

Comparative Efficacy of Pharmacological and Nonpharmacological Interventions in Managing Primary and Secondary Outcomes of Fibromyalgia Syndrome

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Objective: The aim of this literature review is to individually compare the efficacy of pharmacological and nonpharmacological treatments in managing primary and secondary outcomes of fibromyalgia syndrome (FMS). The primary and secondary outcomes under evaluation include pain, fatigue, sleep management, depressed mood, and health-related quality of life. When evaluating for primary and secondary outcomes of FMS, a nonpharmacological approach has greater efficacy in managing a larger scope of fibromyalgia symptoms.

Methods: Research analysis was performed through searching online databases and journals by using specific words and phrases that were relevant to the topic of choice. Journal article searches were filtered by publications no earlier than 2006 to help ensure relevancy and accuracy of data. An evidence table was further created to better organize and evaluate the articles found.

Results: Analysis of seven trials with a total of 2,795 patients and four active interventions (duloxetine, pregabalin, aerobic exercise, and cognitive behavioral therapy) were included. Nonpharmacological intervention trials (exercise and cognitive behavioral therapy) were small but did show promising effects for improving pain and quality of life. In larger trials, the pharmacological treatment had an advantage over placebo when pain and quality of life were assessed. Efficacy toward secondary outcomes of sleep and depression were either statistically nonsignificant or of questionable clinical relevance regardless of numerical significance for all trials except pregabalin. The nonpharmacological trials were unable to assess a broader range of fibromyalgia symptoms such as sleep difficulties and depression.

Conclusions: Nonpharmacological interventions did not show clinical significance in managing a broader range of fibromyalgia symptoms. A larger study sample size is needed to compare the efficacy of pharmacological and nonpharmacological interventions in primary and secondary outcomes of fibromyalgia.

Keywords: fibromyalgia; treatment; exercise; pharmacological; cognitive behavioral therapy; duloxetine; pregabalin

Fibromyalgia syndrome (FMS) is characterized by chronic widespread musculoskeletal pain and is one of the most common disorders seen by rheumatologists.¹ According to the Centers for Disease Control and Prevention (CDC), the prevalence of fibromyalgia is around 2% and is seen more often in women than in men (3.4% vs. 0.5%).¹ The precise pathophysiology of FMS is unclear but is hypothesized to be largely due to central or peripheral hyperexcitability at the spinal or brainstem level.² Although the etiology of fibromyalgia is unknown, the treatment is mainly focused on identifying and controlling the primary and secondary outcomes of FMS.¹ The most common symptoms aside from widespread

pain include sleep disturbances, fatigue, depressed mood, and impaired daily functioning.² Being a chronic disorder, FMS impairs physical and emotional health, which impacts the overall quality of the patient's life. Pain with various overlapping symptoms becomes a complex and dynamic phenomenon that makes fibromyalgia a challenging disorder to treat. There is no definitive cure for fibromyalgia, which is why a multidisciplinary approach involving medical, self-management, and alternative interventions is suggested as treatment.^{1,2}

The aim of this literature review is to individually compare the efficacy of the first-line pharmacological and nonpharmacological treatments in FMS patients

when evaluating for pain, fatigue, sleep management, depressed mood, and health-related quality of life (HRQOL). Fibromyalgia symptoms affect every aspect of quality of life and have a significant impact on the ability of the patient to work. The underlying chronic pain experienced by patients is likely to contribute to a sedentary lifestyle which leads to poor physical conditions in affected individuals.³ Exercise has been suggested as an important part of FMS treatment when it is individually tailored to the patients' scope of physical abilities. Even with a variety of treatment options available, a stronger recommendation is given to pharmacological rather than nonpharmacological therapies by clinicians.⁴ The primary objective of this review is not limited to assessing the efficacy of treatment options on the main outcome of FMS pain, but to address which treatment options have a broader effect on other domains of fibromyalgia as well. This can potentially help clinicians in selecting a treatment plan tailored to the heterogeneity of symptoms of each individual with fibromyalgia.

Systemic reviews and previous meta-analyses evaluated a wide variety of pharmacological and non-pharmacological treatment options for health care professionals and patients with FMS. The American Pain Society strongly recommends pharmacological interventions including serotonin-norepinephrine reuptake inhibitors (SNRIs), gamma-aminobutyric acid (GABA) analogs, as well as nonpharmacological treatments such as aerobic exercise and cognitive behavioral therapy (CBT).⁵ The following treatment options that fit this study's inclusion criterion will be assessed for their efficacy in the treatment of primary and secondary outcomes of FMS, including pain, sleep, depression, and HRQOL.

ANTIDEPRESSANTS – SNRIS (DULOXETINE)

Duloxetine is a SNRI that has been approved by the US Food and Drug Administration (FDA) for the treatment of major depressive disorder (MDD), and the management of peripheral neuropathic pain. Previous studies support the efficacy of duloxetine in the reduction of pain in FMS patients, with adverse effects of nausea, dry mouth, constipation, and somnolence.⁶

ANTICONVULSANTS: CALCIUM CHANNEL BLOCKERS (PREGABALIN)

Pregabalin is a structural GABA analog but acts by inhibiting high-voltage activated calcium channels.

This results in a decreased release of many excitatory neurotransmitters including glutamate, norepinephrine, and substance P at the nerve terminals, which is assumed to be the basis of the drug's analgesic effects. Pregabalin produces common side effects of dose-related sedation and dizziness.⁷

AEROBIC EXERCISE

Exercise is one of the main nonpharmacological treatments clinically recommended for the management of FMS symptoms. More specifically, aerobic exercise along with the addition of flexibility and strength training programs have been shown to produce positive health benefits when targeting widespread joint pain, stiffness, muscle fatigue, and overall physical function.^{8,9}

COGNITIVE BEHAVIORAL THERAPY

CBT is a psychotherapeutic option used to treat FMS patients by targeting the cognitive and behavioral factors behind the premise of chronic pain. Through the use of relaxation training and stress reduction, CBT leads to modification of pain behavior, dysfunctional thoughts, and health-seeking behavior.^{10,11}

METHODOLOGY

Databases Used

The scientific literature used in this review contained a variety of studies that included randomized control trials (RCT), retrospective and prospective cohort studies, cross-sectional studies, as well as literary reviews. A literature search was conducted through the use of various databases and online journals including but not limited to the following: *Pubmed Central*, *Google Scholar*, *Medscape*, and *the American Journal of Medicine*. Specific journals pertaining to the chosen topic such as *Rheumatology*, *PAIN*[®], and *The Clinical Journal of Pain* were further assessed for relevant studies. Journal article searches were filtered to publications no earlier than 2006 to help ensure the relevancy and accuracy of data.

Search Strategy

The search strategy used for the purpose of this review included FDA-approved, first-line pharmacological treatments and nonpharmacological treatments for patients with fibromyalgia. To narrow the search for the most relevant articles, the title and abstract sections were analyzed accordingly.

Search Terms

First, a broad search was conducted using the following keywords: *fibromyalgia treatment, pharmacological, and nonpharmacological treatment*. A focused search was then conducted to narrow down to the most relevant articles. Search terms used are indicated as follows: *aerobic exercise, antidepressants, calcium channel blockers, and cognitive behavioral therapy*. Based on these terms, the retrieved literature was analyzed for relevancy to the hypothesis and statistical significance.

Eligibility Criteria

Articles and RCTs published in English and no earlier than 2006 that fulfilled the following inclusion criteria were obtained and analyzed: patients of any age diagnosed with fibromyalgia based on the criteria for classification by the American College of Rheumatology were included for analysis. Studies that used treatment options approved by the FDA for FMS management were included. Treatment options reviewed were: antidepressants, GABA analogs, aerobic exercise, and CBT. Studies that assessed primary and a minimum of one secondary outcome were included. Primary outcomes analyzed in FMS patients posttreatment were pain, whereas sleep, depressed mood, and quality of life were specified as secondary outcomes. Studies without randomization and control interventions were excluded.

Data Grading and Organization

RCT and literature review included in this paper were organized in an evidence table (Appendix A). Articles were sorted by publication design, study design, sample size, study population, and exposure. Each study was then ranked according to the Level of Evidence criteria, with level 1 being of highest value. Systematic reviews with RCT were considered level 1. Systematic reviews with cohort studies or prospective cohort studies were considered level 2. Observational studies with controls were considered level 3, while observational studies without control were considered level 4.

RESULTS

Characteristics of Included Trials

Seven trials with a total of 2,579 patients that met the inclusion criteria were included in the literature review and analysis. The articles were published no earlier than 2006, and the trial duration ranged from 6 to 12 months. Two trials evaluated duloxetine (850 patients); two trials, pregabalin (1,498 patients); two trials, Aerobic Exercise

(106 patients); and one trial, CBT (125 patients). The pharmacological trials had a placebo control, while the nonpharmacological trials had a nonintervention or minimally active control, such as attention placebo (AP). The majority of the patients were women of Caucasian descent, with an average age ranging from 47 to 55 years. Table 1 was generated to summarize the comparative data of all trials included in this review and analysis.

Pain and Impairment

Table 1 shows the effect on pain in seven trials after treatment with either active pharmacological or nonpharmacological interventions and placebo. Pain and impairment were assessed by either the Brief Pain Inventory (BPI) average pain score or the Fibromyalgia Impact Questionnaire pain score (FIQ) in each trial. The BPI is a short form that assesses average pain during the past 24 h on a scale from 0 to 10 (no pain to very severe pain).¹² The FIQ is a 20-item patient-administered survey that measures the patient's physical functioning, well-being, and outcomes over the past week. Primary and secondary outcomes of pain, fatigue, stiffness, difficulty working, and other symptoms of FMS are assessed. Total scores range from 0 to 80, where a higher score indicates a more negative impact of the intervention.¹³

Although the Chappell et al.¹⁴ trial showed numerical improvement in duloxetine-treated patients in the primary measures of mean change in the BPI average pain score (duloxetine -1.62 , placebo -1.13 , $p = 0.053$), the differences between the two groups were not considered statistically significant. Treatment with duloxetine showed no significant difference in the BPI average pain severity response rate, defined as $>50\%$ reduction from baseline to end point (duloxetine 29.1%, placebo 25.1%, $p = 0.455$). Average pain severity scores in BPI based on $>30\%$ reduction from baseline also showed no significant difference between duloxetine (38.0%, $p = 0.355$) and placebo (32.9%). Secondary measures in the FIQ pain score compared to the placebo-treated patients did show statistically significant improvement (mean change duloxetine -1.69 , placebo -1.06 , $p = 0.03$).¹⁴

Analysis of the Russell et al.¹⁵ trials showed that patients treated with duloxetine 120 mg/day improved significantly more on primary outcomes in the BPI average pain severity at 3 months (duloxetine -2.31 , placebo -1.39 , $p < 0.001$) and at 6 months (duloxetine -2.26 , placebo -1.43 , $p = 0.003$). Response rates for the BPI average pain severity at $>50\%$ reduction from

Appendix A: Evidence Table

First Author	Date of publication	Study Design	Evidence Rating	Sample Size	Study Population	Exposure	Results
Arnold, L.M	2008	Randomized, Double Blinded controlled trial	1	750	>18 y/o patients who met ACR fibromyalgia criteria with VAS pain score > 40mm	Pregabalin 300/450/600 mg twice daily	Mean changes in pain score, improvement on PGIC and sleep patterns with pregabalin compared to placebo along with common side effects of dizziness and drowsiness
Bernardy, K.	2010	Systemic review with Meta-analysis	2	1482	Female fibromyalgia patients age range 16-54 years	CBT	Reduction in depressed mood and self efficacy pain at follow up. Limited reduction in pain, fatigue, sleep disturbances and HRQOL
Castel, A	2012	Randomized control trial	1	93	18-65 y/o patients who met ACR fibromyalgia criteria	CBT, CBT with hypnosis, Standard drug therapy	patients receiving CBT or CBT with hypnosis showed greater improvements than patients who received standard drug therapy
Chappell, A.	2008	Randomized, Double Blinded controlled trial	1	330	>18 y/o patients who met ACR fibromyalgia criteria with or without MDD	Duloxetine 60/120 mg once daily	Significant improvement in FIQ pain score, BPI lease pain score, BDI-1, and SF-36. No significant difference in BPI pain scores, Nausea and headache most common adverse effect
Hauser, W.	2010	Systemic review with Meta-analysis	2	2494	13-59 y/o patients	AE: cycling walking, aquatic jogging, games, dance, boxing	Post treatment: Positive effects on reducing pain, fatigue, depressed mood. No effect on sleep. Follow up: No positive affection on pain, fatigue or sleep. Continuing AE necessary to maintain positive effects upon follow ups
Mease, P.	2008	Randomized, Double Blinded controlled trial	1	748	>18 y/o patients who met ACR fibromyalgia criteria	Pregabalin 300/450/600 mg twice daily	Significant improvement in mean pain scores, FIQ total scores, sleep assessment and global improvement scale. Dizziness and somnolence most common adverse effects
Russell, J.	2008	Randomized, Double Blinded controlled trial	1	520	>18 y/o patients who met ACR fibromyalgia criteria with average pain severity >4	Duloxetine 20/60/120 mg once daily	Improvement in BPI pain scores at 3 and 6 month treatment intervals. No positive effects on sleep quality or depression scale. Nausea and headache most common adverse effect
Sanudo, B.	2010	Randomized, Double Blinded controlled trial	1	64	Women who met ACR fibromyalgia criteria	Aerobic Exercise twice weekly	14-15% improvement in FIQ pain scores from baseline and decrease in BDI pain scores
Sanudo, B.	2018	Randomized, Double Blinded controlled trial	1	42	Women age 18-65 y/o patients who met ACR fibromyalgia criteria	Aerobic, strength, flexibility exercises	Improvement in FIQ pain scores and health related quality of life (SF-36) scores.
Thieme, K.	2006	Randomized, Double Blinded controlled trial	1	125	>18 y/o patients who met ACR fibromyalgia criteria	CBT weekly 2 hour sessions	Significant reduction in pain intensity, improvement in cognitive functioning, physical functioning, and coping mechanism

ACR: American College of Rheumatology, **AE:** Aerobic Exercise, **BPI:** Brief Pain Inventory, **BDI:** Beck Depression Inventory, **BDI-1:** Beck Depression Inventory, **CBT:** Cognitive Behavioral Therapy, **FIQ:** Fibromyalgia Impact Questionnaire, **HRQOL:** Health-Related Quality of Life, **MDD:** Major Depressive Disorder, **PGIC:** Patients' Global Impression of Change, **SF-36:** Short Form Health Survey 36, **VAS:** Visual Analogue Scale

Table 1. Summary of average pain, sleep, depression and health-related quality of life scores from all seven included trials.^{5,14-19}

Study	Year	Subject	Mean Age	Sample Size	Treatment	Duration	Outcomes	Adverse Effects
PHARMACOLOGICAL INTERVENTIONS								
Chappell	2008	Female (93.3%) Caucasian (90.9%)	50	330	Duloxetine 60/120 mg once daily	6 months	Pain (BPI): -1.22, Placebo -0.73 P=0.046 Pain (FIQ): -1.69, Placebo -1.03 P=0.009 Sleep: N/A Depressed mood (BDI): -3.42, Placebo -1.45, P=0.017 HRQOL (SF-36): 3.37 (Mental), Placebo: 0.79 P=0.026	Nausea, headache, dry mouth, diarrhea, constipation, arthralgia, somnolence
Russell	2008	Female (94.8%) Caucasian (84.2%)	51	520	Duloxetine 20/60/120 mg once daily	6 months	Pain (BPI): -2.26, Placebo: -1.43 P<0.003 Pain (FIQ): N/A Sleep: N/A Depression (HAMMD): -5.2/-6.9/-7.2, Placcbo: -4.8 P=0.022 HRQOL (SF-36): 2.56/3.68/4.41 (Mental) Placebo: 1.75	Nausea, dry mouth, constipation somnolence
Arnold	2008	Female (94.5%) Caucasian (91.0%)	50	750	Pregabalin 300/450/600 mg twice daily	14w	Pain (BPI): -1.75/-2.03/-2.05; Placcbo:-1.04 P<0.001 Pain (FIQ): -10.70, -12.98, -13.08; Placcbo: -7.74 P<0.005 Sleep Quality: -1.90/-2.28/-2.51; Placebo:-1.16 P<0.005 Depression (HADS): -0.39/-0.85/-0.81 Placcbo: -0.53 P<0.7 HRQOL: N/A	Dizziness, somnolence
Mease	2008	Female (94%) Caucasian (90%)	49	748	Pregabalin 300/450/600 mg twice daily	13w	Pain (BPI): -1.84/-1.87/-2.06; Placebo: -1.40 P<0.05 Pain (FIQ): -16.15/-15.71/-14.88; Placebo:-13.66 P<0.6 Sleep Quality: -2.19/-2.29/-2.53; Placebo: -1.32 P<0.0001 Depression (HADS): N/A HRQOL: N/A	Dizziness, somnolence
NON-PHARMACOLOGICAL INTERVENTIONS								
Sañudo	2010	Female (100%)	55	64	Aerobic Exercise twice weekly	6 months	Pain (BPI): N/A Pain (FIQ):-8.8 P<0.02 Sleep: N/A Depression (BDI): -8.5 P<0.001 HRQOL (SF-36): 8.9 P<0.01	
Sañudo	2011	Female (100%)	50	42	Aerobic, strength, flexibility exercises	6 months	Pain (BPI): N/A Pain (FIQ):-8.2 Control: 2.9 P=0.027 Sleep: N/A Depression (BDI): -6.2; Control: 3.6 P=0.556 HRQOL (SF-36): 7.9; Control: -1.4 P=0.043	
Thieme	2006	Female (100%)	47	125	CBT weekly 2 hour sessions	12 months	Pain (BPI): N/A Pain (FIQ):-0.93 Control: 1.01 P<0.001 Sleep: N/A Depression (HADS): N/A HRQOL: N/A	

BPI: Brief Pain Inventory, **BDI:** Beck Depression Inventory, **CBT:** Cognitive Behavioral Therapy, **FIQ:** Fibromyalgia Impact Questionnaire, **HADS:** Hospital Anxiety and Depression Scale, **HAMD:** Hamilton Depression Rating Scale, **HRQOL:** Health-Related Quality of Life, **N/A:** Not Applicable, **SF-36:** Short Form Health Survey 36

baseline to 6 months end point were significantly greater for duloxetine 20/60 mg/day (36.4%, $p = 0.025$), 60 mg/day (32.6%; $p = 0.045$), and 120 mg/day (35.9%; $p = 0.009$), compared to placebo (21.6%). Analysis showed that response rates defined as >30% reduction from baseline to 6 months' end point were significantly greater for duloxetine 20/60 mg/day (51.9%; $p = 0.045$) but not for 60 mg/day (47.2%, $p = 0.118$) or 120 mg/day (49.3%; $p = 0.054$) compared with placebo (37.4%). Secondary measures in FIQ scores showed that duloxetine 60 and 120 mg/day demonstrated significantly greater improvements compared with placebo-treated patients.¹⁵

Trials by Arnold et al.¹⁶ demonstrated significant mean changes in pain scores at end point in all three pregabalin monotherapy patient groups compared to placebo-treated patients (300 mg/day -1.71 , 450 mg/day -2.03 , 600 mg/day -2.05 , placebo -1.04 , $p < 0.001$). Response rates for the average pain severity at >30% and >50% reduction from baseline were significantly greater in all treatment groups when compared to placebo treatment groups. Response rates defined at >30% reduction from baseline for 300 mg/day was 42% ($p = 0.0172$), 50% in the 450 mg/day ($p = 0.0002$), and 48% in the 600 mg/day pregabalin ($p = 0.0006$), compared to 30% in placebo treatment group. Whereas, response rates defined as >50% reduction from baseline for 300 mg/day was 24% ($p = 0.0372$), 27% in the 450 mg/day ($p = 0.0038$), and 30% in the 600 mg/day pregabalin ($p = 0.001$), compared to 15% in the placebo treatment group. Patients reported improvements in total FIQ scores for 450 and 600 mg/day doses when compared with the placebo treatment groups.¹⁶

Pregabalin trials by Mease et al.⁵ showed statistically significant improvements in mean pain in all three treatment groups from baseline compared with patients receiving placebo treatment (300 mg/day -1.84 , 450 mg/day -1.87 , 600 mg/day -2.06 , placebo -1.04 , $p < 0.005$). The 600 mg/day treatment group showed the most improvement compared to 350 mg/day, 450 mg/day, and placebo treatment group. Response rates defined at >30% reduction from baseline for 300 mg/day was 40%, 43% in the 450 mg/day, and 44% in the 600 mg/day pregabalin, compared to 35% in the placebo treatment group. Although the response rates were higher in all three treatment groups compared to the placebo treatment group, the differences were not statistically significant for any pregabalin dosage. FIQ pain scores for all three pregabalin treatment groups

were numerically but not statistically greater than the placebo treatment group.⁵

Two randomized controlled trials by Sañudo et al.^{17,18} showed significant improvements in health status in patients assigned to the exercise group over the control group. Significant improvements were seen in the FIQ pain score after the 24-week intervention period (RCT 2010: -8.8 , $p < 0.02$, RCT 2011: -8.2 $p < 0.027$).^{17,18} Trials including CBT as a primary intervention by Thieme et al. also showed a significant reduction in pain intensity and impairment which was assessed by the FIQ score reports (-0.93 , $p < 0.001$).¹⁹

Sleep

Table 1 summarizes the effect on sleep in seven trials after treatment with either active pharmacological or nonpharmacological interventions and placebo. Sleep quality and outcomes were assessed by the mean sleep quality or Medical Outcomes Study (MOS)-Sleep scale. The MOS-Sleep scale is a 12-item form that assesses the quality of sleep including parameters such as sleep disturbance, snoring, awakening with a headache, and somnolence. Scores range from 0 to 100 with higher scores indicating higher impairment in quality of sleep with treatment intervention.²⁰

Effect on sleep quality did not have a positive outcome in the Chappell et al.¹⁴ or Russell et al.¹⁵ trials with duloxetine. Sleep disturbance and somnolence were the reported adverse events that occurred in >5% of duloxetine-treated patients.^{14,15} Pregabalin trials by Arnold et al.¹⁶ and Mease et al.⁵ were both associated with significant improvements in sleep quality and outcomes in all three dosage groups. (Arnold et al.; $1.90/-2.28/-2.51$; Placebo: -1.16 $p < 0.005$, Mease et al.; $-2.19/-2.29/-2.53$; placebo: -1.32 $p < 0.001$).^{5,16} Secondary outcomes of sleep with nonpharmacological treatments were unknown in trials by Sañudo et al. and Thieme et al.¹⁷⁻¹⁹

Depressed Mood

Table 1 summarizes the effect on depressed mood in seven trials after treatment with either active pharmacological or nonpharmacological interventions and placebo. Depressed mood and outcomes were assessed by the Hamilton Depression Rating Scale (HAM-D), Beck Depression Inventory-II total score (BDI-II), or Hospital Anxiety and Depression Scale (HADS). The HAM-D is a 17-item observational rating that measures the severity of depression and improvement during the treatment intervention period. The multiple item questionnaire

scores range from 0 to 52, indicating no depression to severely depressed.²¹ The BDI is a 21-item questionnaire designed to measure the severity of depression during the course of the treatment. The total score ranges from 0 to 63 with a higher score indicating severe depressive symptoms.²² The HADS is a 14-item questionnaire that measures the levels of anxiety and depression the patient is experiencing during the course of the treatment.²¹

The Chappell et al.¹⁴ and Russell et al.¹⁵ trials showed that duloxetine-treated patients improved numerically more than placebo-treated patients on the BDI-II total score (Chappell et al.; duloxetine -3.42 , placebo -1.45 , $p = 0.017$) and on the HAMD scale (Russell et al.; duloxetine 20 mg -5.2 , 60 mg -6.9 , 120 mg -7.2 , placebo: -4.8 $p = 0.022$). Analysis of secondary outcomes of depression assessed by the HADS scale in pregabalin trials by Arnold et al.¹⁶ and Mease et al.⁵ did not show significant improvements compared to placebo.^{5,16} No significant improvements in the BDI scores for depression were reported by Sañudo et al. in either trial.^{17,18} No depression scale was used by Thieme et al. for their CBT trials.¹⁹

Health-Related Quality of life

Table 1 summarizes the effect on HRQOL in seven trials after treatment with either active pharmacological or nonpharmacological interventions and placebo. HRQOL was assessed by the Short Form Health Survey (SF-36), a 36-item self-administered questionnaire that measures the physical functioning, social functioning, and emotional and mental health of the patient through the treatment course. Scores range from 0 to 100, where higher scores indicate a better HRQOL experienced by the patient.²³

In trials by Chappell et al.¹⁴ and Russell et al.,¹⁵ duloxetine-treated patients improved significantly more compared with placebo-treated patients in the SF-36 mental component summary score (Chappell et al.; duloxetine 6.63, placebo 1.19, $p = 0.005$). The Russell et al.¹⁵ trial with duloxetine-treated patients at the 3-month phase showed increased improvement in the SF-36 mental component score but did not achieve statistical significance compared to placebo. Significant improvement and statistical significance were demonstrated at the 6-month treatment phase in all duloxetine treatment groups compared to the placebo group (duloxetine 20 mg 2.56, 60 mg 3.68, 120 mg 4.41, placebo 1.75, $p = 0.05$).¹⁵ Pregabalin trials by Arnold et al.¹⁶ and Mease et

al.⁵ showed improvement in SF-36 scores compared with the placebo group.^{5,16} Exercise intervention trials by Sañudo et al. showed significant improvements in SF-36 scores in most domains such as physical function, and general and mental health.^{17,18} Improvement in quality of life was not assessed in CBT intervention trials by Thieme et al.¹⁹

DISCUSSION

Over the past 20 years, fibromyalgia has been one of the leading causes of visits to rheumatologists and has been estimated to affect 5 million US adults, with its prevalence still on the rise.¹ The long-term course of fibromyalgia characterized by severe impairment and chronic pain makes it difficult to draw a definitive conclusion for the most appropriate first-line therapy in managing this disease. Current research shows a wide array of pharmacological and nonpharmacological interventions that can be effective in reducing primary symptoms such as chronic pain. Chronic pain is likely to cause physical and psychological impairment leading to an impact on the quality of life. Additional psychological symptoms are often present including sleep abnormalities, cognitive impairment, anxiety, and depression.⁴

The aim of this literature review was not limited to analyzing the effects of treatment on the primary symptom of pain but also to compare the broader effects of the recommended interventions on secondary domains of fibromyalgia. The high variability in measuring treatment outcomes in each trial for reporting results was a barrier for conducting this literature review and analysis. In order to accept the hypothesis that a nonpharmacological treatment plan has greater efficacy in managing a larger scope of fibromyalgia symptoms, evidence in the literature needed to show statistically significant improvement in a broader range of FMS symptoms for treatments such as aerobic exercise and CBT over the control treatment group.

The first pharmacological trial reviewed for this analysis was a 6-month, double-blind, placebo-controlled, randomized clinical trial of duloxetine by Chappell et al.¹⁴ published in the *International Journal of General Medicine*. Duloxetine-treated patients had significantly greater improvement in the FIQ pain scores compared to placebo-treated patients. However, no statistically significant differences were seen between treatment and placebo groups for primary measures of pain using the BPI average pain score.¹⁴ In Chappell's trial, the overall change in BPI pain scores from baseline to end point

were not consistent with those reported in other clinical trials evaluating duloxetine as a treatment option for fibromyalgia.

Analysis of the randomized, double-blind control trial by Russell et al.¹⁵ with duloxetine 60 mg/day and 120 mg/day showed greater efficacy in reducing pain severity after 3 and 6 months of treatment compared to placebo. Analysis showed that patients treated with 120 mg/day improved significantly on primary outcomes in the BPI average pain severity at 3 and 6 months. The 20 mg dose did not significantly improve the pain severity score compared to placebo and was included in the trial to determine the minimum effective dose for the treatment of fibromyalgia. The trial also showed significant improvement in the total FIQ scores and SF-36 mental component summary at 3 and 6 months in both duloxetine groups compared to placebo. In both duloxetine trials, the most common adverse effects within the first 3 months of treatment were headache, dry mouth, and nausea. Less common adverse effects reported were somnolence and sleep-related issues.¹⁵

As of 2007, pregabalin was the first drug to be approved by the FDA and the European registry for the treatment of fibromyalgia.⁷ In the 14-week, randomized, double-blinded control trial by Arnold et al.¹⁶ with 300–600 mg/day pregabalin therapy, statistically significant improvements in pain scores were demonstrated in all treatment groups. In all three treatment groups of pregabalin, more patients had >30% and >50% decrease in pain rating over the treatment course compared to patients in the placebo group. Pregabalin treatment groups also showed improvements in the secondary outcomes of fibromyalgia including sleep quality.¹⁶ Surveys found that poor sleep is one of the key symptoms of fibromyalgia and that sleep problems have been cited as an aggravating factor by 79% of FMS patients.²⁴ Compared to the placebo group, patients in all three pregabalin groups showed significant improvement in sleep outcomes as measured by the MOS index and the sleep quality diary. These results provided important evidence that pregabalin has statistically significant effects on primary outcomes of pain as well as secondary sleep problems in patients with fibromyalgia. Other secondary outcomes such as anxiety and depression did not statistically improve when assessed with the HADS scores in all pregabalin groups. Treatment groups with 450 mg/day and 600 mg/day did show significant improvements in the Vitality score on the SF-36. However, a lack of significant improvement in all parameters of the SF-36 scores

indicates that a 14-week treatment plan might not be sufficient time to evaluate significant changes in HRQOL.¹⁶

The 13-week RCT by Mease et al.⁵ showed similar results with pregabalin treatment dosages of 300, 450, and 600 mg/day. All three pregabalin treatment groups showed statistically significant improvement in pain scores compared to the placebo group at the end of the treatment trials. However, the FIQ total score was not significantly improved in any of the three treatment groups compared to placebo. Along with improvements in pain scores in all three treatment groups, patients also showed significant improvements in sleep quality assessed by the daily sleep diary and MOS-Sleep scale. These statistically significant data show that pregabalin may be beneficial for FMS patients with both pain and sleep problems. The most common adverse effects of dizziness and somnolence were dose-dependent in both treatment trials.^{5,16} The high incidence of dizziness and somnolence may indicate that patients with fibromyalgia might be more sensitive to Central Nervous System (CNS)-related adverse effects. Overall, pregabalin was generally well tolerated with a favorable benefit to risk ratio.⁵

The two presented trials by Sañudo et al.^{17,18} showed positive effects of aerobic exercise in patients with fibromyalgia, but the study sample was relatively small, making the results not fully comparable for analysis. The 6-month trial with aerobic exercise showed an improvement in HRQOL, FIQ scores, BDI depression scale, and SF-36 scores. The improvement in FIQ scores showed 14–15% magnitude of improvement, a clinically relevant improvement seen in patients with FMS. Improvement in average BDI scores indicated that aerobic exercise can potentially improve depressive symptoms in patients with FMS.^{17,18}

Another nonpharmacological trial included the analysis of the efficacy of CBT in treating psychological pain in patients with FMS. This CBT trial conducted by Thieme et al. (2006) reported significant improvements in physical functioning, pain, and emotion distress at 6- and 12-month posttreatment compared with the AP group which showed significant deterioration. The most significant changes with CBT were seen in pain and cognitive variables. The results indicate that CBT treatment successfully targeted the coping strategies of patients and reduced affective distress.¹⁹

LIMITATIONS AND FUTURE DIRECTION

The results presented were limited due to the small number of trials analyzed in this review. Other limitations arise

from the exclusion criteria of selecting FMS patients with no other psychiatric or medical comorbidities, resulting in the exclusion of more severely affected FMS patients. The results cannot be generalized toward patients with unstable psychiatric or medical disorders or secondary fibromyalgia pain. Fibromyalgia is a chronic condition, but the trials discussed in this review were of acute duration ranging from 6 to 12 months. Therefore, the results discussed cannot be generalized to a longer duration of treatment for a patient with fibromyalgia.^{5,14-19} The pharmacological trials did not include an active medication as a comparison since the study was intended to evaluate the efficacy of monotherapy in the treatment of FMS outcomes.^{5,14-16} The nonpharmacological trials with aerobic exercise were also limited by sample size, which may have resulted in a type II error.^{17,18} Along with the small sample size, these trials were also limited by the range of outcomes assessed after treatment.¹⁷⁻¹⁹

For results to be clinically comparable, the impact of nonpharmacological treatments on secondary key factors such as sleep patterns, depression, and anxiety should also be assessed in future studies. Future trials should assess the long-term efficacy of the presented pharmacological and nonpharmacological treatment plans because FMS is a chronic condition that will likely require treatment for longer than 6–12 months. Future research should analyze a larger number of trials that directly compare pharmacological treatments with nonpharmacological interventions which have been shown to be efficacious in the treatment of FMS symptoms. Larger studies are needed to duplicate the results of trials with a small sample size.

CONCLUSION

The purpose of this review was to individually compare the efficacy of pharmacological and nonpharmacological interventions in the treatment of primary and secondary outcomes of FMS. In these seven trials with a total of 2,795 patients with FMS, the nonpharmacological trials were very small, but aerobic exercise and CBT showed promising effects in reducing pain and improving the quality of life.¹⁷⁻¹⁹ In larger trials, the pharmacological treatment had an advantage over placebo when pain and quality of life were assessed. Efficacy toward secondary outcomes of sleep and depression were either not statistically significant or of questionable clinical relevance, regardless of numerical significance for all trials except pregabalin.^{5,14-16} The nonpharmacological trials were

unable to assess a broader range of FMS symptoms such as sleep difficulties and depression compared to the pharmacological treatment trials, therefore rejecting the proposed hypothesis. Evidence toward effective first-line treatment for fibromyalgia is limited. No single monotherapy is completely effective in treating the wide array of primary and secondary symptoms in patients with fibromyalgia. This suggests that a multidisciplinary treatment plan that targets different outcomes of fibromyalgia may be the best strategy in clinical practice.

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