Comparative Effectiveness Review
Number 148

Effective Health Care Program

Treatments for Fibromyalgia in Adult Subgroups

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]

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**.

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

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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

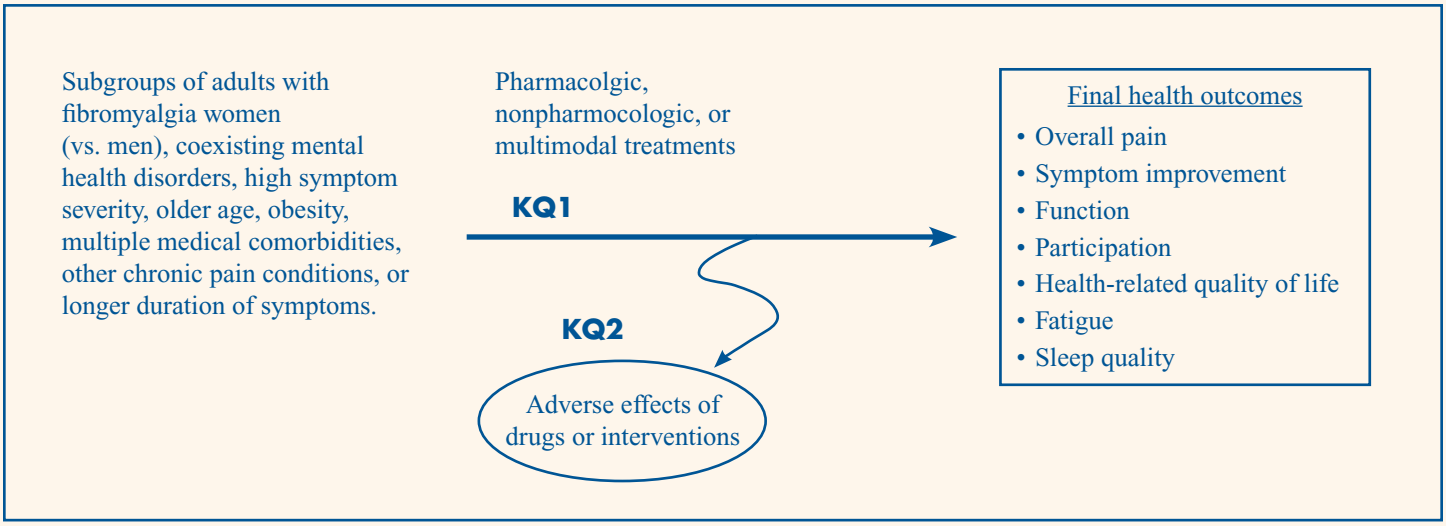
Key Question 2. What are the harms of treatments for fibromyalgia in each of these specific adult subpopulations?

- 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 framwork for treatments for fibromyaligia in adult subgroups



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 [33,57] 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)
	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)

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)	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.

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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Full Report

This executive summary is part of the following document: Forte ML, Butler M, Andrade KE, Vincent A, Schousboe JT, Kane RL. Treatments for Fibromyalgia in Adult Subgroups. Comparative Effectiveness Review No. 148. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2012-00016-I.) AHRQ Publication No. 15-EHC006-EF. Rockville, MD: Agency for Healthcare Research and Quality; January 2015. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

AHRQ Pub. No. 15-EHC006-1-EF
January 2015