Treatment of Fibromyalgia Syndrome With Antidepressants: A Meta-analysis

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Treatment of Fibromyalgia Syndrome With Antidepressants

A Meta-analysis

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Context Fibromyalgia syndrome (FMS) is a chronic pain disorder associated with multiple debilitating symptoms and high disease-related costs. Effective treatment options are needed.

Objectives To determine the efficacy of antidepressants in the treatment of FMS by performing a meta-analysis of randomized controlled clinical trials.

Data Sources MEDLINE, PsycINFO, Scopus, and the Cochrane Library databases were searched through August 2008. Reference sections of original studies, meta-analyses, and reviews on antidepressants in FMS were reviewed.

Study Selection Randomized placebo-controlled trials with tricyclic and tetracyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs) were analyzed.

Data Extraction and Data Synthesis Two authors independently extracted data. Effects were summarized using standardized mean differences (SMDs) by a random-effects model.

Results Eighteen randomized controlled trials (median duration, 8 weeks; range, 4-28 weeks) involving 1427 participants were included. Overall, there was strong evidence for an association of antidepressants with reduction in pain (SMD, –0.43; 95% confidence interval [CI], –0.55 to –0.30), fatigue (SMD, –0.13; 95% CI, –0.26 to –0.01), depressed mood (SMD, –0.26; 95% CI, –0.39 to –0.12), and sleep disturbances (SMD, –0.32; 95% CI, –0.46 to –0.18). There was strong evidence for an association of antidepressants with improved health-related quality of life (SMD, –0.31; 95% CI, –0.42 to –0.20). Effect sizes for pain reduction were large for TCAs (SMD, –1.64; 95% CI, –2.57 to –0.71), medium for MAOIs (SMD, –0.54; 95% CI, –1.02 to –0.07), and small for SSRIs (SMD, –0.39; 95% CI, –0.77 to –0.01) and SNRIs (SMD, –0.36; 95% CI, –0.46 to –0.25).

Conclusion Antidepressant medications are associated with improvements in pain, depression, fatigue, sleep disturbances, and health-related quality of life in patients with FMS.

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FIBROMYALGIA SYNDROME (FMS) has an estimated prevalence in North America and Europe of 0.5% to 5.8%.[1] According to the criteria of the American College of Rheumatology (ACR), FMS is defined as chronic widespread pain and tenderness at a minimum of 11 of 18 defined tender points.[2] Other symptoms of FMS are fatigue and nonrestorative sleep. Most patients report additional somatic and psychological symptoms.[3,4] Patients with FMS experience disability and reduced health-related quality of life (HRQOL).[5] Fibromyalgia syndrome is also associated with high direct[6,7] and indirect disease-related costs.[8] Effective treatment of FMS is therefore necessary for medical and economic reasons.[9]

Whether FMS is a distinct disorder or a manifestation of another underlying disorder is controversial. The spectrum of possible underlying disorders ranges from inflammatory arthritic diseases to depression. Others classify FMS as a functional somatic syndrome.[10]

CME available online at www.jamaarchivescme.com and questions on p 227.

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Evidence-based guidelines on the management of FMS from the American Pain Society[11] and the European League Against Rheumatism[12] included published literature through 2004 and 2005, respectively. Antidepressants are the drugs most often studied for treatment of FMS. However, no meta-analyses on antidepressant therapy for FMS have been published since 2000.[13,14]

We therefore performed a meta-analysis with 3 goals: to evaluate the effects of treatment with antidepressants on FMS-related symptoms; to examine possible differences in the efficacy of distinct antidepressant classes in therapy for FMS; and to determine the internal validity (methodological quality) and external validity (generalizability) of randomized controlled trials (RCTs) with antidepressants in FMS.

METHODS

The meta-analysis was performed according to the QUORUM guidelines (Quality of Reporting of Meta-analyses)[15] and the recommendations of the Cochrane Collaboration.[16]

Data Sources and Searches

The electronic databases screened were MEDLINE (1966 through August 2008), PsycINFO (1966 through August 2008), Scopus (1980 through August 2008), and the Cochrane Library (1993 through August 2008). Using Medical Subject Headings terms, searches were limited to *human* and performed for all languages. The keyword *fibromyalgia* was used in combination with *tricyclic antidepressant* or *serotonin reuptake inhibitors* or *monoamine oxidase inhibitors* or *antidepressant* or *antidepressive agents* and *randomized controlled trial* or *controlled clinical trial* or *review*. After consulting with the German center of the Cochrane Collaboration, we did not use a filter such as the highly sensitive search strategy[17] because limiting the number of reports with a filter did not seem reasonable considering the potential number of studies. Reference sections of relevant original articles, reviews, meta-analyses,[13,14] and evidence-based guidelines[11,12] were screened manually and independently by 2 of us (K.B., W.H.).

Study Selection

Study inclusion criteria were as follows: use of recognized criteria to define FMS (ACR,[2] Smythe and Moldofsky,[18] or Yunus[19]); RCT design with a control group receiving pharmacological placebo; and treatment with antidepressants (tricyclic and tetracyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs], serotonin and noradrenaline reuptake inhibitors [SNRIs], or monoamine oxidase inhibitors [MAOIs]).

We did not include studies assessing cyclobenzaprine, *S*-adenosylmethionine, or combinations of antidepressants. Cyclobenzaprine combines characteristics of an antidepressant and a muscle relaxant. *S*-adenosylmethionine is a dietary supplement. We contacted corresponding authors of RCTs with incomplete data presentation (eg, missing means, standard deviations of pretest and posttest data, or standard deviations of change scores). Studies in which only categorical data were provided and those for which we were not able to obtain missing data were excluded.

Data Extraction

Two of us (K.B., W.H.) independently screened the titles and abstracts of potentially eligible studies identified. The full text articles were examined independently by 2 of us (C.S., W.H.) to determine whether they met the inclusion criteria. Two of us (N.U., W.H.) independently extracted data (study characteristics and results) using data extraction forms. Point estimates for selected variables were extracted and checked by the other 2 reviewers. We used κ statistics to assess agreement between reviewers. All discrepancies were rechecked and consensus was achieved by discussion.

We selected the following outcome measures, which are features of FMS[20]: pain, fatigue, sleep, and depressed mood. Health-related quality of life was an additional outcome. When researchers reported more than 1 measure for an outcome, we used the following priority for inclusion in the meta-analysis:

1. Pain: visual analog scale (VAS), VAS Fibromyalgia Impact Questionnaire (FIQ), Numeric Rating Scale (NRS), other pain questionnaire
2. Fatigue: VAS, VAS FIQ, other questionnaire
3. Sleep: VAS, VAS FIQ, NRS, other questionnaire
4. Depressed mood: VAS, VAS FIQ, other questionnaire
5. HRQOL: FIQ total score, other HRQOL scale.

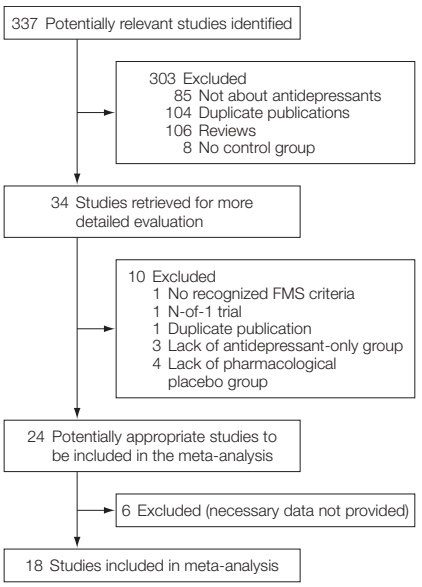
The van Tulder test (11 items)[21] and the Jadad test (5 items)[22] were applied for assessing methodological quality. The van Tulder items were used to arbitrarily classify quality as high (scores 8-11), moderate (scores 5-7), or low (scores 1-4). The Jadad score was used to classify quality as high (score 5), moderate (score 4), or low (scores 1-3).

Data Synthesis and Analysis

We analyzed intention-to-treat data whenever available. For the comparison of proportions, the χ^2 test was applied. Nonparametric tests (Mann-Whitney test, Kruskal-Wallis test) were used for comparing continuous variables. A 2-sided *P* value of .05 or lower was considered significant. Meta-analyses were conducted using RevMan analyses software (RevMan 4.2.10).[23]

Because most outcomes were presented as continuous data (mean value or mean changes), we used either the weighted mean differences (WMDs) or the standardized mean difference (SMDs) as effect measures. Weighted mean differences were calculated when the outcome measure in all trials was determined on the same scale, SMDs when outcomes were measured using different scales. To calculate WMDs or SMDs, we used means and change scores and their standard deviations. When only the standard error was reported, it was converted into standard deviation.[24]

Figure 1. Study Selection



FMS indicates fibromyalgia syndrome.

I^2 statistics were used to measure heterogeneity of the RCTs. If the I^2 value was less than 50%, a fixed-effects meta-analysis was applied. If the I^2 value was 50% or more, the random-effects meta-analysis was used.[23] We used Cohen categories[25] to evaluate the magnitude of the effect size, calculated by WMD or SMD, and designated a D greater than 0.2 through 0.5 as a small effect size, a D greater than 0.5 up to 0.8 as a medium effect size, and a D greater than 0.8 as a large effect size. We used the following descriptors to classify meta-analysis results[21]: "strong" indicated consistent findings in multiple (at least 2) high- or moderate-quality RCTs; "moderate" indicated consistent findings in multiple low-quality RCTs or 1 high- or moderate-quality RCT; "limited" indicated 1 low-quality RCT; and "conflicting" indicated inconsistent findings among multiple RCTs.

A sensitivity analysis was conducted to determine whether different classes of antidepressants (TCA, SSRI, SNRI, MAOI) influenced the results by calculating the effect sizes of the outcomes assessed of each class of antidepressants.

Potential publication bias (ie, the association of publication probability with the statistical significance of study results) was investigated using visual assessment of the funnel plot (plots of effect estimates against sample size) calculated by RevMan Analyses software. Publication bias may lead to asymmetrical funnel plots.[26] Furthermore, we tested the sensitivity of our results to potential unpublished studies using a file-drawer test for meta-analysis. This test determines how many negative studies with an effect size of D=0.01 would be needed to negate our findings (fail-safe number). If the fail-safe number exceeds the file-drawer number, the results of the meta-analysis can be regarded as robust against potential reporting bias.[27-29] The file-drawer number is calculated as 5k + 10; where k is the number of study groups in the meta-analysis.

RESULTS

Study Selection

The literature search yielded 337 citations. Initially, 34 studies met our inclusion criteria. The excluded 303 studies contained duplicate publications, review articles, uncontrolled studies, and studies without an antidepressant group. On more detailed review, an additional 16 papers were excluded for the following reasons: no recognized criteria for FMS,[30] duplicate publication,[31] report of N-of-1 trials,[32] lack of an antidepressant-only group,[33-35] lack of a pharmacological placebo group,[36-39] outcome measures not suitable for meta-analysis,[40] or means or standard deviations of pretest and posttest data or standard deviations of change scores were not included in the publication and were not provided by the authors on request.[41-46] The remaining 18 studies met our selection criteria and were included in the meta-analysis (FIGURE 1).[47-64] The interrater reliability for this assessment was $\kappa = 0.92$.

Meta-analyses

The effect sizes for all antidepressants are shown in FIGURES 2, 3, 4, 5, and 6. There was strong evidence for a reduction of pain (SMD, –0.43; 95% confidence interval [CI], –0.55 to –0.30; $P < .001$), fatigue (SMD, –0.13; 95% CI, –0.26 to –0.01; $P = .04$), and depressed mood (SMD, –0.26; 95% CI, –0.39 to –0.12; $P < .001$) and improved sleep (SMD, –0.32; 95% CI, –0.46 to –0.18; $P < .001$) and HRQOL (SMD, –0.31; 95% CI, –0.42 to –0.20; $P < .001$). Based on Cohen categories for evaluating the magnitude of effect sizes, the effect of antidepressant therapy was negligible for fatigue and small for remaining outcomes.

TABLE 1 gives a comparison of the effect sizes of each antidepressant class. There was strong evidence for the efficacy of the TCA amitriptyline in reducing pain (SMD, –1.64; 95% CI, –2.57 to –0.71; $P < .001$), fatigue (SMD, –1.12; 95% CI, –1.87 to –0.38; $P = .003$), and sleep disturbances (WMD, –1.84; 95% CI –2.62 to –1.06; $P < .001$). Based on Cohen categories, these effect sizes were large. The effect size on depressed mood (WMD, –0.60; 95% CI, –4.53 to 3.33; $P = .76$) was not significant. The effect on HRQOL was small (WMD, –0.31; 95% CI, –0.60 to –0.01; $P = .04$).

There was strong evidence for the efficacy of the SSRIs fluoxetine and paroxetine in reducing pain (SMD, –0.39; 95% CI, –0.77 to –0.01; $P = .04$). The effects were small on depressed mood (WMD, –0.37; 95% CI, –0.66 to –0.07, $P = .02$) and HRQOL (WMD, –0.41; 95% CI, –0.78 to –0.05, $P = .03$). There were no effects on fatigue (WMD, –0.17; 95% CI, –0.47 to 0.12, $P = .25$) or sleep (SMD, –0.23; 95% CI, –0.56 to 0.10, $P = .18$).

There was strong evidence for the efficacy of the SNRIs duloxetine and milnacipran in reducing pain (SMD, –0.36; 95% CI, –0.46 to –0.25; $P < .001$) and sleep disturbances (SMD, –0.31; 95% CI, –0.47 to –0.14; $P < .001$). There was strong evidence for the efficacy of duloxetine in improving depressed mood (SMD, –0.26; 95% CI, –0.42 to –0.10; $P = .001$) and HRQOL (SMD, –0.31; 95% CI, –0.44 to –0.17; $P < .001$). Based on Cohen categories for the magnitude of effect size, these effect sizes were

small. There was no effect of duloxetine on fatigue (WMD, –0.08; 95% CI, –0.20 to 0.05; *P*=.23).

There was strong evidence for the efficacy of the MAOIs moclobemide and pirlindole in reducing pain (SMD, –0.54; 95% CI, –1.02 to –0.07; *P*=.03). There was no evidence of efficacy for moclobemide on fatigue (WMD, 0.30; 95% CI, –1.04 to 1.64; *P*=.66) or sleep disturbances (WMD, 1.00; 95% CI, –0.49 to 2.49; *P*=.19). There was no effect of pirlindole on depressed mood (WMD, 0.18; 95% CI, –2.16 to 2.52; *P*=.88).

Median rates of reported adverse effects (antidepressants, 75.5%, vs placebo, 62.5%; *P*=.49) and dropout due to adverse effects (antidepressants, 15.7%; placebo, 8.1%; *P*=.18) did not differ between treatment and placebo groups. Only 3 studies differentiated the degree of adverse effects (slight, moderate, severe).[50,59,64] The median frequency of severe adverse effects was not different between treatment and placebo (2.30% vs 2.95%; *P*=.60).

Validity Analysis

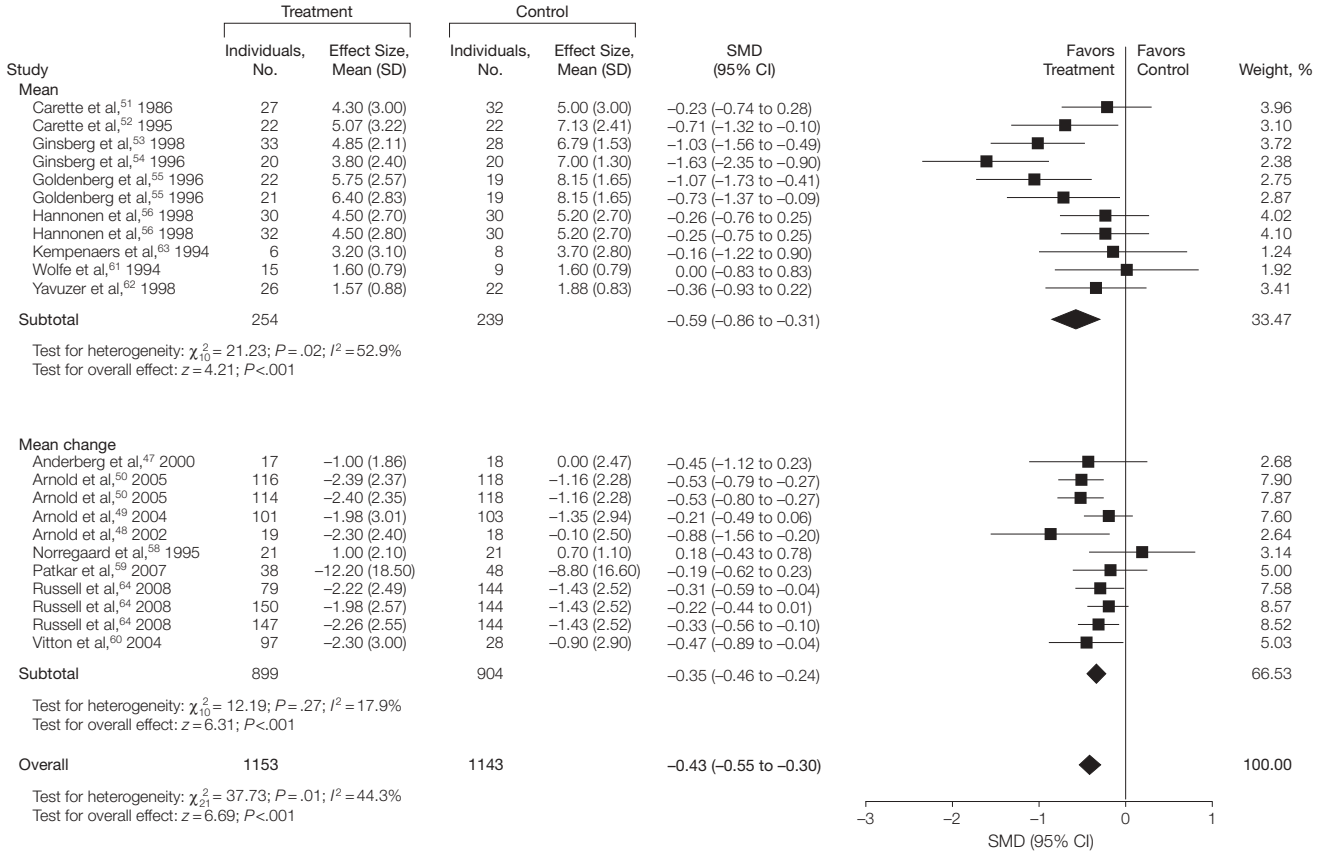
Characteristics of included studies are presented in TABLE 2. Interrater reliability for characteristics shown in Table 2 was κ=0.89.

Seven studies had a multicenter design. Eleven had a single-center design. Sixteen studies used a parallel design and 2 used a crossover design. Tricyclic or tetracyclic antidepressants were investigated in 7 studies (amitriptyline in 7, nortriptyline in 1), and MAOIs in 3 (moclobemide in 2, pirlindole in 1). Selective serotonin reuptake inhibitors were investigated in 6 studies (fluoxetine in 3, citalopram in 2, paroxetine in 1). Four RCTs studied SNRIs (duloxetine in 3, milnacipran in 1). Five studies had multiple groups: Arnold et al[50] compared duloxetine (60 and 120 mg/d) with placebo. Russell et al[64] compared duloxetine (20-60 mg/d, 60 mg/d, and 120 mg/d) with placebo. Goldenberg et al[55] compared fluoxetine, amitriptyline, and the combination of both drugs with placebo. Hannonen et al[56] compared moclobemide and amitriptyline with placebo. Heymann et al[57] compared amitriptyline and nortriptyline with placebo.

The median duration of the RCTs was 8 weeks (range, 4-28 weeks). Outcomes were assessed at the end of the treatment. No study measured outcomes at an additional follow-up visit after treatment cessation.

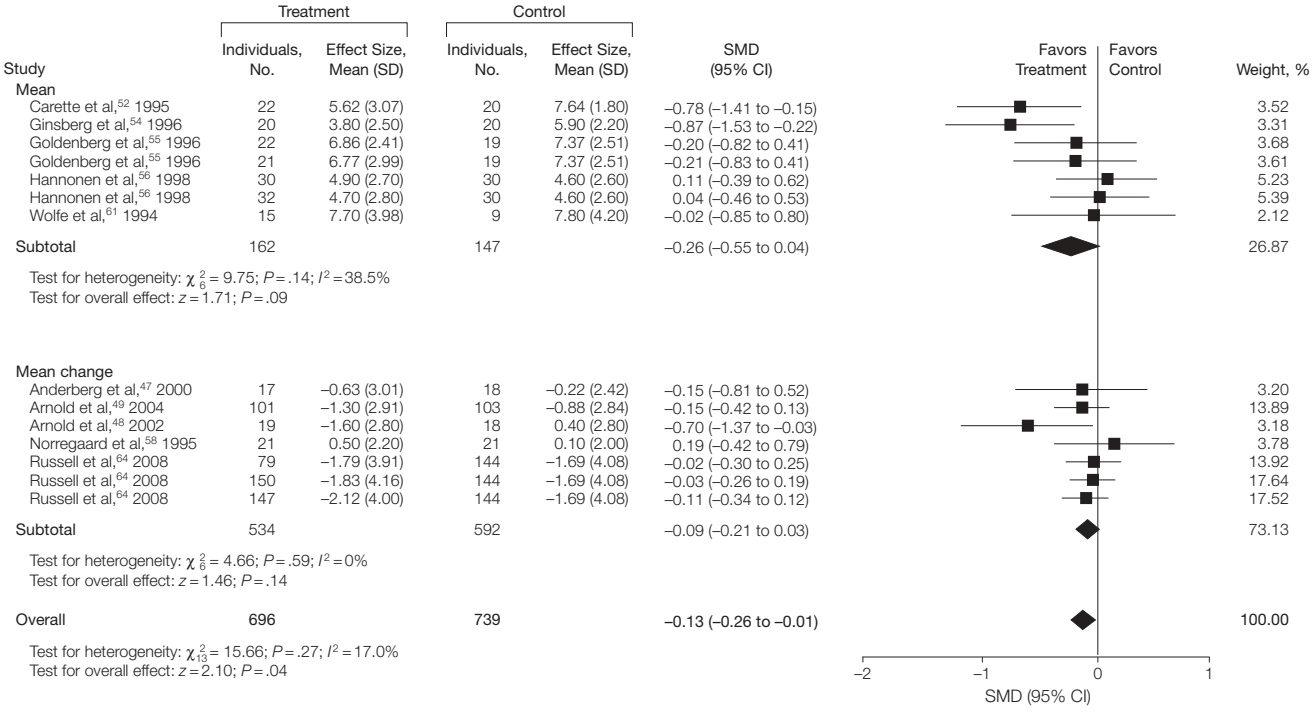
Serum antidepressant levels were not measured in any RCTs to assess

Figure 2. Effectiveness of Antidepressants in Fibromyalgia for the Outcome Pain



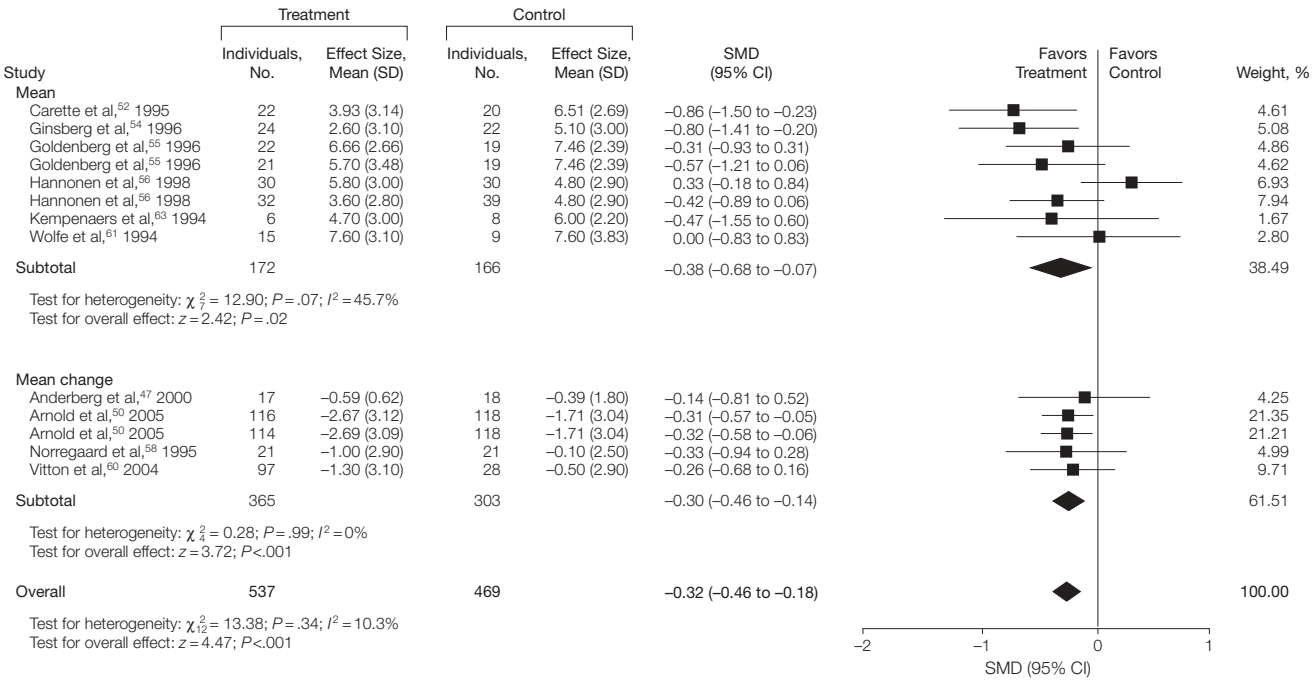
CI indicates confidence interval; SMD, standardized mean difference.

Figure 3. Effectiveness of Antidepressants in Fibromyalgia for the Outcome Fatigue



CI indicates confidence interval; SMD, standardized mean difference.

Figure 4. Effectiveness of Antidepressants in Fibromyalgia for the Outcome Sleep

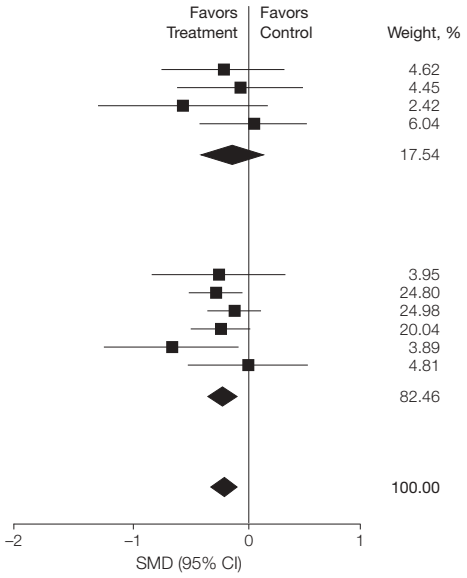


CI indicates confidence interval; SMD, standardized mean difference.

patients' adherence. All RCTs allowed additional therapy with paracetamol or acetaminophen. Eight allowed therapy with paracetamol or acetaminophen in combination with acetylsalicylic acid or nonsteroidal anti-inflammatory drugs or codeine. Seven studies reported a defined dosage of the allowed comedication. No study controlled for additional therapy with comedication. No study provided detailed information about

Figure 5. Effectiveness of Antidepressants in Fibromyalgia for the Outcome Depressed Mood

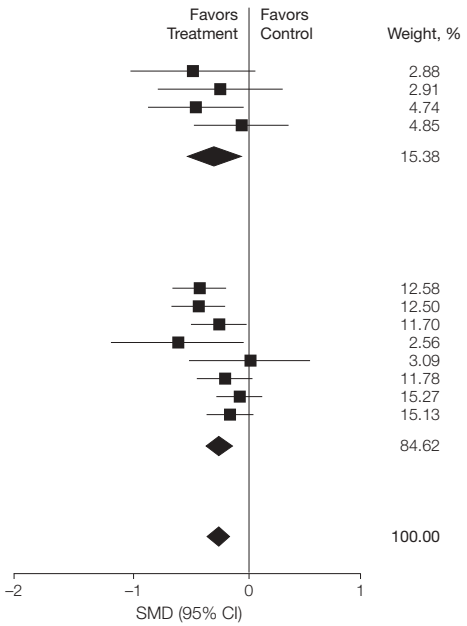
Study	Treatment Individuals, No.	Treatment Effect Size, Mean (SD)	Control Individuals, No.	Control Effect Size, Mean (SD)	SMD (95% CI)	Weight, %
Mean						
Goldenberg et al,[55] 1996	22	7.80 (4.70)	19	9.30 (6.50)	−0.26 (−0.88 to 0.35)	4.62
Goldenberg et al,[55] 1996	20	8.70 (6.00)	19	9.30 (6.50)	−0.09 (−0.72 to 0.53)	4.45
Wolfe et al,[61] 1994	15	8.30 (5.86)	9	13.90 (10.82)	−0.67 (−1.53 to 0.18)	2.42
Yavuzer et al,[62] 1998	28	5.54 (5.56)	25	5.36 (2.68)	0.04 (−0.50 to 0.58)	6.04
Subtotal	85		72		−0.17 (−0.49 to 0.14)	17.54
Test for heterogeneity: $\chi^2_3 = 2.07$; $P = .56$; $I^2 = 0\%$						
Test for overall effect: $z = 1.07$; $P = .29$						
Mean change						
Anderberg et al,[47] 2000	17	−1.13 (2.87)	18	−0.33 (2.14)	−0.31 (−0.98 to 0.36)	3.95
Arnold et al,[50] 2005	111	−3.79 (4.34)	109	−2.24 (4.70)	−0.34 (−0.61 to −0.08)	24.80
Arnold et al,[50] 2005	110	−2.97 (4.72)	109	−2.24 (4.70)	−0.15 (−0.42 to 0.11)	24.98
Arnold et al,[49] 2004	88	−3.32 (7.97)	89	−1.02 (7.83)	−0.29 (−0.59 to 0.01)	20.04
Arnold et al,[48] 2002	19	−1.50 (2.80)	18	0.50 (2.10)	−0.79 (−1.46 to −0.12)	3.89
Norregaard et al,[58] 1995	21	−1.00 (6.10)	21	−0.90 (7.90)	−0.01 (−0.62 to 0.59)	4.81
Subtotal	366		364		−0.27 (−0.42 to −0.13)	82.46
Test for heterogeneity: $\chi^2_5 = 4.00$; $P = .55$; $I^2 = 0\%$						
Test for overall effect: $z = 3.66$; $P < .001$						
Overall	451		436		−0.26 (−0.39 to −0.12)	100.00
Test for heterogeneity: $\chi^2_9 = 6.39$; $P = .70$; $I^2 = 0\%$						
Test for overall effect: $z = 3.77$; $P < .001$						



CI indicates confidence interval; SMD, standardized mean difference.

Figure 6. Effectiveness of Antidepressants in Fibromyalgia for the Outcome Health-Related Quality of Life

Study	Treatment Individuals, No.	Treatment Effect Size, Mean (SD)	Control Individuals, No.	Control Effect Size, Mean (SD)	SMD (95% CI)	Weight, %
Mean						
Goldenberg et al,[55] 1996	22	47.60 (19.80)	19	58.50 (17.10)	−0.57 (−1.20 to 0.05)	2.88
Goldenberg et al,[55] 1996	21	52.30 (22.90)	19	58.50 (17.10)	−0.30 (−0.92 to 0.33)	2.91
Heymann et al,[57] 2001	37	39.97 (19.88)	33	51.68 (22.90)	−0.54 (−1.02 to −0.06)	4.74
Heymann et al,[57] 2001	36	49.78 (21.84)	33	51.68 (22.90)	−0.08 (−0.56 to 0.39)	4.85
Subtotal	116		104		−0.36 (−0.62 to −0.09)	15.38
Test for heterogeneity: $\chi^2_3 = 2.35$; $P = .50$; $I^2 = 0\%$						
Test for overall effect: $z = 2.61$; $P = .009$						
Mean change						
Arnold et al,[50] 2005	114	−16.72 (16.34)	115	−8.35 (16.40)	−0.51 (−0.77 to −0.25)	12.58
Arnold et al,[50] 2005	112	−16.81 (16.30)	115	−8.35 (16.40)	−0.52 (−0.78 to −0.25)	12.50
Arnold et al,[49] 2004	101	−13.46 (18.29)	102	−7.93 (17.47)	−0.31 (−0.58 to −0.03)	11.70
Arnold et al,[48] 2002	19	−11.50 (14.80)	18	−0.40 (15.00)	−0.73 (−1.40 to −0.06)	2.56
Norregaard et al,[58] 1995	21	0.00 (0.40)	21	0.00 (0.40)	0.00 (−0.60 to 0.60)	3.09
Russell et al,[64] 2008	79	−14.77 (16.71)	144	−10.42 (17.52)	−0.25 (−0.53 to 0.02)	11.78
Russell et al,[64] 2008	150	−12.28 (17.64)	144	−10.42 (17.52)	−0.11 (−0.33 to 0.12)	15.27
Russell et al,[64] 2008	147	−13.86 (17.10)	144	−10.42 (17.52)	−0.20 (−0.43 to 0.03)	15.13
Subtotal	743		803		−0.31 (−0.44 to −0.18)	84.62
Test for heterogeneity: $\chi^2_7 = 11.16$; $P = .13$; $I^2 = 37.3\%$						
Test for overall effect: $z = 4.54$; $P < .001$						
Overall	859		907		−0.31 (−0.42 to −0.20)	100.00
Test for heterogeneity: $\chi^2_{11} = 13.66$; $P = .25$; $I^2 = 19.5\%$						
Test for overall effect: $z = 5.59$; $P < .001$						



CI indicates confidence interval; SMD, standardized mean difference.

nonpharmacological therapies or controlled for nonpharmacological therapies.

Ten studies performed a power analysis to ensure an adequate sample size. Five studies had a Jadad score of 5, 8 had a Jadad score of 4, and 5 had a Jadad score less than 4. Eleven studies had a van Tulder score of 5 to 7, and 7 studies had scores of 8 to 11. Only 4 studies were high on both measures.[49,56,57,59] Interrater reliability for this assessment was $\kappa = 0.89$.

There was significant heterogeneity between the analyzed RCTs in most outcome measures. The large ranges of the 95% CIs are also indicative of marked variations between the studies.

Eleven studies were performed in North America or Puerto Rico, 1 was performed in Brazil, 5 were performed in western Europe (Scandinavia, Belgium), and 1 was performed in Turkey. All studies were outpatient-based. Patients were recruited from rheumatology departments in 11 studies, from research centers in 3 studies, and from a psychiatric department in 1 study. Three publications did not report the recruitment setting.

All studies excluded patients with severe somatic diseases. Eleven excluded patients with severe mental disorders. Ten excluded specific age categories (<18 or >60 years). Four excluded patients with pending applications for disability. A total of 1427 individuals completed treatment. Of these, 916 were receiving antidepressants. The median percentages of patients completing the trials were 71.0% for participants randomized to antidepressants and 78.0% for participants randomized to placebo ($P = .78$). The median age of study participants was 47.0 years. Seven studies included only women; 10 included both men and women, and 1 study did not specify participant sex. The median percentage of women in all studies was 98%. Ten studies reported the participants' race. Among these, the median percentage of white participants was 89.5%. Fibromyalgia syndrome was defined in 16 studies according to the ACR criteria.[2] One study defined FMS according to Yunus,[19] and 1 study defined FMS according to Smythe and Moldofsky.[18] No study provided data on nonpsychiatric comorbidities. Five studies provided data on the prevalence of major depressive disorder (up to 35%). Three studies provided information on working status (working, sick leave, or disability). Potential participants considered treatment refractory were excluded in 2 studies.

Table 1. Effect Sizes of the Different Classes of Antidepressants on Selected Outcome Variables

Outcome	No. of Studies	Patients Taking Antidepressants, No.	Statistical Method	Effect Size (95% CI)	Test for Overall Effect *P* Value
Tricyclic Antidepressants					
Pain	6	128	SMD (random)	−1.64 (−2.57 to −0.71)	<.001
Fatigue	4	95	SMD (random)	−1.12 (−1.87 to −0.38)	.003
Sleep	5	105	WMD (fixed)	−1.84 (−2.62 to −1.06)	<.001
Depressed mood	1	20	WMD (fixed)	−0.60 (−4.53 to 3.33)	.76
HRQOL	3	94	WMD (fixed)	−0.31 (−0.60 to −0.01)	.04
Selective Serotonin Reuptake Inhibitors					
Pain	6	132	SMD (random)	−0.39 (−0.77 to −0.01)	.04
Fatigue	5	94	WMD (fixed)	−0.17 (−0.47 to 0.12)	.25
Sleep	4	75	SMD (random)	−0.23 (−0.56 to 0.10)	.18
Depressed mood	5	94	WMD (fixed)	−0.37 (−0.66 to −0.07)	.02
HRQOL	3	62	WMD (fixed)	−0.41 (−0.78 to −0.05)	.03
Serotonin and Noradrenaline Reuptake Inhibitors					
Pain	3	804	SMD (random)	−0.36 (−0.46 to −0.25)	<.001
Fatigue	1	477	WMD (fixed)	−0.08 (−0.20 to 0.05)	.23
Sleep	2	327	SMD (random)	−0.31 (−0.47 to −0.14)	<.001
Depressed mood	2	309	SMD (random)	−0.26 (−0.42 to −0.10)	.001
HRQOL	2	703	SMD (random)	−0.31 (−0.44 to −0.17)	<.001
Monoamine Oxidase Inhibitors					
Pain	3	89	SMD (random)	−0.54 (−1.02 to −0.07)	.03
Fatigue	1	30	WMD (fixed)	0.30 (−1.04 to 1.64)	.66
Sleep	1	30	WMD (fixed)	1.00 (−0.49 to 2.49)	.19
Depressed mood	1	28	WMD (fixed)	0.18 (−2.16 to 2.52)	.88
HRQOL	NA	NA	NA	NA	NA

Abbreviations: CI, confidence interval; HRQOL, health-related quality of life; NA, not assessed; SMD, standardized mean difference; WMD, weighted mean difference.

Publication Bias

Visual scanning of forest plots for subgroup analysis suggested a random distribution with results in the same direction for most outcomes, indicating that although study effect sizes differed, results were mostly consistent (data not shown). The fail-safe number with a D = 0.01 as the selected criterion value to "nullify" the average effect on pain was n = 924; on fatigue, n = 168; on sleep, n = 403; on depressed mood, n = 250; and on HRQOL, n = 360. Thus the fail-safe numbers were larger than Rosenthal rule of thumb[28] of n = 120 for pain, n = 80 for fatigue, n = 75 for sleep, n = 60 for depressed mood, and n = 70 for HRQOL. These results indicate that a publication bias is unlikely to change the overall results of this meta-analysis.

COMMENT

The primary aim of this meta-analysis was to determine the efficacy of antidepressants for treatment of FMS. We found strong evidence for the efficacy of antidepressants in reducing pain, sleep disturbances, and depressed mood and for improving HRQOL. All effect

sizes were small. We found strong evidence against a favorable effect of antidepressants on fatigue.

We found large effect sizes of TCAs for reducing pain, fatigue, and sleep disturbances; small effect sizes of SSRIs for reducing pain, sleep disturbances, and depressed mood; and small

Table 2. Main Study Characteristics

Source (Location)	Female Sex/ White Race, %	Age, Mean, y	Exclusion Criteria	Study Population		Treatment Group		Placebo Group, Completed, No./ Total (%)	Method Quality, Jadad Score (van Tulder Score)	Outcome Measures Used for Meta-analysis
				Randomized/ Screened, No. (%)	Completed, No./ Total (%)	Duration, Treatment, and Design	Completed, No./ Total (%)			
Tricyclic Antidepressants: Amitriptyline										
Carette et al,[51] 1986 (Canada)	92.6/NR	41.8	SSD, IRD	NR	59/70 (84.3)	9 wk, amitriptyline 50 mg/d, parallel	27/34 (79.4)	32/36 (88.9)	4 (9)	Pain, VAS
Kempenaers et al,[63] 1994 (Belgium)	100/NR	38.7	SSD, IRD, mental disorder	NR	14/24 (58.3)	8 wk, amitriptyline 50 mg/d, parallel	6/12 (50.0)	8/12 (75.0)	3 (7)	Pain, VAS; sleep, VAS
Carette et al,[52] 1995 (Canada)	95.5/NR	43.8	SSD, IRD	NR	20/22 (90.9)	8 wk, amitriptyline 25 mg/d, crossover	20/22 (90.9)	20/22 (90.9)	4 (8)	Pain, VAS; sleep, VAS
Ginsberg et al,[54] 1996 (Belgium)	83/92	46	Age, SSD, IRD	NR	46/51 (90.2)	8 wk, sustained-release amitriptyline 25 mg/d, parallel	24/26 (92.3)	22/25 (88)	4 (8)	Pain, VAS; fatigue, VAS; sleep, VAS
Goldenberg et al,[55] 1996 (United States)	90/100	43.2	Age, somatic disease, major depression	NR	19/31 (61.3)	6 wk, amitriptyline 25 mg/d, crossover	19/31 (61.3)	NR	5 (7)	Pain, VAS; fatigue, VAS; sleep, VAS; depression, BDI; quality of life, FIQ total score
Hannonen et al,[56] 1998 (Finland)	100/NR	49.7	Age, SSD, severe mental disorder	130/184 (70.6)	92/130 (70.8)	12 wk, amitriptyline 12.5 mg/d, parallel	32/42 (76.2)	30/45 (66.7)	5 (10)	Pain, VAS; fatigue, VAS; sleep, VAS; quality of life, NHP
Heymann et al,[57] 2001 (Brazil)	100/65	53.4	Age, SSD, IRD	NR	106/118 (89.8)	8 wk, amitriptyline 25 mg/d, parallel	37/40 (92.5)	33/40 (82.5)	5 (8)	Quality of life, FIQ total score
Tricyclic Antidepressants: Nortriptyline										
Heymann et al,[57] 2001 (Brazil)	100/65	53.4	Age, SSD, IRD	NR	106/118 (89.8)	8 wk, nortriptyline 25 mg/d, parallel	36/38 (94.7)	33/40 (82.5)	5 (8)	Quality of life, FIQ total score
Selective Serotonin Reuptake Inhibitors: Paroxetine										
Patkar et al,[59] 2007 (United States)	94/NR	47.9	Age, SSD, IRD, mental disorder, pending disability review	116/983 (11.8)	86/116 (74.1)	12 wk, paroxetine controlled release 62.5 mg/d (mean, 39.1 mg/d), parallel	38/58 (65.5)	48/58 (82.8)	5 (9)	Pain, VAS
Selective Serotonin Reuptake Inhibitors: Fluoxetine										
Wolfe et al,[61] 1994 (United States)	100/100	48	IRD	NR	24/42 (57.1)	6 wk, fluoxetine 20 mg/d, parallel	15/21 (71.4)	9/21 (42.8)	3 (7)	Pain, VAS; fatigue, VAS; sleep, VAS; depression, BDI
Goldenberg et al,[55] 1996 (United States)	90/100	43.2	Age, somatic disease, major depression	NR	19/31 (61.3)	6 wk, fluoxetine 20 mg/d, crossover	NA	19/31 (61.3)	5 (7)	Pain, VAS; fatigue, VAS; sleep, VAS; depression, BDI; quality of life, FIQ total score
Arnold et al,[48] 2002 (United States)	100/90	46	Age, SSD, IRD, mental disorder	NR	37/60 (61.7)	12 wk, fluoxetine 20-80 mg/d, parallel	19/30 (63.3)	18/30 (60)	4 (7)	Pain, FIQ; fatigue, FIQ; depression, FIQ; quality of life, FIQ total score

(continued)

Table 2. Main Study Characteristics (continued)

Source (Location)	Female Sex/ White Race, %	Age, Mean, y	Exclusion Criteria	Study Population: Randomized/ Screened, No. (%)	Study Population: Completed, No./ Total (%)	Treatment Group: Duration, Treatment, and Design	Treatment Group: Completed, No./ Total (%)	Placebo Group, Completed, No./ Total (%)	Method Quality, Jadad Score (van Tulder Score)	Outcome Measures Used for Meta-analysis
Selective Serotonin Reuptake Inhibitors: Citalopram										
Nørregaard et al,[58] 1995 (Denmark)	NR/NR	48	SSD, IRD, mental disorder	42/150 (28)	33/42 (78.6)	8 wk, citalopram 20-40 mg/d, parallel	12/21 (57.1)	21/21 (100)	4 (6)	Pain, NRS; fatigue, NRS; sleep, NRS; depression, BDI; quality of life, FIQ physical score
Anderberg et al,[47] 2000 (Sweden)	100/NR	48.6	SSD, major depression	NR	35/40 (87.5)	16 wk, citalopram 20-40 mg/d, parallel	17/21 (80.9)	18/19 (95)	4 (9)	Pain, FIQ; fatigue, FIQ; sleep, MADRS; depression, FIQ
Serotonin and Noradrenaline Reuptake Inhibitors: Duloxetine										
Arnold et al,[49] 2004 (United States)	88.5/ 88.5	49.9	Age, SSDs, IRD, mental disorder except major depressive disorder, pending disability review	207/555 (37.3)	124/207 (59.9)	12 wk, duloxetine 120 mg/d, parallel	58/104 (55.7)	66/103 (64.1)	5 (8)	Pain, FIQ; fatigue, FIQ; depression, BDI; quality of life, FIQ total score
Arnold et al,[50] 2005 (United States)	100/89.5	49.6	Age, SSD, IRD, mental disorder except major depressive disorder, pending disability reviews, patients judged refractory to treatment	354/745 (47.5)	215/354 (60.7)	12 wk, duloxetine 60 mg/d or 120 mg/d, parallel	147/234 (61.5)	68/120 (56.7)	3 (7)	Pain, BPI; sleep, BPI; depression, HDRS; quality of life, FIQ total score
Russell et al,[64] 2008 (United States)	94.8/ 84.2	51.0	Age, SSD, IRD, mental disorder except major depressive disorder, pending disability reviews, patients judged refractory to treatment	520/1010 (51.8)	323/520 (62.1)	28 wk, duloxetine 20 mg/d or 60 mg/d or 120 mg/d, parallel	251/376 (66.7)	72/144 (50)	4 (8)	Pain, BPI; fatigue, MFI; quality of life, FIQ total score
Serotonin and Noradrenaline Reuptake Inhibitors: Milnacipran										
Vitton et al,[60] 2004, (United States)	96-98/ 79-89	46-48	Age, somatic disease, severe mental disorder	125/184 (67.9)	90/125 (72)	12 wk, milnacipran 100 mg/d or 200 mg/d, parallel	69/97 (71.1)	21/28 (75)	3 (7)	Pain, VAS; sleep, Jenkins scale
Monoamine Oxidase Inhibitors: Moclobemide										
Hannonen et al,[56] 1998 (Finland)	100/NR	49.7	Age, SSD, severe mental disorder	130/184 (70.6)	92/130 (70.8)	12 wk, moclobemide 150 mg/d, parallel	30/43 (69.8)	30/45 (66.7)	5 (10)	Pain, VAS; fatigue, VAS; sleep, VAS
Yavuzer et al,[62] 1998 (Turkey)	58.3/NR	33.2	SSD, IRD	NR	53/60 (88.3)	6 wk, moclobemide 300 mg/d, parallel	26/28 (92.9)	22/25 (88)	1 (6)	Pain, NRS; depression, HDRS
Monoamine Oxidase Inhibitors: Pirlindole										
Ginsberg et al,[53] 1998 (Belgium)	87.9/NR	39.7	Age, somatic disease	100/200 (50)	61/100 (61)	4 wk, pirlindole 150 mg/d, parallel	33/50 (66)	28/50 (56)	3 (7)	Pain, VAS; fatigue, VAS; sleep, VAS

Abbreviations: BDI, Beck Depression Inventory; BPI, Brief Pain Inventory; FIQ, Fibromyalgia Impact Questionnaire; HDRS, Hamilton Depression Rating Scale; IRD, inflammatory rheumatologic disease; MADRS, Montgomery Asberg Depression Rating Scale; MFI, Multidimensional Fatigue Inventory; NHP, Nottingham Health Profile; NA, not assessed; NR, not reported; NRS, Numeric Rating Scale; SSD, severe somatic disease; VAS, visual analog scale.

effect sizes of MAOIs for reducing pain. Conclusions regarding the efficacy of single drugs on outcomes were limited because of small sample sizes. Of the antidepressants studied, duloxetine is the only one that has been approved by the Food and Drug Administration for treating FMS.[65]

Three studies that did not meet inclusion criteria for this meta-analysis were head-to-head comparisons of antidepressant drugs. Of these, 1 study found that paroxetine was superior to amitriptyline in reducing pain,[41] while another study found that amitriptyline was superior to paroxetine in reducing pain and sleep disturbances.[42] A third study found no difference between amitriptyline and fluoxetine in reducing sleepiness.[40] Overall, none of these head-to-head comparisons of different antidepressant classes nor this meta-analysis allows a definitive conclusion regarding superiority of one class of antidepressants over another.

Doses of TCAs used in the studies, between 12.5 and 50 mg per day, were typical for pain treatment but far below the doses of TCAs necessary for an antidepressant benefit. This likely explains the positive association of TCAs for reducing pain in the absence of a benefit for depressive symptoms. In contrast, doses of SSRIs and SNRIs were equal to those used for treating affective disorders. However, we could only find an effect of SNRIs on depressed mood.

The internal validity of the RCTs analyzed was limited for the following reasons. First, serum antidepressant levels were not measured in any RCTs to assess patients' adherence. Second, no study controlled for consumption, dose, or adverse effects of concomitant analgesic medications. The influence of this comedication on study outcomes is unclear. Third, 3 studies of duloxetine used a 1-week, single-blind, placebo-lead-in phase. Medication adverse effects indicating the presence of active drug may have biased the duloxetine trials more than other studies. Finally, some studies did not report the results of all outcomes assessed.

The external validity of the RCTs analyzed was limited by the following. First, the short duration of most studies and the lack of follow-up after treatment cessation leave unanswered whether antidepressants have long-term beneficial effects on FMS symptoms and the optimal treatment duration. One excluded RCT failed to demonstrate an advantage of amitriptyline over placebo regarding pain, sleep disturbances, and fatigue after 26 weeks.[43] Second, despite evidence of higher prevalences of mental disorders in FMS,[10] only 6 studies performed a standardized psychiatric interview. Only 3 studies performed subgroup analyses among participants with vs without major depressive disorder. The effects of duloxetine on pain did not differ between FMS patients with vs without major depressive disorder.[49,50,64] Therefore, only duloxetine has demonstrated efficacy in FMS patients both with and without major depressive disorder. Third, no definitive statements are possible on the efficacy of antidepressants in men, nonwhite individuals, patients older than 65 years, children, and adolescents because these subgroups were not analyzed, with the exception of 2 studies with duloxetine: 1 study found no significant response in primary and secondary outcomes in male patients.[49] Another study reported similar significant pain reduction between women and men.[64] One study reported similar results among racial groups and patients aged 65 years and younger.[64] Fourth, since most studies excluded patients with severe somatic diseases, including inflammatory arthritic diseases, it is unknown whether antidepressants are effective in these patients with FMS. Finally, 2 duloxetine studies excluded patients who were judged by the investigator to be treatment refractory.[50,64] This procedure could have favored the outcomes of the treatment group.

Our findings are mainly consistent with published literature. The meta-analysis of O'Malley et al[13] included 9 studies with TCAs, 3 studies with SSRIs, and 2 studies with *S*-adenosylmethionine. Medium effect sizes were reported for improving pain, sleep, and fatigue. Sensitivity analysis by way of meta-regression revealed no effect of drug class.[13] Differences between results of the meta-analysis of O'Malley et al and our review regarding class effects are due to the fact that we analyzed more studies with TCAs and SSRIs and included RCTs of MAOIs and SNRIs. In addition, the studies failing to demonstrate an advantage of citalopram over placebo[47,58] were published after the meta-analysis by O'Malley et al. Arnold et al[14] included 9 studies (6 with TCAs and 3 with cyclobenzaprine) into a meta-analysis and found a global effect size of 0.44 for pain, sleep, tenderness, fatigue, and sleep.

This review has limitations. First, since demographics and comorbidities of study participants and the amount of comedication were not reported, these possible sources of heterogeneity could not be examined. Second, we did not seek to identify unpublished studies. Third, 6 RCTs were excluded because the published data were not suitable for meta-analysis, and necessary data were not provided by the authors on request. With the exception of 1 study, which failed to demonstrate an advantage of amitriptyline over placebo regarding pain, sleep disturbances, and fatigue after 26 weeks,[43] the other 5 studies excluded from the meta-analysis reported an advantage of amitriptyline[41,42,45,46] or paroxetine[41,42,44] over placebo regarding pain and sleep disturbances that was consistent with our results. Fourth, there are limitations of some methods used in this article, such as using I^2 for assessing the amount of heterogeneity in random-effects meta-analysis[66,67] and fail-safe numbers[68] for excluding a publication bias.

CONCLUSION

Short-term usage of amitriptyline and duloxetine can be considered for the treatment of pain and sleep distur-

bances in FMS. This recommendation is based on the number of patients studied (duloxetine) and on the effect sizes (amitriptyline). Before treatment is initiated, concomitant diseases related to potential adverse effects of the drugs and patients' preferences should be considered. Goals of pharmacological therapy should be defined (no cure, but possible symptom reduction). Since evidence for a long-term effect of antidepressants in FMS is still lacking, their effects should be reevaluated at regular intervals to determine whether benefits outweigh adverse effects.

Studies of longer duration than those currently available are needed to investigate the long-term efficacy of antidepressant therapy for FMS. It is currently unknown whether benefits of antidepressants for treatment of FMS persist after cessation of therapy. It is also unknown whether antidepressants reduce FMS-related costs.[9] The identification of patient characteristics associated with positive and negative therapeutic outcomes are needed to better target antidepressant therapy for FMS. Future studies of the effects of antidepressants on FMS should include patients with somatic and mental comorbidities and fully report all patient characteristics and outcomes assessed.[69]

Author Contributions: Dr Häuser had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Häuser, Üçeyler, Sommer.
Acquisition of data: Häuser, Bernardy, Üçeyler, Sommer.
Analysis and interpretation of data: Häuser, Bernardy, Üçeyler, Sommer.
Drafting of the manuscript: Häuser, Bernardy.
Critical revision of the manuscript for important intellectual content: Häuser, Bernardy, Üçeyler, Sommer.
Statistical analysis: Häuser, Bernardy.
Obtained funding: Häuser, Bernardy, Üçeyler.
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Study supervision: Häuser, Sommer.
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