimmune disease -Unstable medical of psychiatric illness -Current primary psychiatric diagnosis other than MDD -Primary anxiety disorder within the past year -Serious suicide risk -Pregnancy or breastfeeding -Patients, who, in the opinion of the investigator, were treatment refractory or may have had involvement in disability reviews that may compromise treatment response -Severe allergic reaction to multiple medications -Prior participation in duloxetine study	-Medications or herbal agents with CNS activity (including anti-depressants) -Regular use of analgesics other than acetaminophen and aspirin -Chronic use of sedatives, antiemetics, or antispasmodics -Initiation or change in unconventional or alternative therapies	Not reported (in pooled manuscript)

Author, Year, Country, Funder, Studies Pooled	Diagnostic Criteria	Additional Inclusion Criteria*	Exclusion Criteria*	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Milnacipran					
Arnold, 2012[27] USA, Canada Industry Funded **Pooled**: Arnold, 2010[28] Mease, 2009[29] Clauw, 2008[30]	1990 ACR criteria	-Male & Female -18-70 years -Mean VAS Score ≥40 or 50 at end of baseline period (0-100 scale) -Score ≥4 on FIQ physical function component (Arnold, 2010,[28] Clauw, 2008[30]	Not reported in article. Source articles indicate: Clauw, 2008[30] -Experimental agent in past 30 days or had prior exposure to milnacipran -Severe psychiatric illness or current MDD episode (MINI or BDI score >25) -Significant suicide risk -History of drug abuse -History of behavior that would prohibit compliance for duration of study -Active cardiovascular, pulmonary, hepatic, renal, GI, or autoimmune disease (except Hashimoto's or Graves' disease that had been stable for 3 months before screening) -Current systematic infection -Active cancer (except basal cell carcinoma) -Unstable endocrine disease -Severe sleep apnea -Prostate enlargement/other GU disorder (males) -Pregnancy or breastfeeding -Unacceptable contraception Mease, 2009[29] -Severe psychiatric illness or current MDD -Significant suicide risk -History of alcohol or drug abuse -Active cardiovascular, respiratory, endocrine, genitourinary, liver, or kidney disease	-Centrally acting medications used to manage fibromyalgia symptoms, such as anti-depressants, anticonvulsants, opioids, and muscle relaxants	-Weight-related interventions not specifically prohibited

Author, Year, Country, Funder, Studies Pooled	Diagnostic Criteria	Additional Inclusion Criteria*	Exclusion Criteria*	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
			-Active peptic ulcer or inflammatory bowel disease -Autoimmune disease -Cancer or current chemotherapy -Significant sleep apnea -Pregnancy or breastfeeding -Unacceptable contraception Arnold, 2010[28] -Rheumatic or medical disorders with symptoms similar to FM -Prior milnacipran or investigational drug in past 30 days -Current MDD as defined by MINI -BDI score >25 at screening or randomization -Significant suicide risk -Lifetime history of psychosis, hypomania or mania, substance abuse, other severe psychiatric illness -History of behavior that would prohibit compliance for duration of study -Active or pending disability claim, worker's compensation claim, or litigation -Active or unstable medical illness -Prostate enlargement or other GU disorder (men) -Pregnancy or breastfeeding -Unacceptable contraception		

Author, Year, Country, Funder, Studies Pooled	Diagnostic Criteria	Additional Inclusion Criteria*	Exclusion Criteria*	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Geisser, 2011[31] USA Industry Funded **Pooled**: Mease, 2009[29] Clauw, 2008[30]	1990 ACR criteria	-Male & Female -18–70 years -Score ≥50 (Mease, 2009[29] or ≥40 (Clauw, 2008[30]) on mean 24-hour recall VAS pain intensity recording on a scale of 0-100 (measured on an electronic PED)	-Severe psychiatric illness or a current major depressive episode, as defined by MINI -Active cardiac, hepatic, renal, or immune disorder -Active cardiovascular, respiratory, endocrine, genitourinary, liver, or kidney disease -Autoimmune disease	-Central nervous system-active pharmacologic therapies commonly used for FM (anti-depressants, anticonvulsants, dopamine agonists, mood stabilizers, muscle relaxants, opioids) -Nonpharmacologic treatments such as transcutaneous electrical nerve stimulation, biofeedback, tender and trigger point injections, acupuncture	Not reported (in pooled manuscript)
Pregabalin					
Arnold, 2010[32] USA Industry-funded **Pooled**: Arnold, 2008[33] Mease, 200[34] Crofford, 2005[35]	1990 ACR criteria	-Male & Female - ≥18 years -At both screening and randomization: score ≥40 mm on a 100-mm pain VAS, and average pain score of ≥4 on a daily pain diary 11-point rating scale based on at least 4 entries in week before randomization	-Any active inflammatory disorder or painful conditions that may confound assessment of FM pain -Unstable medical disorder -Creatinine clearance ≤60 ml/minute - Clinically significant or unstable psychiatric conditions (medical history of or investigator judgment)	-Medications taken for pain and sleep disorders -Other psychotropics	-Acetaminophen only rescue analgesic permitted
Bhadra, 2010[36] USA, Canada, Mexico, Denmark, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, United Kingdom, India, Korea, Australia, Venezuela Industry-funded **Pooled**: Arnold, 2008[33] Mease, 2008[34] Crofford, 2005[35] Pauer, 2008[37]	1990 ACR criteria	-Male & Female - ≥18 years -FM duration at least 3 months -In week prior to randomization, score of ≥4 on a daily pain diary 11-point rating scale - At both screening and randomization, score ≥40 mm on a 100-mm pain VAS of the short-form McGill Pain Questionnaire -At least 1 post-baseline score	-Creatinine clearance ≤60 ml/minte -Active inflammatory or rheumatological disorders or painful conditions that may confound assessment of FM pain -Unstable medical or psychological disorder	Not reported (in pooled manuscript)	Not reported (in pooled manuscript)

Author, Year, Country, Funder, Studies Pooled	Diagnostic Criteria	Additional Inclusion Criteria*	Exclusion Criteria*	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Byon, 2010[38] USA, Canada, Mexico, Denmark, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, United Kingdom, India, Korea, Australia, Venezuela Industry-funded **Pooled**: Arnold, 2008[33] Mease, 2008[34] Crofford, 2005[35] Pauer, 2008[37]	1990 ACR criteria	-Male & Female - ≥18 years -FM duration at least 3 months -Creatinine clearance (CLcr) >60 mL/minute -At both screening and randomization, score ≥40 mm on a 100-mm pain VAS of the short-form McGill Pain Questionnaire -In week prior to randomization, score of ≥4 on a daily pain diary 11-point rating scale; and completion of at least 4 pain diary days during baseline phase	-Those reporting >30% decrease on pain VAS during 1-week placebo run-in excluded from randomization (placebo responders) (Arnold, 2008[33] and Pauer, 2008[37])	Not reported (in pooled manuscript)	Not reported (in pooled manuscript)

Abbreviations: BDI=Beck Depression Inventory; BPI=Brief Pain Inventory; CNS=Central nervous system; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, FIQ=Fibromyalgia Impact Questionnaire, GI=gastrointestinal; GU=Genitourinary; MDD=Major Depressive Disorder; MINI=Mini International Neuropsychiatric Interview, PED=Patient experience diary; VAS=Visual Analog Scale 24-hour recall pain score

*Usually determined from source documents since selection criteria were often missing in pooled articles

Appendix Table E3. Sample selection criteria and allowed co-interventions for included fibromyalgia observational studies

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Pharmacologic					
Arnold, 2012[39] USA, Canada Industry funded	1990 ACR criteria	-Male & Female -18-70y -Score ≥ 4 on FIQ physical function raw score (range: 0-33) at screening and between 40-90 on VAS pain scale (range: 0-100) during 14-d baseline period	-Other rheumatic or medical disorders with symptoms similar to FM -Previous exposure to milnacipran -Treatment with an investigational drug within 30 days of screening -BDI >25 (moderate-to-severe depressive symptoms) or current MDD as assessed by MINI -Significant risk of suicide -History of psychosis, hypomania, or mania -Substance abuse -Other severe psychiatric disorder as assessed by investigator -History of behavior that would prohibit compliance for duration of study as assessed by investigator -Pregnancy or breastfeeding -Unacceptable contraception -Any active or unstable medical condition -Prostate enlargement or other genitourinary disorder -Active or pending disability claim, worker's compensation claim, or litigation	-Digitalis -Centrally acting medications for FM -Transcutaneous electrical nerve stimulation, biofeedback, tender and trigger point injections, acupuncture, and anesthetic or narcotic patches	-Acetaminophen, aspirin, and nonsteroidal anti-inflammatory agents -Short term pain rescue medication included tramadol or hydro-codone between randomization and week 4 -Triptans permitted for acute migrant treatment -Nonbenzodiazepine hypnotic agents for treatment of insomnia

Author, Year, Country, Funder	Diagnostic Criteria	Additional Inclusion Criteria	Exclusion Criteria	Disallowed Pharmaceuticals, Nutraceuticals, or Co-interventions	Allowed Pharmaceuticals, Nutraceuticals, or Co-interventions
Younger, 2009[40] USA Nonprofit/ foundation funded	1990 ACR criteria	-Held drug dosages steady for at least 2 previous months	-Joint pain/inflammation -History of autoimmune or rheumatologic condition -Blood test results: RF >20IU/mL, antinuclear antibody >1:80, and ESR >60 mm/hour	-Current or recent use of opioids	-Medications other than opioids -Asked not to modify pain treatment regimen without notifying study personnel
Physical					
Drexler, 2002[41] Austria Funding not reported	1990 ACR criteria	Not reported	Not reported	Not reported	Not reported
Mixed					
Joshi, 2009[42] India No external funding support	1990 ACR criteria	-Male & Female -18-60 years -Symptoms of chronic muscular pain for at least 12 weeks	-Pregnant or lactating -History of trauma, fractures, fever, malignancy, chronic renal or hepatic disorders -Alcohol abuse -Cerebrovascular or neurological abnormality	Not reported	-Allowed to continue previous medications and exercise regimens, if any

Abbreviations: ACR=American College of Rheumatology; BDI=Beck Depression Inventory; ESR=erythrocyte sedimentation rate; FIQ=Fibromyalgia Impact Questionnaire; FM=Fibromyalgia; MDD=Major Depressive Disorder, MINI=Mini International Neuropsychiatric Interview, RF=rheumatoid factor, VAS=Visual Analog Scale 24-hour recall pain score

Appendix Table E4. Fibromyalgia randomized clinical trials with subgroups and mixed samples, by class of treatment

Author, Year, Country, Funder*	Study Aim	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control Group	Outcomes Collected	Followup Duration	Reported Results
Pharmacologic							
Duloxetine							
Arnold, 2012[1] *Efficacy & Safety* USA, Mexico, Israel, Argentina Industry-funded	Assess efficacy and safety of duloxetine in reducing pain severity	**Age:** <65, ≥65 (n NR) **Sex** F: 293 (95) **Race** White: 269 (87) Nonwhite: 39 (13) **T_1:** 22 (14) **C**: 17 (11) **MDD**: 69 (22) **T_1:** 37 (54) **C**: 32 (46) **GAD**: 19 (6) **T_1**: 8 (42) **C**: 11 (58) *A priori* not reported; subgroup rationale not given	N: 308 **T_1**: 155 **C**: 153 M: 5% 51 years	**T_1**: Duloxetine 30 mg/d x 12 weeks **C**: Placebo	Primary: BPI average pain severity (24 hours) Secondary: PGI-I, FIQ, CGI-I, BDI-II, BAI, SF-36, BPI pain severity items (worst pain, least pain, pain right now) & mean interference score	3 months	Subgroups: BPI pain reported in text only; data not shown. Treatment by subgroup interactions not significant except race (NW>W) for BPI avg. pain improvement. Subgroup attrition not reported. AEs not reported by subgroup. Overall: No significant difference in BPI pain in treated vs. controls. Global symptoms and function improved on drug. Study powered for main treatment effect only. Overall attrition 25% (22% treated, 28% control).No difference in serious AEs between groups. More nonserious AEs in treated (65% vs. 52% control). Most common AEs: nausea, dry mouth, somnolence, insomnia.

Author, Year, Country, Funder*	Study Aim	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control Group	Outcomes Collected	Followup Duration	Reported Results
Arnold, 2010[2] *Flexible Dose* USA, Puerto Rico Industry-funded	Investigate efficacy of duloxetine on changes in FM symptoms	**Age**: (n NR) **Sex** F: 494 (93), **Race** W: 410 (77) **MDD**: 97 (18) **T_1**: 44 (17) **C**: 53 (20) **GAD**: 43 (8) **T_1**: 19 (7) **C**: 24 (9) A priori not reported; subgroup rationale given for MDD/GAD	N: 530 **T_1**: 263 **C**: 267 M: 7% 50 years	Titration to **T_1**: Duloxetine 60 or 90 or 120 mg/d x 12 weeks **C**: Placebo	Primary: PGI-I Secondary: BPI, MFI, CGI-S, PGI-S, MGH-CPFQ, BAI, BDI-II, SF-36, 11-point Likert Scales (mood, anxiety, stiffness, how much bothered by sleep difficulty and pain)	3 months	Subgroups: PGI-I reported for subgroups; (text summary only with p values; data not shown). All treatment by subgroup interactions on PGI-I were not significant. Subgroup attrition not reported. AEs not reported by subgroup. Overall: Duloxetine reduced (improved) PGI-I in treated vs. controls. Study powered for main treatment effect only. Overall attrition 32% (33% treated, 30% controls). No difference in serious AEs between groups. Higher proportion treated had nonserious AEs vs. controls (83% vs. 73%). Most common AEs: nausea, headache, constipation, dry mouth, dizziness, diarrhea.

Author, Year, Country, Funder*	**Study Aim**	**Subgroup§, n (%)**	**Total Patients, % Male, Mean Age**	**Specific Intervention(s), Treatment Duration, Control Group**	**Outcomes Collected**	**Followup Duration**	**Reported Results**
Chappell, 2008[3] USA, Germany, Spain, Sweden, UK Industry-funded	To assess the efficacy & safety of duloxetine 60/120mg/day over a 6-month period	**Age:** <65, ≥65 (n NR) **Sex** F: 308 (93) **T_1:** 149 (92) **C**: 159 (95) **Race** White: 300 (91) Nonwhite: 30 (9) **T_1:** 12 (7) **C**: 18 (11) **MDD**: 74 (22) **T_1:** 36 (22) **C**: 38 (22) **Anxiety**: 5 (2) **T_1**: 3 (2) **C**: 2 (1) **Previous Anti-depressant**: 143 (43) **T_1**: 71 (44) **C**: 72 (43) *A priori* not reported; subgroup rationale not given	N: 330 **T_1**: 162 **C**: 168 M: 7% 51 years	**T_1**: Duloxetine 60mg/d, titrated up to 120mg/d starting at week 8, if necessary & tolerated x 27 weeks **C**: Placebo	Co-primary: BPI average pain severity (24 hours), PGI-I Secondary: FIQ, CGI-S, TP score, BPI pain severity items (worst pain, least pain, pain right now) & mean interference score, MFI, $HAMD_{17}$, BDI-II, SDS, EQ-5D	27 weeks	Subgroups: BPI reported in text summary only; data not shown. Treatment by subgroup interactions not significant except for prior antidepressant use. Compared to placebo, patients in treated with prior antidepressant use had greater reductions in BPI average pain severity vs. patients without prior antidepressant use. Subgroup attrition not reported. AEs not reported by subgroup. Overall: No difference between treated vs. controls in co-primary endpoints; effect less than in shorter trials. Greater improvement in treated vs. controls in secondary measures. Study powered for main treatment effect. Overall attrition 38% (38% treated, 40% controls). No significant difference in serious AEs between groups. AEs higher in treated vs. controls (90% vs. 82%). Most common AEs: nausea, headache, dry mouth, diarrhea, constipation

Author, Year, Country, Funder*	Study Aim	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control Group	Outcomes Collected	Followup Duration	Reported Results
Russell, 2008[4] USA, Puerto Rico Industry-funded	Assess efficacy and safety of duloxetine for pain in FM patients with/without major depressive disorder	**Age:** <65, ≥65 (n NR) **Sex** F: 493 (95) **Race** W: 438 (84) **MDD:** 126 (24) **T_1**: 22 (28) **T_2**: 35 (23) **T_3**: 34 (23) **C**: 35 (24) A priori not reported; subgroup rationale given for MDD	N: 520 **T_1**: 79 **T_2**: 150 **T_3**: 147 **C**: 144 M: 5% 52 years	**T_1**: Duloxetine 20mg/d **T_2**: Duloxetine 60mg/d **T_3**: Duloxetine 120mg/d x 15 weeks **C**: Placebo	Primary: BPI average pain severity (24 hours), PGI-I Secondary: FIQ, CGI-S, TPs, MFI, $HAMD_{17}$, SDS, SF-36, EQ-5D	6 months	Subgroups: BPI avg. pain and PGI-I reported for subgroups. Treated patients with and without MDD had similar improvements in BPI pain and PGI-I vs. controls at 3 and 6 months. Treatment by subgroup interactions not significant for age, sex, and race at 3 or 6 months (p-values only; no data). P-values for interactions not reported. Mean change from baseline in BPI and PGI-I by treatment group for with/without MDD are shown (3 and 6 mo.). Among patients with MDD, T_3 had stat. sig improvement compared with placebo on $HAMD_{17}$ total. Study powered for main treatment effect. Subgroup attrition not reported. AEs not reported by subgroups. Overall: Higher doses had more dropouts. Few men per group (2-14). Attrition reported segmentally (0-3 mo. and 4-6 mo.), not overall. Attrition 37% through month 3 (38%=T_1, 35%=T_2, 35%=T_3; 42% in controls). Attrition 15% months 4-6 month using denominator after third month (10%=T_1, 15%=T_2, 17%=T_3; 14% in controls). No difference in SAEs between groups. Proportion who discontinued due to AEs in 6 months differed by group (11% T_1, 15% T_2, 27% T_3, 13% control). Most common AEs: nausea, dry mouth, constipation, somnolence, fatigue.

Author, Year, Country, Funder*	Study Aim	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control Group	Outcomes Collected	Followup Duration	Reported Results
Arnold, 2005[5] *Women with or without MDD* USA Industry-funded	Efficacy and safety of duloxetine in women with or without current MDD Test daily vs. 2x/day dosing	**MDD**: 92 (26) **T_1**: NR **T_2**: NR **C**: NR "NSD across groups in MDD at baseline." Criteria to determine MDD at baseline not specified A priori not reported; subgroup rationale given	N: 354 **T_1**: 118 **T_2**: 116 **C**: 120 M: 0% 49 years	**T_1**: Duloxetine 60mg/d **T_2**: Duloxetine 120mg/d x 12 weeks **C**: Placebo	Primary: BPI average pain severity (24 hours) Secondary: BPI pain severity items (worst pain, least pain, pain right now) & mean interference score, FIQ, TPs, CGI-S, PGI-I, $HAMD_{17}$, QoL in Depression Scale, SF-36, SDS	3 months	Subgroups: BPI avg. pain reported for subgroup (text summary only; data not shown). Treatment by MDD interaction not significant; effect of duloxetine on pain (BPI avg. pain) was similar in patients with and without MDD. Study powered for main treatment effect only. Subgroup attrition not reported. AEs not reported by subgroups. Overall: Higher dose had more dropouts from AEs. Overall attrition 39% (35%=T_1, 39%=T_2; 43% controls). No difference in SAEs between groups. Significantly more treated reported TEAEs (92% T_1, 91% T_2, 79% control). Most common AEs nausea, dry mouth, constipation, diarrhea.

Author, Year, Country, Funder*	Study Aim	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control Group	Outcomes Collected	Followup Duration	Reported Results
Arnold, 2004[6] *with or without MDD* USA Industry-funded & managed	Efficacy and safety of duloxetine in patients with or without current MDD	**Sex** F: 184 (89) **MDD**: 79 (38) **T_1**: 42 (41) **C**: 37 (36) A priori not reported; subgroup rationale given for MDD	N: 207 **T_1**: 104 **C**: 103 M: 11% 49 years	**T_1**: Duloxetine 120mg/d x 12 weeks **C**: Placebo	Primary: FIQ (total and pain scores), Secondary: FIQ (fatigue, morning tiredness & stiffness), BPI, CGI-S, PGI-I, SF-36, BDI,SDS, TPs	3 months	Subgroups: Text summary only; subgroup data not shown. Compared with placebo-treated females, women in T_1 group had stat sig improvement in FIQ (total and pain scores). Treatment-sex interaction significant in women for BPI and Sheehan Disability improvement; no difference in any outcome between treated and untreated males. Drug improved FM symptoms and pain (FIQ) regardless of MDD. Study powered for FIQ pain main effect, not treatment-subgroup interactions. Subgroup attrition not reported. AEs not reported by subgroups. Overall: Duloxetine significantly reduced (improved) FIQ total pain score in treated vs. controls; other outcomes not significant. Overall attrition 40% (44% treated, 36% controls). No difference in SAEs between groups. Significantly more treated with nonserious AEs (90% vs. 75%). Most common AEs: insomnia, dry mouth, and constipation.

Author, Year, Country, Funder*	Study Aim	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control Group	Outcomes Collected	Followup Duration	Reported Results
Milnacipran							
Gendreau, 2005[7] USA Industry-funded	Evaluate safety and efficacy of milnacipran in FM treatment	**Depression:** 20(16) **T_1**: 8 (16) **T_2**: 3 (7) **C**: 9 (32) Assessed by MINI A priori not reported; subgroup rationale given	N: 125 **T_1**: 51 **T_2**: 46 **C**: 28 M: 3% 47 years	Titrated up to: **T_1**: Milnacipran 100mg, 2x/d **T_2**: Milnacipran 200mg, 1x/d X 12 weeks **C**: Placebo	Primary: E-diary pain score (using the Gracely scale). Secondary: VAS pain, McGill, PGIC, FIQ, SF-36, Jenkins Sleep Scale, ASEX, Sleep quality and quantity by e-diaries & paper inventories.	3 months	Subgroups: Incomplete outcomes reporting for subgroup. Outcomes reported by 50% pain responders, not by depression alone. More placebo patients had depression than in treatment groups. No differences in pain in 2x/day-treated depressed vs. nondepressed patients. More depressed patients had a positive response to placebo than nondepressed. Similar findings for other pain measures and other outcomes (text, no data). Article Table 3 lacks 1x/day-dosed group outcomes. Most dropouts for AEs (14.4%). No information on power. Subgroup attrition not reported. AEs not reported by subgroup. Overall: Treated improved more than controls in pain and in 9 of 13 outcomes. Overall attrition 28% (27%=T_1, 30%=T_2; 25% in controls). Significantly more treated discontinued prior to endpoint due to AEs (14%=T_1, 22%=T_2; 4% controls). Most common AEs: headache, GI complaints

Author, Year, Country, Funder*	Study Aim	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control Group	Outcomes Collected	Followup Duration	Reported Results
Off-label							
Arnold, 2002[10] *Fluoxetine* USA Industry-funded	Efficacy of fluoxetine in the treatment of FM	**Depression:** 37 (62) **T_1**: 17 (57) **C**: 20 (67) A priori not reported; subgroup rationale given	N: 60 **T_1**: 30 **C**: 30 M: 0% 46 years	**T_1**: Fluoxetine 10-80 mg/d x 12 weeks **C**: Placebo	Primary: FIQ (total and pain scores); Secondary: McGill Pain, change in No. of TPs, total myalgia score	3 months	Subgroups: FIQ (total and pain scores) reported for subgroup (text summary only; data not shown). Treatment by subgroup interaction with history of MDD or baseline level of depression not statistically significant on FIQ. AEs not reported by subgroups. Study powered for main effect. Overall: Fluoxetine reduced (improved) FIQ scores (total, pain) in treated vs. controls. Overall attrition 38% (37% treated, 40% controls). No difference in AEs in treated vs. controls. Most common AEs: headache, insomnia, sedation, nausea.

Author, Year, Country, Funder*	Study Aim	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control Group	Outcomes Collected	Followup Duration	Reported Results
Psychological							
Junghaenel, 2008[19] USA Foundation-funded, with material support through academic institution	Identify differential health benefits of written emotional disclosure	**Coping style** (from baseline MPI) Adaptive coping (AC): 41 (45) **T_1**: NR **C**: NR Dysfunctional (DYS): 15 (16) **T_1**: NR **C**: NR Interpersonally distressed (ID): 36 (39) **T_1**: NR, **C**: NR **Educational level** < High School **T_1**: 7 (23) **C**: 21 (34) Any college **T_1**: 19 (61) **C**: 30 (49) Graduate **T_1**: 5 (16) **C**: 10 (16) A priori not reported; subgroup rationale given for Coping Style study	N: 92 **T_1**: 31 **C**: 61 M: 0% 50 years	**T_1**: Written emotional disclosure (WED): 3 20-minute writing sessions in lab focusing on emotional expression and cognitive reappraisal of stressful event **C**: Neutral writing about daily activities or usual care	MPI (to classify composite measures assessing Pain, fatigue, and psychological well-being)	4 months	Subgroups: Treatment by subgroup interactions not significant for pain or fatigue. Interaction for psychological wellbeing was p=0.08; interpersonally distressed (ID) patients improved more than adaptive coping group. Educational status-treatment-time interaction effect sig. at p<0.01. Only graduate educated had significant improvement in psychological wellbeing (p<0.0001) compared to college (p=0.53) or less (p=0.33) education. Study not powered for subgroup treatment effect. Attrition not specified in text or tables for subgroups or overall. AEs not reported for subgroups or overall.

Author, Year, Country, Funder*	Study Aim	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control Group	Outcomes Collected	Followup Duration	Reported Results
Mixed							
Lera, 2009[23] Spain No funding information	Analyze response of FM patients to two multidisciplinary treatments	Comorbid fatigue: 16 (24) **T_1**: 9 (56) **C**: 7 (44) A priori not reported; subgroup rationale given	N: 66 **T_1**: 35 **C**: 31 M: 0% 51 years	**T_1**: Multidisciplinary treatments (medical, physical training, education and group discussion) + CBT 90 minute sessions/week x 15 sessions **C**: Multidisciplinary treatments only	FIQ (minus 'going to work' subscale), SF-36, SCL-90-R	15 weeks	Subgroups: FIQ reported for subgroup. Fatigued patients showed a better response with (MT plus CBT) than with MT alone on FIQ. Study not powered for subgroup effects. Attrition and AEs not reported for subgroup. Overall: Significant fall in FIQ in treated; nonsignificant improvement in daily functioning and health status in treated. Under-powered study. Overall attrition 20% (19% in treated, 23% in controls). AEs not reported.

*See Appendix Table E10 for further funding details.

§Determined at baseline unless otherwise noted.

Abbreviations: AC=Adaptive Coping; AE=Adverse Effects; ASEX=Arizona Sexual Experiences Scale; BAI=Beck Anxiety Inventory; BDI=Beck Depression Inventory; BDI-II=Beck Depression Inventory-II; BPI=Brief Pain Inventory; C=Control; CBT=Cognitive Behavioral Therapy; CGI-S=Clinical Global Impression of Severity Scale; d=day; dx=diagnosis; DYS=Dysfunctional; E-diary=Electronic diary; EQ-5D=EuroQoL Questionnaire-5 Dimensions; F=Female; FIQ=Fibromyalgia Impact Questionnaire; FM=Fibromyalgia; GAD=Generalized Anxiety Disorder; $HAMD_{17}$=Hamilton Rating Scale for Depression; ID=Interpersonally Distressed; M=Male; MDD=Major Depressive Disorder; MFI=Multidimensional Fatigue Inventory; MGH-CPFQ=Massachusetts General hospital Cognitive and Physical Functioning Questionnaire=MPI-Multidimensional Pain Inventory; MT=Multidisciplinary Treatment; MINI=Mini International Neuropsychiatric Interview; mg=milligrams; NR=Not Reported; NSD=No Significant Difference; NW=Nonwhite; PGI-I=Patient Global Impression of Improvement Scale; PGI-S=Patient's Global Impressions of Severity Scale; QoL=Quality of Life; SAE=Serious Adverse Event; SAEs=serious adverse events per authors; SCL-90-R=Symptom Checklist-90-Revised; SDS=Sheehan Disability Scale; SF-36=Medical Outcomes Study Short-Form 36-item Health Survey; T_1=Treatment group 1 T_2=Treatment group 2 T_3=Treatment group 3; TEAE=Treatment Emergent Adverse Event; TEAEs=treatment-emergent adverse events per authors; TPs=Tender Points; VAS=Visual Analogue Scale; WED=Written Emotional Disclosure; W=White

Appendix Table E5. Fibromyalgia randomized clinical trials with pure subgroup samples, by class of treatment

Author, Year, Country, Funder*	Study Aim	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Outcomes Collected	Followup Duration	Reported Results
Pharmacologic							
Off-label							
Stening, 2011[8] Sweden Funded by Government, Foundation & Academic	Effect of transdermal estrogen on pain	Postmenopausal women (all) Explicitly stated rationale for pure SG study	N: 29 **T_1**: 15 **C**: 14 M: 0% 54 years	**T_1**: Transdermal 17B-estradiol 50 ug/d x 8 weeks **C**: Placebo	Self-estimated pain (Modified Pain Map), Quantitative sensory testing (QST), Hormonal response (serum 17B-estradiol)	5 months	No difference between groups on self-estimated pain. Only half of the planned sample size was enrolled. More patients on antidepressants in placebo group (45% vs. 13% treated). Overall attrition 14%; (0% treated, 28% controls). AEs not reported.
Sadreddini, 2008[9] Iran No funding information	Compare Raloxifen (Evista) with placebo in treatment of FM	Postmenopausal women (all) Explicitly stated rationale for pure SG study	N: 100 **T_1**: 50 **C**: 50 M: 0% 53 years	**T_1**: Raloxifen 60 mg/d x 16 weeks **C**: Placebo	Stanford HAQ, IHAD (Iranian), Sleep Disturbance, VAS (pain & fatigue), TPs	16 weeks	Treated patients had greater pain reduction in all measures except anxiety and depression (IHAD). Placebo group was significantly older than treated. Overall attrition 4% (2% treated, 6% controls). No difference in AEs in treated vs. controls. Most common AEs were increased anxiety, leg cramps, flushing & drowsiness

Author, Year, Country, Funder*	Study Aim	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Outcomes Collected	Followup Duration	Reported Results
Physical							
Gavi, 2014[11] Brazil No funding reported	Assess the chronic effects of strengthening exercises (STRE) on autonomic modulation, pain perception and quality of life in FM patients	Sedentary women (Had not exercised in the past 3 months) Explicitly stated rationale for pure SG study	N: 80 **T_1**: 40 **C**: 40 M: 0% 46 years	**T_1**: Supervised progressive training in standing & sitting positions using weight machines at moderate intensity; 8 major muscle groups were trained in 12 exercises, with 3 sets of 12 repetitions, 2x/week for 45 minutes x 16 weeks **C**: Flexibility exercises in the major muscle groups, 2x/week for 45 minutes x 16 weeks	Primary: VAS pain, HRV Secondary: fitness outcomes (treadmill test, sit and reach test, maximal repetitions test, handgrip dynamometry), FIQ, IDATE, SF-36	4 months	Analysis limited to program completers. Greater improvements in VAS pain and handgrip strength in treated vs. control. Physical fitness scores improved in some but not all measures in treated. No difference in HRV, FIQ, Beck Depression or SF-36 in treated vs. control. Greater improvements in IDATE-TRAIT and IDATE-STATE (anxiety) in control vs. treated. Sufficient study power for VAS pain. Overall attrition 18% (13% treated, 23% control). AEs not reported.
Senna, 2012[12] (non exercise) Egypt No funding information	Effect of weight reduction on FIQ	Obese adults (*obese* criteria not defined in article) Explicitly stated rationale for pure SG study	N: 83 **T_1**: 41 **C**: 42 M: 10% 46 years	**T_1**: Dietary restriction (1200 kcal/d [20% protein, 50% carbs, 30% fat] x 6 months) **C**: No restriction in calories; follow medical treatment by physician	FIQ, BDI-II, Pittsburg Sleep Quality Index, TPs	6 months	Treated group had significant change in FIQ from baseline vs. controls. Depression and sleep quality improved and TP count reduced in weight loss group. No power calculation. Overall attrition 3% (5% treated, 2% controls). AEs not reported.

Author, Year, Country, Funder*	Study Aim	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Outcomes Collected	Followup Duration	Reported Results
Gusi, 2010[13] Spain No funding information	Explore efficacy of whole body vibration and impact of body weight on dynamic balance	Body weight and baseline balance score (post hoc) Did not explicitly state rationale for pure SG study	N: 41 **T_1**: 21 **C**: 20 M: 0% 53 years	**T_1**: Standard care plus Whole Body Vibration: three 30 minutes WBV/week x 12 weeks (6 repetitions of 45-60 seconds 12.5Hz vibrations per session) **C**: Standard care and regular daily activities	Dynamic balance index	3 months	Analysis limited to program completers. Participants with the heaviest weight and worst balance at baseline improved more than others ($p<0.001$). Dynamic balance of treatment group improved by 36%; control group unchanged. No power analysis. Overall attrition 12% (14% treated, 10% control). Only 1 AE reported (pain) in treatment group participant. No AEs reported in controls.
Valkeinen, 2008[14] Adjunctive to existing medications Finland Government and Foundation funded	Examine effectiveness of concurrent strength and endurance training on FM symptoms	Postmenopausal women, age 50 and over Did not explicitly state rationale for pure SG study	N: 26 **T_1**: 15 **C**: 11 M: 0% 60 years	**T_1**: Strength and endurance (aerobic) training at gym, 2-4 sessions of 30-60 minutes per week x 21 weeks **C**: No training	Muscle strength, VO_2, peak, work time, Stanford HAQ, FM symptoms, VAS, Aerobic performance	21 weeks	Muscle strength improved 2% in trained vs. -6% in controls. Walking, stair climbing, and pain significantly improved with training; changes in fatigue, wellbeing, and sleep quality were not significantly different. Small n per group and no power analysis. Overall attrition 8% (13% treated, 0% controls). AEs not reported.
Assis, 2006[15] Brazil Government-funded	Compare clinical effectiveness of water-based vs. land-based aerobic exercise for FM	Sedentary women (Had not performed "regular physical activity" for 6 weeks prior to enrollment) Did not explicitly state rationale for pure SG study	N: 60 **T_1**: 30 **C**: 30 M: 0% 43 years	**T_1**: Deep water running 60 minutes 3x/week x 15 weeks **C**: Land-based exercises (walking & jogging) 60 minutes 3x/week x 15 weeks	Primary: VAS pain Secondary: FIQ, BDI, SF-36, PGART, peak oxygen uptake (VO_2)	15 weeks	Both groups improved significantly from baseline to week 15. FIQ improved more in deep water running group. No differences between groups in VAS pain, BDI, SF-36 physical and PGART. Overall attrition 13% (both groups 13%). No difference in AEs by group. Most common AE: muscle pain.

Author, Year, Country, Funder*	Study Aim	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Outcomes Collected	Followup Duration	Reported Results
Hakkinen, 2002[16] Finland Government & Foundation funded	Effect of strength training on muscle strength and serum hormones	Premenopausal women Did not explicitly state rationale for pure SG study	N: 21 **T_1**: 11 **C_1**: 10 **C_2**: 12 M: 0% 38 years	**T_1**: Supervised experimental strength training on weight machines 2 d/week x 21 weeks **C_1**: Normal low intensity recreational activities; women with FM **C_2**: Supervised experimental strength training on weight machines, 2d/week x 21 weeks; healthy control women	Muscle cross-sectional area (CSA), VAS, Isometric right knee maximal extension and flexion force; serum hormones (testosterone, GH, DHEAS)	4 months	Maximal R knee extension and flexion forces increased significantly in the treated FM group (18% and 13% respectively). Attrition not specified in text or tables. AEs not reported.
Psychological							
Scheidt, 2013[17] Germany Academic funding	Effectiveness of brief psychodynamic psychotherapy on women with FM and substantial psychological comorbidity	Female FM patients suffering from a current depression or anxiety disorder Explicitly stated rationale for pure SG study	N: 47 **T_1:** 24 **C**: 23 M: 0% 49 years	**T_1**: 25 weekly sessions of psychodynamic psychotherapy lasting between 50-60 minutes **C**: 4 primary care consultations/6months with advice on medication and exercise	Primary: FIQ, Secondary: HADS, SCL-27, PDI, SF-36, SOMS-7	1 year	Subgroup: No significant between-group differences on primary and secondary outcome measures. Interventions equally effective. Study not powered for subgroup treatment effect. Overall attrition 25.5% (25% in treated, 26% controls). AEs not reported.
Edinger, 2005[20] USA Government funded	Compare CBT with other behavioral therapy and usual care on sleep and other FM	Patients with both FM and insomnia Explicitly stated rationale for pure SG study	N: 47 **T_1**: 18 **T_2**: 18 **C**: 11 M: 9% 49 years	**T_1**: 6 weekly individual sessions 15-60 minutes each. Audiocassette CBT module, verbal and written stimulus control instructions + ongoing medical care **T_2**: 6 weekly individual sessions 15-60 minutes each. Generic sleep education on audiocassette, verbal and written instructions + ongoing medical care **C**: Ongoing medical care	Polysom-nography, Sleep logs Actigraphy, Insomnia symptom questionnaire, SF-36, MPQ, BPI, Profile of mood states	6 months	T_1 Showed 50% reduction in nocturnal wake time, T_2 showed 20% reduction, Control group showed 2.5 % reduction. 57% of T_1 met strict subjective sleep improvement criteria, compared to 17% of T_2 and 0% of control group. Overall attrition 56% (67%=T_1, 61%=T_2, 36% controls). AEs not reported.

Author, Year, Country, Funder*	Study Aim	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Outcomes Collected	Followup Duration	Reported Results
Mixed							
Martínez, 2014[21] Spain Government funded	Evaluate efficacy of CBT for insomnia vs. a sleep hygiene (SH) education program at improving sleep and other FM symptoms	Women with FM and insomnia Note: Almost all subjects (92%) were receiving medication during study period Explicitly stated rational for pure SG study	N: 64 **T_1**: 32 **C**: 32 M: 0% 48 years	**T_1**: CBT for insomnia; sessions on general sleep education, sleep restriction and stimulus control, psychological deactivation procedures, cognitive therapy to change negative thoughts about insomnia, maintenance and relapse prevention, 1.5 hour group sessions 1x/week x 6 weeks **C**: Education and training on sleep hygiene; sessions on general sleep education, role of environmental and lifestyle factors, diet & physical exercise, maintenance and relapse prevention, 1.5 hour group sessions 1x/week x 6 weeks	Primary: PSQI Secondary: MPQ-SF, MFI, FIQ, CPSS, PCS, SCL-90-R	3 months 6 months	Patients treated with CBT for insomnia improved in total FIQ and sleep quality measures immediately after treatment; effects not sustained at 3 or 6 months. No significant differences between CBT vs. SH in pain intensity, general fatigue, self-efficacy, pain catastrophizing, anxiety, or depression. No information on study power. Overall attrition 7.8% (6% in treated, 9% in control). AEs not reported.

Author, Year, Country, Funder*	Study Aim	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Outcomes Collected	Followup Duration	Reported Results
Fontaine, 2010[22] USA Government funded	Evaluate effects of 30 minutes of lifestyle physical activity (a cognitive-behavioral physical activity promotion program)	Suboptimal physical activity (Had not met U.S. Surgeon General's 1996 recommended physical activity in prior 6 months) Did not explicitly state rationale for pure SG study	N: 84 **T_1**: 46 **C**: 38 M: 4% 48 years	**T_1**: Lifestyle Physical Activity (LPA = a cognitive-behavioral physical activity promotion program), 6 1-hour group sessions x 12 weeks **C**: FM information and support: 6 1-hour group sessions x 12 weeks	Primary: FIQ, Secondary: VAS, FSS, CES-D, TPs, BMI, 6 minute walk	3 months	Treated group increased average daily steps by 54% and had significant reductions in total FIQ and pain. Walking was the most common activity. No differences in 6-minute walk, BMI, fatigue, depression or number of TPs between groups at 12 weeks. 13% dropped out (not reported by group). Baseline power to detect FIQ change was sufficient but dropouts per group were not specified. Overall attrition 13% (both groups). AEs not reported.

* See Appendix Table E10 for further funding details

§Determined at baseline unless otherwise noted

Abbreviations: AE=Adverse Effects; BDI=Beck Depression Inventory; BDI-II=Beck Depression Inventory-II; BMI=Body Mass Index; BPI=Brief Pain Inventory; C=Control; CBT=Cognitive Behavioral Therapy; CES-D=Center for Epidemiologic Studies Depression Scale; CPSS=Chronic Pain Self-efficacy scale; CSA=Cross-sectional area; d=day; DHEAS=Sulfate ester of Dehydroepiandrosterone; FIQ=Fibromyalgia Impact Questionnaire; FM=Fibromyalgia syndrome; FSS=Fatigue Severity Scale; GH=Growth Hormone; HADS=Hospital Anxiety & Depression Scale; HRV=Heart Rate Variability; IDATE=Beck and Idate Trait-State Inventory; IHAD=Iranian version of Hospital Anxiety and Depression questionnaire; HAQ=Health Assessment Questionnaire; M=Male; MDD=Major Depressive Disorder; MFI=Multi-dimensional Fatigue Inventory; MPQ=McGill Pain Questionnaire; MPQ-SF=McGill Pain Questionnaire-Short Form; PCS=Pain Catastrophizing Scale; PDI=Pain Disability Index; PGART=Patient's Global Assessment of Response to Therapy; PSQI=Pittsburg Sleep Quality Index; QST=Quantitative Sensory Testing; R=Right; SCL-27=short version of the Symptom Checklist-90-R; SCL-90-R=Symptom Checklist-90-Revised; SF-36=MOS Short-Form 36-item Health Survey; SG=subgroup; SOMS-7=Somatoform disorders-7 questionnaire; TPs=Trigger Points; T_1=Treatment group 1 T_2=Treatment group 2; VAS=Visual Analogue Scale; VO_2=Peak Oxygen uptake; WBV=Whole Body Vibration

Appendix Table E6. Fibromyalgia pooled studies of patient-level RCT data with subgroup reporting, by pharmacologic treatment

Author, Year, Country, Studies Pooled, Funder*	Study Aim	Subgroup[§], n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Outcomes Collected	Followup Duration	Reported Results
Duloxetine							
Bennett, 2012[24] USA, Puerto Rico, Germany, Spain, Sweden, UK Industry funded **Pooled**: Chappell, 2008[3] Russell, 2008[4] Arnold, 2005[5] Arnold, 2004[6]	Evaluate changes in stiffness using data pooled from 4 clinical trials and determine if any outcomes were correlated with stiffness	**Age** <55: 830 (62) **T_1**: 485 (64) **C**: 345 (67) **BMI** Normal: 365 (27) **T_1**: 208 (27) **C**: 157 (30) Overweight: 37 (28) **T_1**: 230 (30) **C**: 149 (29) Obese: 417 (31 **T_1**: 253 (33) **C**: 164 (32) Morbid Obesity 103 (8) **T_1**: 62 (8) **C**: 41 (8) Did not explicitl state rationale for subgroup investigation	N: 1,332 **T_1**: 797 **C**: 535 M: 5% 50 years	**T_1**: Either Duloxetine 60mg or 120mg/d x 12 weeks **C**: Placebo	BPI average pain severity (24 ho7urs), BPI pain severity items (worst pain, least pain, pain right now) and mean interference score, CGI-S, EQ-5D, FIQ total score, FIQ sub-scale scores, including 1-item FIQ Stiffness Score, 0-10 scale, $HAMD_{17}$, MFI, PGI-I, SDS, SF-36	3 months	Subgroups: Treatment by age and BMI subgroup interactions not significant in FIQ stiffness change. Pooled data shown for subgroup outcome change from baseline. AEs not reported by subgroup. Overall: Statistically significant reduction in FIQ stiffness score in treated vs. controls. Reported that improvement in treated patients was above MCID (13%), but did not account for improvements in the placebo group (making the difference between treated vs. placebo to be less than MCID). No information on study power. AEs reported by treatment not subgroup. TEAEs differed by group (89% treated; 80% placebo). Common TEAEs were nausea, headache, dry mouth, insomnia, fatigue, GI Note: Subgroup *n*'s do not total overall *N*.

Author, Year, Country, Studies Pooled, Funder*	Study Aim	Subgroup[$], n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Outcomes Collected	Followup Duration	Reported Results
Bradley, 2010[25] USA, Puerto Rico, Germany, Spain, Sweden, UK Industry funded **Pooled**: Chappell, 2008[3] Russell, 2008[4] Arnold, 2005[5] Arnold, 2004[6]	Assess whether fatigue/tiredness are negatively associated with efficacy using data pooled from 4 clinical trials	**FIQ Tiredness** Mild (0-3): 49 (4) **T_1**: 29 (4) **C**: 20 (4) Moderate (4-6): 216 (16) **T_1**: 133 (17) **C**: 83 (16) Severe (7-10): 1,064 (80) **T_1**: 634 (80) **C**: 430 (80) Explicitly stated rationale for subgroup investigation	N: 1,332 **T_1**: 797 **C**: 535 M: 5% 50 years	**T_1**: Either Duloxetine 60mg or 120mg/d x 12 weeks **C**: Placebo	BPI average pain severity (24 hours), FIQ total score, FIQ sub-scale scores, PGI-I, SF-36	3 months	Subgroups: Efficacy does not vary by baseline tiredness in any outcome measure. Pooled data shown for subgroup outcomes change from baseline in all but PGI-I, where only text results were provided. Overall: Significantly more treated patients experienced both a 30% and 50% reduction in the average BPI pain score vs. controls. No information on study power. AEs reported by subgroup. Nausea more common in treated patients, but did not differ by subgroup. Common AEs that differed by subgroup were hypoesthesia, arthralgia, cough, and myalgia. Note: Subgroup *n*'s do not total overall *N*.
Arnold, 2009[26] USA, Puerto Rico, Germany, Spain, Sweden, UK Industry funded **Pooled**: Chappell, 2008[3] Russell, 2008[4] Arnold 2005[5] Arnold 2004[6]	Does comorbid MDD influence efficacy and safety of duloxetine using data pooled from 4 clinical trials	**MDD**: 350 (26) **T_1**: 203 (25) **C**: 147 (27) Explicitly stated rationale for subgroup investigation	N : 1,332 **T_1**: 797 **C**: 535 M: 5% 50 years	**T_1**: Either Duloxetine 60mg or 120mg/d x 12 weeks **C**: Placebo	Primary: BPI average pain severity (24 hours), Secondary: BPI pain interference items, FIQ, CGI-S, PGI-I, $HAMD_{17}$, SF-36, SDS, MFI	3 months	Subgroups: KQ1: Treated patients with or without MDD had similar improvement in all outcome and safety measures. All treatment by subgroup interactions not significant. Pooled data shown. KQ2: AEs reported by subgroup. Treatment by MDD subgroup interaction for serious AEs not significant; interaction for nonserious AEs significant (p=0.09). Overall: Significant reduction in all outcomes in treated vs. controls. No information on study power. Most common AEs were nausea, headache, and dry mouth.

Author, Year, Country, Studies Pooled, Funder*	Study Aim	Subgroup[$], n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Outcomes Collected	Followup Duration	Reported Results
Milnacipran							
Arnold, 2012[27] USA, Canada Industry funded **Pooled**: Arnold, 2010[28] Mease, 2009[29] Clauw, 2008[30] (subgroup analysis limited to 3 of 6 trials)	Examine effect of milnacipran on changes in body weight using data pooled from 3 clinical trials	**BMI Group** <25: 711 (23) **T_1**: NR **T_2**: NR **C**: NR 25-30: 886(29) **T_1**: NR **T_2**: NR **C**: NR ≥30: 1,507 (48) **T_1**: NR **T_2**: NR **C**: NR Explicitly stated rationale for subgroup investigation	N: 3,014 **T_1**: NR **T_2**: NR **C**: NR M: 4% 50 years	**T_1**: Milnacipran 100mg/d x 12 weeks **T_2**: Milnacipran 200mg/d x 12 weeks **C**: Placebo	Change in body weight	3 months	Subgroups: Overweight/obese treated patients had greater mean weight loss than normal/underweight patients. No statistical comparisons done. Pooled data shown. AEs not reported by subgroup. Overall: Treated patients lost significantly more weight than controls, regardless of baseline BMI. No information on study power. AEs reported by treatment group, but not by subgroup. Most common AE was nausea.

Author, Year, Country, Studies Pooled, Funder*	Study Aim	Subgroup[§], n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Outcomes Collected	Followup Duration	Reported Results
Geisser, 2011[31] USA Industry funded **Pooled**: Mease, 2009[29] Clauw, 2008[30]	Determine whether improvements in pain measures are dependent on baseline pain severity	**Median VAS Pain** ≤64.7: UTD **T_1**: UTD **T_2**: UTD **C**: UTD >64.7: UTD **T_1**: UTD **T_2**: UTD **C**: UTD Explicitly stated rationale for subgroup investigation	N: 2,084 **T_1**: 624 **T_2**: 623 **C**: 837 M: 4% 50 years	**T_1**: Milnacipran 100mg/d x 12 weeks **T_2**: Milnacipran 200mg/d x 12 weeks **C**: Placebo	Treatment efficacy: VAS, PGIC, SF-36 (Physical) Note: Efficacy defined a priori as 2-measure or 3-measure composite responder. Each scale also analyzed separately.	3 months	Subgroups: Similar % of treated patients met composite responder criteria vs. placebo, regardless of pain severity. More treated patients vs. placebo in both pain subgroups had improvements in VAS pain and PGIC. Significantly higher % of treated patients with low to moderate pain improved physical functioning vs. placebo. Pooled data shown. Subgroup results based on stratified analyses; no interaction tests reported. Overall: Significantly higher % of treated patients met the composite responder criteria vs. controls. No information on study power. AEs reported by treatment group, not subgroup. Most common AEs were nausea, headache, constipation, insomnia. Note: *n* in VAS pain groups changed depending on outcome measure analyzed.

Author, Year, Country, Studies Pooled, Funder*	Study Aim	Subgroup[$], n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Outcomes Collected	Followup Duration	Reported Results
Pregabalin							
Arnold, 2010[32] USA Industry funded **Pooled**: Arnold, 200[33] Mease, 2008[34] Crofford, 2005[35]	Determine whether baseline depressive or anxiety symptoms were associated with improvement in pain symptoms, and evaluate the efficacy of pregabalin on pain and mood symptoms using data pooled from 3 clinical trials	**Change in Anxiety and Depression** Anxiety ≥2 pts: 939 (47) **T_1**: 62 (47) **T_2**: 232 (46) **T_3**: 243 (49) **T_4**: 181 (48) **C**: 221 (44) Depression ≥2 pts: 806 (40) **T_1**: 56 (43) **T_2**: 203 (41) **T_3**: 207 (41) **T_4**: 159 (42) **C**: 181 (36) Explicitly stated rationale for subgroup investigation	N: 2,013 **T_1**: 131 **T_2**: 500 **T_3**: 501 **T_4**: 378 **C**: 503 M: 5% 49 years	**T_1**: Pregabalin 150mg/d x 12 weeks **T_2**: Pregabalin 300mg/d x 12 weeks **T_3**: Pregabalin 450mg/d x 12 weeks **T_4**: Pregabalin 600mg/d x 12 weeks **C**: Placebo	Weekly Mean Pain Diary Score (11 point scale), HADS-A, HADS-D	8-14 weeks	Subgroups: Change in pain score did not depend on changes in anxiety or depression. Pooled data shown. Overall: Except for lowest dose, significant reduction in pain in treated vs. placebo. Significant improvements in HADS-A in patients on 450mg/day and 600mg/day vs. placebo; significant improvements in HADS-D in patients on 450mg/day vs. placebo only. Power discussed only generally. No AEs reported (overall or subgroup).

Author, Year, Country, Studies Pooled, Funder*	Study Aim	Subgroup[§], n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Outcomes Collected	Followup Duration	Reported Results
Bhadra, 2010[36] USA, Canada, Mexico, Denmark, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, UK, India, Korea, Australia, Venezuela Industry funded **Pooled**: Arnold, 2008[33] Mease, 2008[34] Crofford, 2005[35] Pauer, 2008[37]	Evaluate efficacy in patients with comorbid conditions using data pooled from 4 clinical trials	**By 11 conditions** Headache: 970 (37) Immune disorder: 967 (37) GI reflux: 683 (26) Insomnia: 657 (25) Depression: 618 (24) IBS: 509 (20) Neurological: 469 (18) Asthma: 323 (12) Anxiety: 228 (9) Restless legs (RLS): 65 (3) Explicitly stated rationale for subgroup investigation	N: 2,624 **T_1**: 686 **T_2**: 686 **T_3**: 563 **C**: 689 M: NR 49 years	**T_1**: Pregabalin 300mg/d x 12 weeks **T_2**: Pregabalin 450mg/d x 12 weeks **T_3**: Pregabalin 600mg/d x 12 weeks **C**: Placebo	Weekly Mean Pain Diary Score (11 point scale), PGIC	8-12 weeks	Subgroups: Change in pain score and PGIC did not vary by comorbid medical condition. Pooled data shown. Overall: Significant improvements in mean pain score and PGIC in treated vs. placebo. No information on study power. No AEs reported (overall or subgroup). Note: Comorbid conditions not mutually exclusive

Author, Year, Country, Studies Pooled, Funder*	Study Aim	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Outcomes Collected	Followup Duration	Reported Results
Byon, 2010[38] USA, Canada, Mexico, Denmark, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, UK, India, Korea, Australia, Venezuela Industry funded **Pooled**: Arnold, 2008[33] Mease, 2008[34] Crofford, 2005[35] Pauer 2008[37]	Statistical modeling study to assess dose-response in pregabalin vs. placebo on daily pain and PGIC using data pooled from 4 clinical trials, and assess whether effects differ by age and sex	**Age** <40: 534 (19) 40-60: 1,830 (66) >60: 395 (14) **T_1**: NR **T_2**: NR **T_3**: NR **T_4**: NR **C**: NR **Sex** F: 2,568 (93) **T_1**: NR **T_2**: NR **T_3**: NR **T_4**: NR **C**: NR Did not explicitly state rationale for subgroup investigation	N: 2,759 **T_1**: NR **T_2**: NR **T_3**: NR **T_4**: NR **C**: NR M = 7% 49 years	**T_1**: Pregabalin 150mg/d x 12 weeks **T_2**: Pregabalin 300mg/d x 12 weeks **T_3**: Pregabalin 450mg/d x 12 weeks **T_4**: Pregabalin 600mg/d x 12 weeks **C**: Placebo	Treatment Response: Weekly Mean Pain Diary Score (11 point scale), PGIC	8-14 weeks	Subgroups: Reported greater pain reduction in older vs. younger patients and in females vs. males. Statistical modeling paper with insufficient information on actual (vs. predicted) clinical values to evaluate changes from baseline Overall: Exposure-response models were developed to describe the relationship between pregabalin and reductions in pain and improvements in PGIC. No information on study power. No AEs reported (overall or subgroup).

* See Appendix Table E12 for further funding details; § Determined at baseline unless otherwise noted

Abbreviations: AEs=Adverse Effects; BMI=Body Mass Index;-BPI=Brief Pain Inventory; C=Control; CGI-S=Clinical Global Impression of Severity Scale; d=day; EQ-5D=EuroQoL Questionnaire-5 Dimensions; F=Female; FIQ=Fibromyalgia Impact Questionnaire; GI=Gastrointestinal; HADS-A=Hospital Anxiety & Depression Scale-Anxiety; HADS-D=Hospital Anxiety & Depression Scale-Depression; $HAMD_{17}$=Hamilton Rating Scale for Depression; KQ=Key Question; M=Male; MCID=Minimum Clinically Important Difference; MDD=Major Depressive Disorder; MFI=Multidimensional Fatigue Inventory; NR=Not Reported; PGI-I=Patient Global Impression of Improvement Scale; PGIC=Patient Global Impression of Change Score; SAEs=serious adverse events per authors; SDS=Sheehan Disability Scale; SF-36=Short-Form Health Survey; T_1=Treatment group 1 T_2=Treatment group 2; TEAEs=treatment-emergent adverse events per authors; UTD=Unable to Determine; VAS=Visual Analog Scale 24-hour recall pain score

Appendix Table E7. Fibromyalgia observational studies with subgroups, by class of treatment

Author, Year, Country, Funder*	Study Aim Study Design	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Outcomes Collected	Followup Duration	Reported Results
Pharmacologic							
Arnold, 2012[39] USA, Canada Industry funded (Connected to RCT: Arnold 2010)	Post hoc examination of relationships among pain, depressive symptoms and global status in patients taking milnacipran Patients who met criteria for MDD excluded from trial; patients in study may have experienced depressive symptomology rather than satisfied criteria for MDD	**BDI** <10: 599 (58) **T_1**: 294 (57) **C**: 305 (60) 10-18: 317 (31) **T_1**: 168 (33) **C**: 149 (29) 19-25: 109 (11) **T_1**: 54 (10) **C**: 55 (11) **BDI Change** >4: 289 (28) **T_1**: NR **C**: NR ≤4: 291 (28) **T_1**: NR **C**: NR No improvement/ worse: 445 (43) **T_1**: NR **C**: NR Explicitly stated rationale for subgroup investigation	N: 1,025 **T_1**: 516 **C**: 509 M: 5% 49 years	**T_1**: Milnacipran 100mg/d x 12 weeks **C**: Placebo	Pain responder: ≥30% VAS improvement PGIC responder: rates overall change as 1 or 2 2-measure composite responder: Met both criteria	3 months	Subgroups: Pain reduction in treated weakly associated with baseline depressive symptoms. Improvements largely independent of improvements in depressive symptoms. No formal statistical subgroup analysis. Subgroup attrition and AEs not reported. Overall: Significantly greater reduction in mean pain scores and lower mean PGIC in treated vs. controls. No information on study power. Overall attrition not reported AEs not reported.

Author, Year, Country, Funder*	Study Aim Study Design	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Outcomes Collected	Followup Duration	Reported Results
Younger, 2009[40] USA Nonprofit/ Foundation funded	Determine effectiveness of low-dose naltrexone and whether BL characteristics predict treatment response Single-blind crossover trial	**ESR** Subgroups NR Did not explicitly state rationale for subgroup investigation	N: 10 **T_1**: 10 **C**: 10 M: 0% 44 years	**T_1**: Naltrexone 4.5 mg/d x 8 weeks **C**: Placebo x 2 weeks	Primary: VAS pain Secondary: TPs, Avg. daily pain, highest pain, fatigue, sadness, stress, sleep quality, ability to think and remember, GI symptoms, headaches Clinical Significance Threshold: 30% reduction in symptoms over placebo	14 weeks	Subgroups: Correlation between ESR and treatment response 0.91, ($p<0.0005$). Greater VAS pain reduction in those with elevated ESR. Subgroup attrition not reported. AEs not reported by subgroup Overall: Significantly greater reduction in pain in treated vs. placebo. Study powered to find 30% reduction in symptoms. Overall attrition 16.7%. Common AEs were vivid dreams, nausea, insomnia.

Author, Year, Country, Funder*	Study Aim Study Design	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Outcomes Collected	Followup Duration	Reported Results
Psychological							
Drexler, 2002[41] Austria Funding not reported	Determine efficacy of EMG-biofeedback by MMPI score	**MMPI** 24 (100) **Group 1:** Psychologically Abnormal: 12 (50) **Group 2**: Psychologically Normal: 12 (50) Explicitly stated rationale for subgroup investigation	N: 24 **T_1**: 12 **C**: 12 M: 0% 50 years	**Group 1**: Biofeedback therapy as an EMG-reduction training, 2 45-minute sessions/week x 6 weeks **Group 2:** same intervention	Pressure Point Score, Pain Perception Scale, SF-36	3 months	Subgroups: Psychologically abnormal MMPI (Group 1) patients experienced improvements in all measures (symptoms, sensory and affective pain components, QOL). Group 2 (psychologically normal MMPI) patients experienced improvements only in pressure point sensitivity, vitality, and mental health. Group 1 patients were much worse off at baseline in all measures. Subgroup attrition not reported. AEs not reported by subgroup Overall: Long-term improvement only in pressure point sensitivity and sensory pain dimensions. No information on study power. Overall attrition and AEs not reported.

Author, Year, Country, Funder*	Study Aim Study Design	Subgroup§, n (%)	Total Patients, % Male, Mean Age	Specific Intervention(s), Treatment Duration, Control	Outcomes Collected	Followup Duration	Reported Results
Mixed							
Joshi, 2009[42] India No funding	Compare physiotherapy and amitriptyline, and determine whether BL characteristics predict treatment benefit	**FIQ Pain Score** >50: NR ≤50: NR **SES** Low: 82(47) **T_1**: 42(48) **T_2**: 40(45) Did not explicitly state rationale for subgroup investigation	N: 175 **T_1**: 87 **T_2**: 88 M: 5% 39 years	**T_1**: Amitriptyline 25 mg/d x 6 months, titrated to 50 mg/d if no benefit seen **T_2**: Physiotherapy daily, step-up exercise pattern starting at 2 times, 10 minutes/d; Exercise followed by relaxation, stretching, strengthening	FIQ Benefit defined as: ≥2 SD reduction in FIQ score over 6 months	6 months	Subgroups: Low SES and high FIQ score at baseline were only factors that predicted benefit from either therapy. Subgroup attrition not reported. AEs not reported by subgroup Overall: Both strategies significantly reduced disability and were equally effective. No information on study power. Overall attrition not reported. AEs not reported

* See Appendix Table E11 for further funding details; § Determined at baseline unless otherwise noted

Abbreviations: AE=Adverse Effect; Avg.=Average; BDI=Beck Depression Inventory, C=Control; d=day; EMG=electromyographic; ESR=erythrocyte sedimentation rate; FIQ=Fibromyalgia Impact Questionnaire; GI=Gastrointestinal; M=Male; MDD=Major Depressive Disorder; MMPI=Minnesota Multiphasic Personality Inventory; NR=Not Reported; PGIC=Patient Global Impression of Change Score; SD=Standard Deviation; SES=socioeconomic status; T_1=Treatment group 1 T_2=Treatment group 2; TP=Tender Points; VAS=Visual Analog Scale 24-hour recall pain score

Appendix Table E8. Subgroup outcomes reported in the fibromyalgia randomized clinical trial literature

Outcome	Number of Articles	Articles in Which Outcome was Used and for Which Subgroups
Overall Pain		
Visual Analog Scale (VAS) for pain	6	Any mental health condition: Gendreau, 2005[7] Other subgroup: Sadreddini, 2008[9]; Assis, 2006[15]; Fontaine, 2010[22]; Younger, 2009[38]; Gavi, 2014[11]
Brief Pain Inventory	5	Age: Chappell, 2008[3]; Russell, 2008[4]; Arnold, 2012[1] Sex: Chappell, 2008[3]; Russell, 2008[4]; Arnold, 2004[5]; Arnold, 2012[1] Race: Arnold 2012[1]; Chappell, 2008[3]; Russell, 2008[4] Any mental health condition: Arnold, 2005[5]; Arnold, 2012[1]; Chappell, 2008[3]; Russell, 2008[4]
McGill Pain Questionnaire	3	Any mental health condition: Gendreau, 2005[7]; Arnold, 2002[10] Other subgroup: MartÍnez, 2014[21]
Pain Perception Scale	1	Other subgroup: Drexler, 2002[39]
Tender point (TP) assessments	5	Any mental health condition: Arnold, 2002[10] Obesity: Senna, 2012[12] Other subgroup: Sadreddini, 2008[9]; Fontaine, 2010[22]; Drexler 2002[39]
E-diary pain score	1	Any mental health condition: Gendreau, 2005[7]
Modified pain map	1	Other subgroup: Stenning, 2011[8]
Gracely pain scale	1	Any mental health condition: Gendreau, 2005[7]
Fibromyalgia Symptom Improvement		
Fibromyalgia Impact Questionnaire (FIQ)	10	Sex: Arnold, 2004[6] Any mental health condition: Arnold, 2002[10]; Arnold, 2004[6]; Scheidt, 2013[17] Obesity: Senna, 2012[12] Fatigue: Lera, 2009[23] Other subgroup: Assis, 2006[15]; Fontaine, 2010[22]; Gavi, 2014[11]; Joshi, 2009[40]; MartÍnez, 2014[21]
Patient Global Impression of Improvement (PGI-I)	3	Age: Arnold, 2010[2]; Russell, 2008[4] Sex: Arnold, 2010[2]; Russell, 2008[4]; Arnold, 2004[6] Race: Arnold 2012[2] ; Russell, 2008[4] Any mental health condition Arnold, 2004[6]; Arnold, 2010[2]; Russell, 2008[4]

Outcome	Number of Articles	Articles in Which Outcome was Used and for Which Subgroups
Clinical Global Impression of Severity Scale (CGI-S)	2	Age: Russell, 2008[4] Sex: Russell, 2008[4]; Arnold, 2004[6] Race: Russell, 2008[4] Any mental health condition: Russell, 2008[4]; Arnold, 2004[6]
Function		
Sheehan Disability Scale	2	Age: Russell, 2008[4] Sex: Russell, 2008[4]; Arnold, 2004[6] Race: Russell, 2008[4] Any mental health condition: Russell, 2008[4]
6 minute walk	1	Other subgroup: Fontaine, 2010[22]
Isometric strength testing	1	Other subgroup: Hakkinen, 2001[43]
Muscle strength	1	Other subgroup: Valkeinen, 2008[14]
Dynamic balance	1	Obesity: Gusi, 2010[13]
Heart Rate Variability (HRV)	1	Other subgroup: Gavi, 2014[11]
Fitness outcomes (treadmill test, sit and reach test, maximal repetitions test, handgrip dynamometry)	1	Other subgroup: Gavi, 2014[11]
Participation		
Work time	1	Other subgroup: Valkeinen, 2008[14]
Health-Related Quality of Life		
Medical Outcomes Study Short-form 36-item Health Survey (SF-36)	4	Age: Russell, 2008[4] Sex: Russell, 2008[4] Race: Russell, 2008[4] Any mental health condition Russell, 2008[4] Other subgroup: Assis, 2006[15], Drexler 2002[39], Gavi, 2014[11]
Fatigue		
Fatigue Severity Scale (FSS)	1	Other subgroup: Fontaine, 2010[22]
Multidimensional Fatigue Inventory (MFI)	2	Age: Russell, 2008[4] Sex: Russell, 2008[4] Race: Russell, 2008[4] Any mental health condition: Russell, 2008[4] Other subgroup: MartÍnez, 2014[21]

Outcome	Number of Articles	Articles in Which Outcome was Used and for Which Subgroups
Sleep Quality		
Polysomnography	1	Other subgroup: Edinger, 2005[20]
The Pittsburgh Sleep Quality Index (PSQI)	2	Obesity: Senna, 2012[12] Other subgroup: MartÍnez, 2014[21]
Sleep Disturbance	1	Other subgroup: Sadreddini, 2008[9]
Depression and/or Anxiety		
Beck Depression Inventory(BDI) (Beck 1996)	2	Obesity: Senna, 2012[12] Other subgroup: Assis, 2006[15]
Hospital Anxiety and Depression Scale	1	Any mental health condition: Scheidt, 2013[17]
Hospital Anxiety and Depression Questionnaire, Iranian version (IHAD)	1	Other subgroup: Sadreddini, 2008[9]
Quantitative Sensory testing	1	Other subgroup: Stenning, 2011[8]
Hamilton Rating Scale of Depression (HAMD)	1	Any mental health condition: Russell, 2008[4]
Center for Epidemiologic Studies Depression Scale (CES-D)	1	Other subgroup: Fontaine 2010[22]
Depression Quality of Life	2	Any mental health condition: Arnold, 2005[5]; Scheidt, 2013[17]
Symptom Checklist-90-Revised (SCL-90-R)	1	Other subgroup: MartÍnez, 2014[21]
Beck & Idate Trait-State Inventory	1	Other subgroup: Gavi, 2014[11]
Health status		
MPI (composite measure of pain, fatigue, and psychological well-being)	1	Other subgroup: Junghaenel, 2008[19]
Health Assessment Questionnaire (HAQ)	2	Other subgroup: Sadreddini, 2008[9]; Valkeinen, 2008[14]
Patient's Global Assessment of Response to Therapy	1	Other subgroup: Assis, 2006[15]
Chronic Pain Self-efficacy Scale (CPSS)	1	Other subgroup: MartÍnez, 2014[21]
Pain Catastrophizing Scale (PCS)	1	Other subgroup: MartÍnez, 2014[21]
Other outcomes		
VO_2 (peak oxygen uptake)	1	Other subgroup: Valkeinen, 2008[14]
Serum hormone levels	1	Other subgroup: Hakkinen, 2001[43]

Appendix Table E9. Subgroup outcomes reported in pooled randomized clinical trial analyses and observational studies

Outcome	Number of Articles	Articles in Which Outcome was Used and for Which Subgroups
Pooled analyses of patient-level randomized clinical trial data		
Overall Pain		
Brief Pain Inventory (BPI) Average Pain Score	2	Any mental health condition: Arnold, 2009[26] Other subgroup (not defined in protocol) Bradley, 2010[25]
Brief Pain Inventory (BPI) Average Pain Interference Score	1	Any mental health condition: Arnold, 2009[26]
Fibromyalgia Impact Questionnaire Total Score	2	Any mental health condition: Arnold, 2009[26] Other subgroup (not defined in protocol) Bradley, 2010[25]
Fibromyalgia Impact Questionnaire Sub-scales	1	Other subgroup (not defined in protocol) Bradley, 2010[25]
Visual Analog Scale (VAS) for pain	1	Other subgroup (not defined in protocol) Geisser, 2011[31]
Weekly Mean Pain Diary Score	3	Any mental health condition: Arnold, 2010[32] Nonrheumatologic medical comorbidities: Bhadra, 2010[36] Age: Byon, 2010[38] Sex: Byon, 2010 [38]
Fibromyalgia Symptom Improvement		
Clinical Global Impression of Severity Scale (CGI-S)	1	Any mental health condition: Arnold, 2009[26]
Patient Global Impression of Change (PGI-C)	3	Other subgroup (not defined in protocol): Geisser, 2011[31] Nonrheumatologic medical comorbidities: Bhadra, 2010[36] Age: Byon, 2010[38] Sex: Byon, 2010[38]
Patient Global Impression of Improvement (PGI-I)	2	Any mental health condition: Arnold, 2009[26] Other subgroup (not defined in protocol): Bradley, 2010[25]
Function		
FIQ subscale: stiffness item	1	Age: Bennett, 2012[24] Obesity: Bennett, 2012[24]
Sheehan Disability Scale (SDS)	1	Any mental health condition: Arnold, 2009[26]
Health-Related Quality of Life		
Medical Outcomes Study Short-form 36-item Health Survey (SF-36)	2	Any mental health condition: Arnold, 2009[26] Other subgroup (not defined in protocol): Bradley, 2010[25]
Medical Outcomes Study Short-form 36-item Health Survey (SF-36), Physical function score	1	Other subgroup (not defined in protocol): Geisser, 2011[31]
Fatigue		
Multidimensional Fatigue Inventory (MFI)	1	Any mental health condition: Arnold, 2009[26]

Outcome	Number of Articles	Articles in Which Outcome was Used and for Which Subgroups
Sleep Quality		
Other outcomes		
Depression		
Hamilton Depression Rating Scale (HAMD)	1	Any mental health condition: Arnold, 2009[26]
Obesity-Related		
Change in Body Weight	1	Obesity: Arnold, 2012[27]
Observational studies		
Overall Pain		
FIQ subscale: pain item	1	Other subgroup (not defined in protocol) Joshi, 2009[42]
Pain Perception Scale	1	Other subgroup (not defined in protocol): Drexler, 2002[41]
Pressure Point Sensitivity	1	Other subgroup (not defined in protocol): Drexler, 2002[41]
Visual Analog Scale (VAS) for pain	2	Any mental health condition: Arnold, 2012[39] Other subgroup (not defined in protocol): Younger, 2009[40]
Fibromyalgia Symptom Improvement		
Patient Global Impression of Change (PGI-C)	1	Any mental health condition: Arnold, 2012[39]
Health-Related Quality of Life		
Short-form 36-item Health Survey (SF-36)	1	Other subgroup (not defined in protocol): Drexler, 2002[41]

Appendix Table E10. Fibromyalgia risk of bias summary for RCTs: mixed samples and pure subgroups

Study	Overall Risk of Bias Assessment	Rationale
MIXED SAMPLES		
Pharmacologic		
Duloxetine		
Arnold, 2012[1]	High	High attrition, subgroup attrition not separately identified, small subgroup sample size, powered to detect main not subgroup effects
Arnold, 2010[2]	High	High attrition, subgroup attrition not separately identified, small subgroup sample size, powered to detect main not subgroup effects
Chappell, 2008[3]	High	High attrition, subgroup attrition not identified, powered to detect main not subgroup effects, select details regarding blinding not provided, outcome measure scores treated as missing if an individual item was missing
Russell, 2008[4]	High	High attrition, subgroup attrition not separately identified, small subgroup sample size, powered to detect main not subgroup effects, table denominators reflect baseline not followup numbers of patients, drop-outs assigned a score of no change for one primary outcome in analyses.
Arnold, 2005[5]	High	High attrition, subgroup attrition not separately identified, subgroup sample size within treatment group not specified, powered to detect main not subgroup effects
Arnold, 2004[6]	High	High attrition, subgroup attrition not separately identified, small subgroup sample size in some instances (though authors stated study adequately powered to detect subgroup effect), power calculations based on main and not subgroup effect, selective outcome reporting.
Milnacipran		
Gendreau, 2005[7]	High	High attrition, subgroup attrition not separately identified, small subgroup sample size, no information on study power, no adjustment for multiple comparisons, incomplete outcomes reporting for subgroup analysis
Off-label		
Arnold, 2002[10]	High	High attrition, subgroup attrition not separately identified, small subgroup sample size, no information on study power, subgroup analysis not specified a priori
Psychological		
Junghaenel, 2008[19]	High	Small sample size, no randomization detail given, not powered for main outcomes or subgroups, blinding not possible
Mixed		
Lera, 2009[23]	High	High attrition, subgroup attrition not separately identified, small subgroup sample size, study not powered for main outcome or subgroup effect, subgroup not determined a-priori, inadequate blinding
PURE SUBGROUPS		
Pharmacologic		
Off-label		
Stening, 2011[8]	High	Small sample size, not powered, no randomization detail given, double-blinded, low attrition, larger proportion of subjects in placebo group on anti-depressants.
Sadreddini, 2008[9]	High	Nature of treatment precludes blinding, no adjustment for multiple comparisons, outcomes assessors not blinded, low attrition, study powered for main outcome, no details on how randomization carried out

Study	Overall Risk of Bias Assessment	Rationale
Physical		
Gavi, 2014[11]	High	Inadequate randomization (simple sequential randomization strategy), clinician not blinded to treatment, no adjustment for multiple comparisons, analysis limited to program completers, insufficient reporting Blinded patients and study staff by using an active control condition, low overall attrition (18%)
Senna, 2012[12]	High	Small sample size, study not powered for main outcome, researchers not blinded to intervention due to nature of the study but outcomes assessors were blinded, randomization process not detailed ("concealed envelope method, block size of 4). Low attrition
Gusi, 2010[13]	Moderate	Nature of treatment precludes full blinding, post-hoc defined subgroups, subgroup sample size not reported and small sample size overall, no information on study power, and no adjustment for multiple comparisons Low attrition (<15%, similar in each group), blinded patients and study staff to the extent possible for type of intervention
Valkeinen, 2008[14]	High	Randomization process not detailed, small sample size, no blinding, no power analysis
Assis, 2006[15]	Moderate	Nature of treatment precludes blinding, no adjustment for multiple comparisons, lacking detail on blinding of outcome assessors and permitted co-interventions Low attrition (<15%, same in each group), blinded patients and investigators to the extent possible for type of intervention, study adequately powered to detect difference in primary outcome
Hakkinen, 2002[16]	High	No randomization details, not powered for main outcome, no binding, no inclusion/exclusion criteria stated, small sample size
Psychological		
Scheidt, 2013[17]	High	Randomization process not specified ("randomized into groups by blocks of 10), sufficient power and sample size, >20% attrition, no information on baseline characteristics of drop-outs.
Edinger, 2005[20]	High	Small sample size, high attrition, excluded questionnaires with missing data, no power analysis, lack of blinding/blinding not possible, randomization process not specified
Mixed		
Martínez, 2014[21]	High	High attrition, interventions not easily replicable, analysis limited to program completers, no adjustment for multiple comparisons despite extensive analyses, no information on study power, no blinding due to type of intervention
Fontaine, 2010[22]	High	High attrition rate, randomization process not detailed, no blinding, interventions not easily replicable, study powered for main outcome

Appendix Table E11. Fibromyalgia risk of bias summary for observational studies

Study	Overall Risk of Bias Assessment	Rationale
Pharmacologic		
Arnold, 2012[39]	High	No information on study power, other variables that might have influenced outcome not taken into consideration (e.g., fatigue), subgroups not clearly defined (Hints at "Comorbid depression," but not adequately measured).
Younger, 2009[40]	High	Subgroup N not reported, subjects used as self-control so no randomization, no meaningful comparison between placebo and intervention, small total sample size (n=20) though powered for main effect, single-blinded
Psychological		
Drexler, 2002[41]	High	Small sample size, no information on study power, self-controls (quasi-experimental design), uncertain blinding, significant differences in all baseline characteristics between groups
Mixed		
Joshi, 2009[42]	High	Small sample size, no randomization detail given, patients lost to followup not described, significant difference (p=0.04) in a parameter in baseline characteristics, no information on study power.

Appendix Table E12. Quality issues and risk of bias summary for pooled analyses of patient-level randomized clinical trial data on fibromyalgia subgroups

Study	Pooled RCTs	Overall Risk of Bias Assessment	Rationale
Pharmacologic (all)			
Duloxetine			
Bennett, 2012[24]	Chappell, 2008[3] Russell, 2008[4] Arnold, 2005[5] Arnold, 2004[6]	RCT inputs: High Pooled: issues detailed in rationale	Pooled: No a priori hypothesis of direction of treatment effect in subgroups, outcome measure is subscale of common tool but subscale has not been formally validated, study power not discussed, no adjustments made for multiple comparisons and less stringent statistical criteria used to evaluate treatment-by-subgroup interaction, attrition not discussed despite high attrition in input RCTs, small sample size in certain subgroup strata (e.g., extreme obesity) Used optimal individual patient data (IPD) pooled analytic technique (Fischer et al. 2011)[44] study blinding input RCTs: High risk of bias (all 4 studies)
Bradley, 2010[25]	Chappell, 2008[3] Russell, 2008[4] Arnold, 2005[5] Arnold, 2004[6]	RCT inputs: High Pooled: issues detailed in rationale	Pooled: No a priori hypothesis of direction of treatment effect in subgroups, study power not discussed, no adjustments for multiple comparisons and less stringent statistical criteria used to evaluate treatment-by-subgroup interactions, attrition not discussed despite high attrition in input RCTs, some selective reporting in results presentation, small sample size in certain subgroup strata (e.g., FIQ tiredness, mile group), different duloxetine doses combined analysis (with rationale) Used optimal individual patient data (IPD) pooled analytic technique (Fischer et al. 2011)[44] study blinding input RCTs: High risk of bias (all 4 studies)
Arnold, 2009[26]	Chappell, 2008[3] Russell, 2008[4] Arnold, 2005[5] Arnold, 2004[6]	RCT inputs: High Pooled: issues detailed in rationale	Pooled: No a priori hypothesis of direction of treatment effect in subgroups, study power not discussed, no adjustments for multiple comparisons and less stringent statistical criteria used to evaluate treatment-by-subgroup interactions, attrition not discussed despite high attrition in input RCTs, some selective reporting in results presentation, different duloxetine doses combined analysis (with rationale) Used optimal individual patient data (IPD) pooled analytic technique (Fischer et al. 2011)[44] study blinding input RCTs: High risk of bias (all 4 studies)

Study	Pooled RCTs	Overall Risk of Bias Assessment	Rationale
Milnacipran			
Arnold, 2012[27]	Subgroup analysis: Arnold, 2010[28] Mease, 2009[29] Clauw, 2008[30]	RCT inputs: High Pooled: issues detailed in rationale	Pooled: No a priori hypothesis of direction of treatment effect in subgroups, study power not discussed, no adjustments for multiple comparisons, attrition not discussed despite high attrition in input RCTs, unable to determine subgroup sample size within each treatment group Used optimal individual patient data (IPD) pooled analytic technique (Fischer et al. 2011)[44] study blinding input RCTs: High risk of bias (all 3 input studies)
Geisser, 2011[31]	Mease, 2009[29] Clauw, 2008[30]	RCT inputs: High Pooled: issues detailed in rationale	Pooled: No a priori hypothesis of direction of treatment effect in subgroups, study power not discussed, no adjustments for multiple comparisons, attrition not discussed despite high attrition in input RCTs, unable to determine subgroup sample size, only patients classified as responders included in subgroup analyses Used optimal individual patient data (IPD) pooled analytic technique (Fischer et al. 2011)[44] study blinding input RCTs: High risk of bias (both input studies)
Pregabalin			
Arnold, 2010[32]	Arnold, 2008[33] Mease, 2008[34] Crofford, 2005[35]	RCT inputs: High Pooled: issues detailed in rationale	Pooled: No a priori hypothesis of direction of treatment effect in subgroups, study power not discussed, no adjustments made for multiple comparisons, outcome assessment timing varies by study, attrition not discussed despite high attrition in input RCTs, unable to determine effect of treatment in subgroups as reported Used optimal individual patient data (IPD) pooled analytic technique (Fischer et al. 2011)[44] study blinding input RCTs: High risk of bias (all)
Bhadra, 2010[36]	Arnold, 2008[33] Mease, 2008[34] Crofford, 2005[35] Pauer, 2008[37]	RCT inputs: High Pooled: issues detailed in rationale	Pooled: No a priori hypothesis of direction of treatment effect in subgroups, study power not discussed, no adjustments made for multiple comparisons, outcome assessment timing varies by study, attrition not discussed despite high attrition in input RCTs, only those with given co-morbid medical condition are shown in results and not those without Used optimal individual patient data (IPD) pooled analytic technique (Fischer et al. 2011)[44], study blinding input RCTs: High risk of bias (3 of 4 studies, 4th study unable to determine; Pauer et al. is an abstract only)

Study	Pooled RCTs	Overall Risk of Bias Assessment	Rationale
Byon, 2010[38]	Arnold, 2008[33] Mease, 2008[34] Crofford, 2005[35] Pauer 2008[37]	RCT inputs: High Pooled: issues detailed in rationale	Pooled: No a priori hypothesis of direction of treatment effect in subgroups, study power not discussed, outcome assessment timing varies by study, attrition not discussed despite high attrition in input RCTs, insufficient information on actual (vs. predicted) clinical values to evaluate changes from baseline in subgroups input RCTs: High risk of bias (3 of 4 studies, 4th study unable to determine; Pauer et al. is an abstract only – unable to assess quality)

Appendix Table E13. Funding source and corresponding author information in fibromyalgia randomized clinical trials, mixed samples

Author, Year	Funding Source*	Corresponding Author Information
Pharmacologic		
Duloxetine		
Arnold, 2012[1] *Safety & Efficacy*	Eli Lilly & Company	Corresponding author not listed. Reprints addressed to industry author (Eli Lilly & Company). Two of three authors were full time employees and stockholders in the company; third author received grants and was a company consultant.
Arnold, 2010[2] *Flexible Dosed Duloxetine*	Funding source not reported. ClinicalTrials.gov listed sponsor as Eli Lilly & Company; collaborator as Boehringer Ingelheim	Industry author (Eli Lilly & Company)
Chappell, 2008[3]	Eli Lilly & Company and Boehringer Ingelheim	Industry author (Eli Lilly & Company)
Russell, 2008[4]	Eli Lilly & Company and Boehringer Ingelheim	Industry author (Lilly Research Laboratories) with joint appointment in the Indiana University School of Medicine
Arnold, 2005[5] *Duloxetine*	Eli Lilly & Company	Academic (no conflict of interest information provided). Of six authors, four were employees at Eli Lilly; two were in academics (one also worked as a consultant).
Arnold, 2004[6] *Duloxetine MDD*	Eli Lilly & Company. Clinical Operations staff and Statistical Analyst group of the Cymbalta product team implemented trial and provided statistical programming support	Academic (received consulting fees or honoraria in excess of $10,000 in the prior 2 years from Eli Lilly and Co). Of seven authors, three were employees of Eli Lilly, one had an appointment at two academic centers and was an employee of Eli Lilly, and one was at an academic institution but also worked as a consultant.
Milnacipran		
Gendreau, 2005[7]	Supported by Cypress Biosciences	Corresponding author not listed. Reprints addressed to industry author (Cypress Biosciences). Of ten authors, three were employees of Cypress Biosciences, three were paid consultants and shareholders, and two were consultants.
Off-label		
Arnold, 2002[10] *Fluoxetine*	Investigator-initiated grant from Eli Lilly & Company	Corresponding author not listed, reprints addressed to academic author
Psychological		
Junghaenel, 2008[19]	Supported by Rheumatology Health Professional Investigator Award from the American College of Rheumatology Research & Education Foundation. Material support provided by Applied Behavioral Medicine Research Institute, Stony Brook University	Academic
Mixed		
Lera, 2009[23]	Funding source not reported	Academic

* Information obtained from article unless otherwise noted

Appendix Table E14. Funding source and corresponding author information in fibromyalgia randomized clinical trials with pure subgroup samples

Author, Year	Funding Source*	Corresponding Author
Off-label		
Stening, 2011[8]	Swedish Research Council – Medicine, the Swedish Brain Foundation, the Health Research Council (SE Sweden) and the Linnaeus University.ClinicalTrials.gov listed sponsor as Ostergotland County Council, Sweden	Academic
Sadreddini, 2008[9]	Funding source not reported	Academic
Gavi 2014[11]	Authors have no support or funding to report	Academic
Senna, 2012[12]	Funding source not reported	Corresponding author not stated; academic contact provided.
Gusi, 2010[13]	Funding source not reported	Academic
Valkeinen, 2008[14]	Ministry of Education of Finland and the Peurunka-Medical Rehabilitation Foundation, Laukaa, Finland	Corresponding author not listed; reprints addressed to academic author
Assis, 2006[15]	Grant from FAPESP, the Research Support Fund of the State of São Paulo	Academic
Hakkinen, 2002[16]	Supported in part by grants from the Finnish Social Insurance Institution and the Yrjö Jahnsson Foundation	Corresponding author not listed; reprints addressed to academic author
Scheidt, 2013[17]	Supported as part of an Interdisciplinary Research Project by the Freiburg Institute of Advance Studies (FRIAS)	Academic
Edinger, 2005[20]	Federal grant (R21) from National Institutes of Health/National Institute of Arthritis and Musculoskeletal & Skin Diseases	Academic, Veterans Affairs Medical Center
Martínez, 2014[21]	Supported by the Spanish Ministry of Science and Innovation	Academic
Fontaine, 2010[22]	Federal grant, National Institutes of Health/National Institute of Arthritis and Musculoskeletal & Skin Diseases	Academic

* Information obtained from article unless otherwise noted

Appendix Table E15. Funding source and corresponding author information in fibromyalgia pooled studies of individual patient data from randomized clinical trials

Author, Year	Funding Source*	Corresponding Author
Arnold, 2009[26]	Eli Lilly and Co.	Industry: Lilly Research Labs, Eli Lilly and Company.
Arnold. 2010[32] Pregabalin	Pfizer Inc., USA.	Academic (also received consultation fees from Cypress Biosciences, Forest Lab, AstraZeneca, Eli Lilly and Co., Pfizer, Boehringer Ingelheim, Allergan). Three other authors were employees of Pfizer.
Arnold, 2012[27] Milnacipran	Forest Laboratories Inc. and Forest Research Institute Inc.	Academic (also received consultation fees from Cypress Biosciences, Forest Lab, AstraZeneca, Eli Lilly and Co., Pfizer, Boehringer Ingelheim, Allergan, etc.)
Bennett, 2012[24]	Eli Lilly and Company	Academic (also received consulting fees from Eli Lilly). Two authors were employees and stockholders of Eli Lilly and Company.
Bhadra, 2010[36]	Pfizer Inc.	Industry. Authors were employees of Pfizer
Bradley, 2010[25]	Eli Lilly and Company and Boehringer Ingelheim, Inc.	Academic (also a consultant for Eli Lilly and Co, Pfizer and Forest Laboratories Inc.). Two authors work on industry advisory boards and one had been paid as a consultant and speaker for Pfizer, Eli Lilly and Company, Forest laboratories, etc.
Byon, 2010[38]	Pfizer Inc.	Industry. Authors were full-time employees of Pfizer Inc.
Geisser, 2011[31]	Forest Laboratories Inc.	Academic (also vice president, chief medical director, and shareholder at Cypress Biosciences Inc., and had received research grant support from Cypress Biosciences). One author was a senior medical director at Forest Research Institute, one was a full time employee at Forest Research Institute and one author was an academic who served as a consultant and had received grant support from Cypress Biosciences.

* Information obtained from article unless otherwise noted

Appendix Table E16. Funding source and corresponding author information in fibromyalgia observational studies

Author, Year	Funding Source*	Corresponding Author
Arnold, 2012[39]	Forest laboratories Inc. and Pfizer Inc.	Academic (had received consultation fees from Cypress Biosciences, Forest Lab, AstraZeneca, etc.) Two authors were full-time employees of Forest Laboratories Inc.
Drexler, 2002[41]	Funding source not reported.	Academic
Joshi, 2009[42]	No funding. No conflict of interest declared.	Academic (declared no conflict of interest)
Younger, 2009[40]	Supported by American Fibromyalgia Syndrome Association, Oxnard Foundation (nonprofit) and Arthritis Foundation, and private contributions	Academic

* Information obtained from article unless otherwise noted

Appendix Table E17. Justification for retaining potentially overlapping individual RCTs and associated pooled patient-level data duloxetine studies that differed in outcome or timing of outcome assessment

Author, Year *RCTs Pooled**	N[§] Randomized	Treatment	Timing of Outcome Assessment	Subgroup(s)	Outcome(s) for Subgroup Analysis	Interaction Reporting
RCTs						
Arnold, 2004[6]	207	**T** - 120mg/day **C** - placebo	12 weeks	Sex MDD	FIQ, BPI average pain severity, SDS (MDD)	Text with interaction p value; no data
Arnold, 2005[5] (*females only*)	354	**T_1** - 60mg/day **T_2** - 120mg/day **C** - placebo	12 weeks	MDD	BPI average pain severity	Text with interaction p value; no data
Chappell, 2008[3]	330	**T** - 60mg, titrated up to 120mg/day starting at week 8 if necessary, and if tolerated **C** - placebo	27 weeks *"6 months"*	Age (<65 vs. ≥65) Sex Race MDD Anxiety Past antidepressant	BPI average pain severity	6 months. only: text plus interaction p value; data (in text) for prior anti-depressant use only
Russell, 2008[4]	520 325 started 6mo phase	**T_1** - 20mg/day **T_2** - 60mg/day **T_3** - 120mg/day **C** - placebo	15 & 24 weeks	Age (<65 vs. ≥65) Sex Race MDD	BPI average pain severity, PGI-I *Table 7 of our report shows 24 week outcomes*	Data and text; no interaction p value
Pooled						
Arnold, 2009[26] *Arnold 2005[5]* *Arnold 2004[6]* *Chappell 2008[3]* *Russell 2008[4]*	1,332	**T** - 60mg or 120mg/day **C** - placebo	12 weeks	MDD	BPI average pain severity, $HAMD_{17}$, FIQ, CGI-S, SDS, SF-36, MFI	Data, text and interaction p value
Bennett, 2012[24] *Arnold 2005[5]* *Arnold 2004[6]* *Chappell 2008[3]* *Russell 2008[4]*	1,332	**T** - 60mg or 120mg/day **C** - placebo	12 weeks	Age (<55 vs. ≥55) BMI groups	FIQ stiffness score	Data, text and interaction p value
Bradley, 2010[25] *Arnold 2005[5]* *Arnold 2004[6]* *Chappell 2008[3]* *Russell 2008[4]*	1,332	**T** - 60mg or 120mg/day **C** - placebo	12 weeks	FIQ tiredness score	BPI average pain severity, FIQ total & FIQ subscales, SF-36	Data, text and interaction p value (in text)

*Pertains only to pooled studies of individual patient-level randomized clinical trial (RCT) data

§Only numbers of patients randomized to initial RCTs were reported by authors. Column values (per authors) do not account for attrition in RCTs or pooled analyses.

Abbreviations: BPI=Brief Pain Inventory; C=Control; CGI-S=Clinical Global Impression of Severity Scale; FIQ=Fibromyalgia Impact Questionnaire; $HAMD_{17}$=Hamilton Rating Scale for Depression; MDD=Major Depressive Disorder; MFI=Multidimensional Fatigue Inventory; PGI-I=Patient Global Impression of Improvement Scale; SDS=Sheehan Disability Scale; SF-36=Medical Outcomes Study Short-Form 36-item Health Survey; T_1=Treatment group 1 T_2=Treatment group 2 T_3=Treatment group 3

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