Drug Class Review

Drugs for Fibromyalgia

Final Original Evidence Tables

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The Agency for Healthcare Research and
Quality has not yet seen or approved this report

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Abbreviations used in evidence tables

Abbreviation	Full term
ACR	American College of Rheumatology
ACT	Active-control trial
AE	Adverse event
AIMS	Arthritis Impact Measurement Scale
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ARA	American Rheumatism Association
BAI	Beck Anxiety Index
BDI	Beck Depression Inventory
bid	Twice daily
BMI	Body mass index
BOCF	Baseline Observation Carried Forward
BPI	Brief Pain Inventory
BPI-SF	Brief Pain Inventory-Short Form
CCT	Controlled clinical trial
CGIC	Clinical Global Impression of Change
CGIS	Clinical Global Impression of Severity
CI	Confidence interval
CNS	Central nervous system
CR	Controlled release
CV	Cardiovascular
CVS	Cardiovascular system
d	Day
DB	Double-blind
DEXA	Dual Energy X-ray Absorptiometry
dL	Deciliter
ECG	Electrocardiogram
EEG	Electroencephalogram
EF	Ejection fraction
ER	Extended release
FDA	US Food and Drug Administration
FIQ	Fibromyalgia Impact Questionnaire
FU	Follow-up
g	Gram
GI	Gastrointestinal
GLMM	Generalized Linear Mixed Model
GP	General practitioner
h	Hour

Abbreviation	Full term
HAD	Hospital Anxiety and Depression scale
HAMD	Hamilton Depression Scale
HAQ	Health Assessment Questionnaire
HDL-C	High density lipoprotein cholesterol
HMO	Health maintenance organization
HR	Hazard ratio
HRQOL	Health-related quality of life
ICD-10	International Classification of Diseases, Tenth Revision
ICD-9	International Classification of Diseases, Ninth Revision
IGF-1	Insulin-like growth factor 1
IR	Immediate release
ITT	Intention-to-treat
L	Liter
LA	Long acting
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
LS means	Least squares means
LTR	Loss of Therapeutic Response
MADRS	Montgomery Åsberg Depression Rating Scale
MAF	Multidimensional Assessment of Fatigue
MANCOVA	Multivariate analysis of covariance
MASQ	Multiple Ability Self-Report Questionnaire
mcg	Microgram
MCS	Mental Component Summary
MDD	Major Depressive Disorder
MFI	Multidimensional Fatigue Inventory
mg	Milligram
min	Minute
mL	Milliliter
mo	Month
MOS	Medical Outcomes Study
N	Sample size (entire sample)
n	Subgroup sample size
NA	Not applicable
NR	Not reported
NS	Not significant
NSAIDs	Nonsteroidal antiinflammatory drugs
NSD	No significant difference
OC	Observed cases
OR	Odds ratio

Abbreviation	Full term
P	*P* value
P	Placebo
PCS	Physical Component Summary
PCT	Placebo-controlled trial
PED	Patient Experience Diary
PGIC	Patient's Global Impression of Change
PPY	Per person year
PVA	Pain Visual Analog
qd	Once daily
QOL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
REM	Rapid eye movement
RR	Relative risk
SB	Single-blind
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SF-36	Short-Form 36 Health Survey
SF-MPQ	Short-Form McGill Pain Questionnaire
SIP	Sickness Impact Profile
SMR	Skeletal muscle relaxants
SQ	Subcutaneous
SR	Sustained release
SSRI	Selective Serotonin Reuptake Inhibitor
STAI-S	State-Trait Anxiety Inventory, State-related
TEAE	Treatment-emergent adverse event
tid	Three times daily
VAS	Visual analog scale
vs.	Compared with (versus)
WD	Withdrawal
XR	Extended release
y	Year

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Anderberg, 2000 Sweden Fair	Female fibromyalgia patients who fulfilled the ACR criteria, with no severe heart diseases.	A: Citalopram 20-40 mg/d B: Placebo For 4 months Dosing schedule: The patients started with either 10 or 20 mg/day for the first week, taken in one dosage in the morning, and increased the dose by 10 mg every fifth day up to either 30 or 40 mg/day.	Paracetamol 500 mg bid or acetylsalicylic acid 1 g bid. In exceptional cases, stronger analgesics were allowed due to ethical reasons and the long duration of the study. Physical training, warm water baths and transcutaneous nerve stimulation were also allowed when needed.	48.6 years (SD 7.5) 100% female Ethnicity NR
Arnold, 2002 United States Fair	Women ≥18 years of age who met the ACR criteria for fibromyalgia, with no evidence of traumatic injury, inflammatory rheumatic disease, or infectious or endocrine-related arthropathy.	A: Fluoxetine 10-80 mg/d B: Placebo For 12 weeks Dosing schedule: Began the DB treatment at 20 mg/d for the first 2 weeks. If this dose was not tolerated, it was decreased to 20 mg qod. After 2 weeks, the dose could be titrated in 10- to 20-mg increments every 2 weeks to a maximum of 80 mg/d. Adjustments within the range of 1 capsule qod to 4 capsules per day were made at the discretion of the investigator and until a patient improved or intolerance occurred.	Acetaminophen, NSAIDs	46 years (SD 11.5) 100% female White: 93.3%

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Anderberg, 2000 Sweden Fair	Mean duration of disease: 11.9 years (SD 7.0)	40	5/0/40
Arnold, 2002 United States Fair	Duration of fibromyalgia: 11 years (SD 8.5) History of MDD: 61.7% Married: 63.3% Employment status: Working: 70% On disability for fibromyalgia: 3.3%	60	23/4/51

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Anderberg, 2000 Sweden Fair	Citalopram vs Placebo Global judgment of changes in pain: Improved: 6 (28.6%) vs 3 (15.8%) Unchanged or deteriorated: 15 (71.4%) vs 16 (84.2%) Global judgment of changes in well-being: Improved: 9 (42.9%) vs 4 (21.1%) Unchanged or deteriorated: 12 (57.1%) vs 15 (78.9%) Changes in total score on MADRS from baseline to endpoint: -4.25 vs 0; P<0.01 Changes in pain scores (VAS) from baseline to 2 months: -1.2 vs -0.55; P<0.05 Changes in pain scores (VAS) from baseline to endpoint: -0.7 vs -0.3
Arnold, 2002 United States Fair	Fluoxetine vs Placebo FIQ total score (0-80), mean (SD): -8.6 (14.5) vs 2.9 (13.6); Between-group difference: -11.5 (95% CI, -19.4 to -3.6); P=0.005 Tender points (0-18), mean (SD): -1.9 (3.7) vs -0.4 (2.6); Between-group difference: -1.5 (95% CI, -3.7 to 0.7); P=0.17 Myalgic score: 7.4 (16.8) vs 2.5 (12.1); Between-group difference: 4.9 (95% CI, -4 to 13.8); P=0.27 McGill Pain Questionnaire (0-78): -10.8 (12.3) vs -1.8 (11.9); Between-group difference: -9.1 (95% CI, -15.9 to -2.3); P=0.01 FIQ subscores, mean (SD): Physical Impairment (0-9.99): -1.1 (2.3) vs -0.4 (2.1); Between-group difference: -0.7 (95% CI, -1.9 to 0.6); P=0.28 Days felt good (0-10.01): -1.5 (3.7) vs 0.2 (3.1); Between-group difference: -1.7 (95% CI, -3.6 to 0.2); P=0.08 Work missed (0-10): 0.4 (1.5) vs 0.4 (1.3); Between-group difference: -0.1 (95% CI, -1.0 to 0.9); P=0.88 Work impairment (0-10): 0.0 (3.2) vs 1.2 (3.6); Between-group difference: -1.2 (95% CI, -3.4 to 1.0); P=0.27 Pain (0-10): -1.8 (2.4) vs 0.4 (2.4); Between-group difference: -2.2 (95% CI, -3.6 to -0.9); P=0.002 Fatigue (0-10): -1.2 (3.0) vs 0.3 (2.3); Between-group difference: -1.5 (95% CI, -3.0 to 0.0); P=0.05 Feeling tired upon awakening (0-10): -0.7 (2.6) vs 0.3 (2.5); Between-group difference: -1.0 (95% CI, -2.5 to 0.4); P=0.15 Stiffness (0-10): -1.1 (3.0) vs 0.3 (2.4); Between-group difference: -1.4 (95% CI, -2.9 to 0.1); P=0.07 Anxiety (0-10): -0.3 (2.5) vs 0.7 (2.9); Between-group difference: -1.0 (95% CI, -2.5 to 0.5); P=0.19 Depression (0-10): -0.9 (2.8) vs 1.1 (2.5); Between-group difference: -2.0 (95% CI, -3.5 to -0.5); P=0.01

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Anderberg, 2000 Sweden Fair	Citalopram vs Placebo Dry mouth: 1 (4.8%) vs 0 (0%) Nausea: 7 (33.3%) vs 2 (10.5%) Fatigue: 3 (14.3%) vs 2 (10.5%) Headache: 6 (28.6%) vs 4 (21.1%) Vertigo: 5 (23.8%) vs 0 (0%) Tremor: 1 (4.8%) vs 0 (0%) Sweating: 2 (9.5%) vs 0 (0%) Sexual side-effects: 2 (9.5%) vs 0 (0%) Weight gain: 0 (0%) vs 1 (5.3%)	Citalopram vs Placebo Total withdrawals: 5 total, NR by group Due to AE: 3 (14.3%) vs 0 (0%)	H. Lundbeck AB, Söderström Königska Foundation, the Swedish Association of Physicians, the Märta and Nicke Nasvell Foundation, the Swedish Health Insurance System, the Uppsala County Council and 'Förenade Liv' Mutual Group Life Insurance Company, and the Swedish Medical Research Council	
Arnold, 2002 United States Fair	The most common adverse events reported by the fluoxetine-treated subjects were headache, insomnia, sedation, and nausea. There were NSD between the treatment groups in the incidence of these events. (Data NR.)	Fluoxetine vs Placebo Total withdrawals: 11 (36.7%) vs 12 (40%) Due to AE: 12 total, NR by group	Eli Lilly	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Arnold, 2007 United States Fair	Patients ≥18 years old who met the ACR criteria for fibromyalgia, and a score of ≥4 on the average pain severity item of the BPI at screening and randomization.	A: Gabapentin 1,200-2,400 mg/d B: Placebo For 12 weeks Dosing schedule: Week 1: 300 mg qd Week 2: 300 mg bid Weeks 3-4: 300 mg bid + 600 mg qd Weeks 5-6: 600 mg tid Week 7+ (for at least 4 consecutive weeks): 600 mg bid + 1200 mg qd Tapering phase: dose steadily decreased by 300 mg qd	Episodic use of sedating antihistamines; acetaminophen or over-the-counter NSAIDs	48.2 years (SD 11.2) 90% female White: 97% African-American: 1% Asian: <1%

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Arnold, 2007 United States Fair	Mean baseline BPI pain severity score: 5.9 (SD 1.5) Mean baseline BPI pain interference score: 5.0 (SD 2.0); Statistically significant between-group difference: gabapentin 4.7 (SD 2.0) vs placebo 5.3 (SD 1.9); P<0.05	150	31/5/119 for efficacy outcomes, 150 for safety outcomes

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Arnold, 2007 United States Fair	Gabapentin vs Placebo, 12 wk timepoint for all outcomes BPI average pain severity score (primary outcome): 3.2 (SD 2.0) vs 4.6 (SD 2.6); mean between group difference: 1.4 (SD 0.6); mean change from baseline: -2.5 vs -1.4 BPI average pain interference score: 2.2 (SD 2.2) vs 3.6 (SD 2.8); mean between group difference: 1.4 (SD 0.6); mean change from baseline: -2.5 vs -1.7 FIQ total score: 26.2 (SD 15.1) vs 37.3 (18.1); mean between group difference: 11.1 (SD 3.0); mean change from baseline: -20.1 vs -10.4 CGI-S score: 3.1 (SD 1.0) vs 3.8 (SD 1.3); mean between group difference: 0.7 (SD 0.3); mean change from baseline: -1.3 vs -0.7 Mean tender point pain threshold: 2.0 (SD 0.9) vs 1.8 (SD 1.0); mean between group difference: 0.2 (SD 0.1); mean change from baseline: 0.2 vs 0.1 MOS Sleep Problems Index: 33.4 (SD 19.5) vs 47.8 (20.9); mean between group difference: 14.4 (SD 1.4); mean change from baseline: -22.6 vs -0.1 MADRS: 9.1 (SD 9.4) vs 13.9 (SD 8.9); mean between group difference: 4.8; mean change from baseline: -6.8 vs -3.2

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Arnold, 2007 United States Fair	Gabapentin vs Placebo Headache: 20 (26.7%) vs 16 (21.3%) Dizziness: 19 (25.3%) vs 7 (9.3%); P<0.05 Sedation: 18 (24.0%) vs 3 (4.0%); P<0.001 Nausea: 16 (21.3%) vs 16 (21.3%) Somnolence: 14 (18.7%) vs 6 (8.0%) Edema: 12 (16.0%) vs 6 (8.0%) Lightheadedness: 11 (14.7%) vs 1 (1.3%); P<0.01 Insomnia: 9 (12.0%) vs 6 (8.0%) Diarrhea: 8 (10.7%) vs 5 (6.7%) Pharyngitis: 7 (9.3%) vs 11 (14.7%) Asthenia: 6 (8.0%) vs 5 (6.7%) Depression: 6 (8.0%) vs 3 (4.0%) Flatulence: 6 (8.0%) vs 4 (5.3%) Nervousness: 6 (8.0%) vs 1 (1.3%) Weight gain: 6 (8.0%) vs 0 (0%); P<0.05 Amblyopia: 5 (6.7%) vs 1 (1.3%) Anxiety: 5 (6.7%) 2 (2.7%) Cold virus: 5 (6.7%) vs 11 (14.7%) Dry mouth: 5 (6.7%) vs 3 (4.0%)	Gabapentin vs Placebo: Total withdrawals: 18 (24%) vs 13 (17.3%) Due to AE: 12 (16%) vs 7 (9.3%); P=0.34	NIH grant from National Institute of Arthritis and Musculoskeletal and Skin Diseases	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Arnold, 2008 United States Fair	Adult patients meeting ACR criteria for fibromyalgia and had a pain score of ≥40 mm on a 100 mm VAS, who completed 4 out of 7 daily entries in the pain diaries during single blind period.	A: Pregabalin 300-600 mg/d B: Placebo For 14 weeks Dosing schedule: 1 week single-blinded placebo run-in followed by a 2 week double-blinded dose escalation period, and a 12 week fixed-dose phase (300-600 mg/d).	Acetaminophen ≤4 g/d and aspirin ≤325 mg/d for cardiac prophylaxis	50.1 years (SD 11.4) 94.5% female White: 91.0% Black: 4.4% Other: 4.6%

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Arnold, 2008 United States Fair	Weight: 83.1 kg (SD 20.1) Duration of fibromyalgia: 10.0 years (SD 8.0) Baseline mean pain score: 6.7 (SD 1.3) Number of painful tender points: 16.9 (SD 1.8)	750	259/69 (includes those who withdrew consent and were lost to follow-up)/745

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Arnold, 2008 United States Fair	Placebo vs Pregabalin 300 mg vs Pregabalin 450 mg vs Pregabalin 600mg, LS mean (SE) at 14 weeks Mean pain score: 5.64 (0.15) vs 4.93 (0.16) vs 4.66 (0.15) vs 4.64 (0.15) FIQ total score: 51.99 (1.34) vs 49.03 (1.34) vs 46.75 (1.31) vs 46.65 (1.33) Mean sleep quality: 5.07 (0.16) vs 4.33 (0.16) vs 3.96 (0.15) vs 3.73 (0.15) MOS overall sleep problem index: 51.63 (1.40) vs 46.89 (1.39) vs 45.43 (1.37) vs 43.19 (1.38) MAF: 32.42 (0.71) vs 31.51 (0.71) vs 31.02 (0.70) vs 30.92 (0.70) HAD Anxiety total: 8.33 (0.24) vs 7.71 (0.23) vs 7.82 (0.23) vs 7.54 (0.23) HAD Depression Total: 6.51 (0.24) vs 6.65 (0.24) vs 6.19 (0.24) vs 6.23 (0.24)

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Arnold, 2008 United States Fair	Pregabalin 300mg vs Pregabalin 450mg vs Pregabalin 600mg vs Placebo Patients reporting AE: 81% vs 88% vs 88% vs 72% Dizziness: 27.9% vs 37.4% vs 42.0% vs 7.6% Somnolence: 12.6% vs 19.5% vs 21.8% vs 3.8% Weight increased: 12.0% vs 12.6% vs 13.8% vs 2.2% Headache: 7.7% vs 12.2% vs 7.4% vs 10.3% Peripheral edema: 6.6% vs 6.3% vs 12.2% vs 2.7% Fatigue: 8.2% vs 5.9% vs 9.0% vs 4.3% Blurred vision: 3.8% vs 6.8% vs 11.7% vs 0.5% Nausea: 6.0% vs 8.4% vs 8.0% vs 8.7% Constipation: 2.7% vs 7.4% vs 10.1% vs 3.8% Disturbance in attention: 4.9% vs 6.3% vs 7.4% vs 1.1% Balance disorder: 1.6% vs 9.5% vs 6.9% vs 0.5% Euphoric mood: 4.4% vs 5.8% vs 7.4% vs 0.0% Sinusitis: 4.9% vs 6.9% vs 4.3% vs 4.3% Back pain: 4.4% vs 7.9% vs 3.2% vs 2.7% Dry mouth: 3.8% vs 4.2% vs 6.9% vs 0.5% Increased appetite: 3.3% vs 3.7% vs 6.4% vs 0.5% Memory impairment: 4.4% vs 5.3% vs 3.2% vs 0.5% Diarrhea: 4.4% vs 2.6% vs 4.3% vs 6.3% Upper UTI: 2.2% vs 4.7% vs 3.2% vs 6.5%	Placebo vs Pregabalin 300 mg vs Pregabalin 450 mg vs Pregabalin 600mg Total withdrawals: 59 (32.1%) vs 60 (32.8%) vs 65 (34.2%) vs 75 (39.9%) Due to AE: 20 (10.9%) vs 31 (16.9%) vs 43 (22.6%) vs 50 (26.6%)	Pfizer Global Research & Development	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Arnold, 2010 United States Fair	Women ≥18 years of age who met the ACR criteria for fibromyalgia, with no evidence of traumatic injury, inflammatory rheumatic disease, or infectious or endocrine-related arthropathy.	A: Milnacipran 100 mg/d B: Placebo For 4-6 weeks of flexible dose escalation followed by 12 weeks of stable-dose treatment	Acetaminophen, aspirin, and NSAIDS; triptans for acute migraine; nonbenzodiazepine hypnotic agents for insomnia. Patients requiring short-term pain rescue medication were allowed tramadol or hydrocodone between randomization and week 4 (end of dose escalation).	48.9 years (SD 10.7) 95.3% female White: 91% Black/African American: 6% Asian: 0.2% Other: 2.8%

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Arnold, 2010 United States Fair	Weight: 183 lbs (SD 44.1) BMI: 30.9 kg/m2 Duration of fibromyalgia: 10.9 years (SD 8.0)	1025	315/24/1025

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Arnold, 2010 United States Fair	Placebo vs Milnacipran 3-Measure Composite Responders (≥30% improvement from baseline in 24-hour recall VAS pain scores, PGIC scores ≤2, and ≥6-point improvement from baseline in the SF-36 PCS score: BOCF analysis: 11.1% vs 20.1%; P<0.001 LOCF analysis: 12.5% vs 22.5%; P<0.001 OC Analysis: 16.2% vs 29.9%; P<0.001 GLMM: 10.7% vs 23.6%; P<0.001 Responders: PED 24-hour recall pain score - 30% improvement from baseline: 156 (30.6%) vs 230 (44.6%); P<0.001 PED 24-hour recall pain score - 50% improvement from baseline: 92 (18.1%) vs 143 (27.7%); P<0.001 PGIC, score ≤2: 132 (25.9%) vs 216 (41.9%); P<0.001 SF-36 score, PCS, 6-point improvement from baseline: 157 (30.8%) vs 206 (39.9%); P=0.001 Physical function domain, physical functioning:158 (31.0%) vs 200 (38.8%); P=0.005 Physical function domain, role limit--physical: 156 (30.6%) vs 193 (37.4%); P=0.013 Physical function domain, bodily pain: 149 (29.3%) vs 207 (40.1%); P<0.001 Physical function domain, general health perception: 96 (18.9%) vs 154 (29.8%); P<0.001 Time-weighted average of scores normalized by week, LS mean (SEM) AUC: PED 24-hour recall pain score: 48.31 (1.04) vs 41.93 (1.04); LS Mean Difference: -6.38 (95% CI, -8.56 to -4.19); P<0.001 PGIC score: 3.49 (0.08) vs 2.96 (0.08); LS Mean Difference: -0.53 (95% CI, -0.69 to -0.38); P<0.001 SF-36 PCS score: 36.20 (0.38) vs 37.84 (0.38); LS Mean Difference: 1.65 (95% CI, 0.86 to 2.44); P<0.001 PGIC score, LS mean (SEM): 3.53 (0.08) vs 3.06 (0.08); LS Mean Difference: -0.47 (95% CI, -0.64 to -0.29); P<0.001 Change in score from baseline, LS mean (SEM) PED VAS pain score, 24-hour recall pain: -10.76 (1.23) vs -17.70 (1.23); LS Mean Difference: -6.94 (95% CI, -9.53, -4.35); P<0.001 PED VAS pain score, Weekly recall pain: -11.17 (1.30) vs -18.21 (1.30); LS Mean Difference: -7.04 (95% CI, -9.78 to -4.31); P<0.001 PED VAS pain score, Real-time pain: -8.94 (1.21) vs -15.62 (1.21); LS Mean Difference: -6.68 (95% CI, -9.22 to -4.13); P<0.001 VAS pain score, 24-hour recall pain: -12.83 (1.55) vs -19.96 (1.57); LS Mean Difference: -7.13 (95% CI, -10.41 to -3.85); P<0.001 VAS pain score, Weekly recall pain: -12.66 (1.56) vs -20.80 (1.58); LS Mean Difference: -8.14 (95% CI, -11.43 to -4.85); P<0.001 BPI score, Average pain severity: -0.81 (0.12) vs -1.46 (0.12); LS Mean Difference: -0.65 (95% CI, -0.90 to -0.40); P<0.001 BPI score, Pain interference: -0.91 (0.13) vs -1.49 (0.14); LS Mean Difference: -0.58 (95% CI, -0.86 to -0.29); P<0.001 FIQ score, Total: -7.12 (1.08) vs -12.34 (1.09); LS Mean Difference: -5.22 (95% CI, -7.46 to -2.98); P<0.001 FIQ score, Physical function: -0.17 (0.03) vs -0.27 (0.03); LS Mean Difference: -0.10 (95% CI, -0.17 to -0.03); P=0.005 MFI total score: -2.61 (0.77) vs -4.31 (0.77); LS Mean Difference: -1.69 (95% CI, -3.27 to -0.11); P=0.036 MASQ total score: -2.36 (0.77) vs -3.89 (0.77); LS Mean Difference: -1.52 (95% CI, -3.11 to 0.06); P=0.060 BDI total score: -1.24 (0.31) vs -2.12 (0.31); LS Mean Difference: -0.89 (95% CI, -1.54 to -0.23); P=0.008 BAI total score: -1.73 (0.40) vs -0.74 (0.40); LS Mean Difference: 0.99 (95% CI, 0.15 to 1.82); P=0.020 SF-36 score - PCS: 2.89 (0.42) vs 4.62 (0.43); LS Mean Difference: 1.73 (95% CI, 0.84 to 2.62); P<0.001 SF-36 score - MCS: -0.50 (0.54) vs 1.54 (0.54); LS Mean Difference: 2.04 (95% CI, 0.91 to 3.17); P<0.001 SF-36 score - Physical functioning: 2.16 (0.44) vs 3.98 (0.45); LS Mean Difference: 1.82 (95% CI, 0.89 to 2.74); P<0.001 SF-36 score - Role limit - physical: 1.75 (0.47) vs 3.43 (0.47); LS Mean Difference: 1.68 (95% CI, 0.70 to 2.67); P<0.001 SF-36 score - Bodily pain: 2.87 (0.44) vs 5.47 (0.44); LS Mean Difference: 2.60 (95% CI, 1.68 to 3.52); P<0.001 SF-36 score - General health perception: 0.19 (0.43) vs 1.85 (0.43); LS Mean Difference: 1.67 (95% CI, 0.76 to 2.57); P<0.001 SF-36 score - Energy/vitality: 2.56 (0.56) vs 4.43 (0.57); LS Mean Difference: 1.87 (95% CI, 0.69 to 3.05); P=0.002 SF-36 score - Social functioning: 2.04 (0.55) vs 4.00 (0.55); LS Mean Difference: 1.96 (95% CI, 0.81 to 3.11); P<0.001 SF-36 score - Role limit - emotional: -1.28 (0.59) vs 1.01 (0.60); LS Mean Difference: 2.29 (95% CI, 1.04 to 3.53); P<0.001 SF-36 score - Mental health: -0.18 (0.51) vs 1.83 (0.51); LS Mean Difference: 2.00 (95% CI, 0.94 to 3.07); P<0.001

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Arnold, 2010 United States Fair	Placebo vs Milnacipran Any treatment-emergent AE: 382 (75.0%) vs 434 (84.1%) Nausea: 106 (20.8%) vs 189 (36.6%) Headache: 80 (15.7%) vs 92 (17.8%) Constipation: 20 (3.9%) vs 76 (14.7%) Hot flush: 18 (3.5%) vs 56 (10.9%) Dizziness: 26 (5.1%) vs 54 (10.5%) Insomnia: 41 (8.1%) vs 51 (9.9%) Hyperhidrosis: 7 (1.4%) vs 40 (7.8%) Palpitations: 15 (2.9%) vs 38 (7.4%) Fatigue: 22 (4.3%) vs 31 (6.0%) Tachycardia: 5 (1.0%) vs 28 (5.4%) Hypertension: 5 (1.0%) vs 27 (5.2%) Dyspepsia: 31 (6.1%) vs 25 (4.8%) Diarrhea: 26 (5.1%) vs 23 (4.5%) Upper respiratory tract infection: 27 (5.3%) vs 19 (3.7%)	Placebo vs Milnacipran Total withdrawals: 152 (29.9%) vs 161 (31.2%) Due to AE: 73 (14.3%) vs 93 (18%)	Forest Laboratories, Inc.	Patients unable to tolerate the stable dosage of milnacipran 100 mg/day were discontinued from the study.

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Ataoglu, 1997 Turkey Fair	Outpatients with widespread pain and tenderness to the diagnostic criteria of the ACR for fibromyalgia.	A: Paroxetine 20mg/d B: Amitriptyline 100 mg/d For 6 weeks Dosage schedule: On day 1 of treatment, amitriptyline-treated patients received 50 mg/d at bedtime. On days 4 and 5 the dosage was increased to 100 mg of amitriptyline and for the final 5 weeks the patients received 100 mg/d of amitriptyline.	NR	36.1 years 100% female Ethnicity NR

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Ataoglu, 1997 Turkey Fair	Duration of fibromyalgia: 35.7 months	68	7/0/61

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Ataoglu, 1997 Turkey Fair	Paroxetine vs Amitriptyline Treatment scores, mean change from baseline at 45 days: Pain: 2.16 (P<0.001 vs baseline) vs 0.34 (P<0.05 vs baseline) General condition: 1.44 (P<0.001 vs baseline) vs 0.51 (P<0.05 vs baseline) Sleep: 3.06 (P<0.001 vs baseline) vs 1.04 (P<0.001 vs baseline) Fatigue: 0.68 vs 0.86 (P<0.01 vs baseline) HAMD Scores: 4.62 (P<0.05 vs baseline) vs 1.14 (P<0.05 vs baseline) Tender points: 0.63 (P<0.05 vs baseline) vs 1.14 (P<0.01 vs baseline) Clinical global assessment: Marked improvement: 3 (9.4%) vs 2 (6.9%) Moderate improvement: 4 (12.5%) vs 3 (10.3%) Slight improvement: 7 (21.9%) vs 6 (20.7%) No change: 18 (56.2%) vs 18 (62.1%)

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Ataoglu, 1997 Turkey Fair	Paroxetine vs Amitriptyline Patients reporting any AE: 27 (93.1%) vs 12 (37.5%) Dry mouth: 2 (6.3%) vs 9 (31%) Nausea: 1 (3.1%) vs 3 (10.3%) Dizziness: 1 (3.1%) vs 2 (6.8%) Sweating: 1 (3.1%) vs 2 (6.8%) Constipation: 1 (3.1%) vs 2 (6.8%) Vomiting: 0 (0%) vs 1 (3.4%) Headache: 1 (3.1%) vs 2 (6.8%) Sedation: 1 (3.1%) vs 2 (6.8%) Insomnia: 2 (6.3%) vs 0 (0%) Urinary retention: 0 (0%) vs 1 (3.4%) Fatigue: 2 (6.3%) vs 1 (3.4%) All anticholinergic-type side effects (including dry mouth, constipation, urinary retention: 3 (9%) vs 12 (41%); P<0.004	Paroxetine vs Amitriptyline Total withdrawals: 2 (5.8%) vs 5 (14.7%) Due to AE: 2 (5.8%) vs 5 (14.7%)	NR	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Bennett, 1988 United States Fair	Patients with fibrositis, according to the following major criteria: 1) widespread musculoskeletal pain of at least 3 months duration, not explicable by any other diagnosis; 2) presence of 7 or more tender points; 3) increased tension in the musculature of the shoulders and neck, 4) sleep disturbance, characterized by a sensation of fatigue upon arising; 5) accentuation of stiffness and aching in the early morning. Patients were also required to exhibit at least 2 of the following minor criteria: 1) modulation of symptoms by changes in the weather; 2) temporary relief of symptoms by heat modalities; 3) exacerbation of symptoms by strenuous exertion and/or emotional stress; 4) dermatographism.	A: Cyclobenzaprine 10-40 mg/d B: Placebo For 12 weeks Dosing schedule: Patients were initially given 10 mg at night, and the dosage was increased during the first 2 weeks of treatment if symptoms did not improve. Maximum dose allowed was 40 mg/d. Medication dosages could be altered as dictated by tolerance. All patients had reached an optimum therapeutic dosage within the first 2 weeks of treatment. Overall distribution: 21% taking 10 mg, 34% taking 20 mg, 23% taking 30 mg, 21% taking 40 mg	Aspirin or NSAIDs at constant dose for patients with fibrositis associated with RA	49.4 years (SD 12) 96.7% female Ethnicity NR

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Bennett, 1988 United States Fair	Primary fibrositis: 53 (44%) Fibrositis associated with trauma or arthritis: 67 (56%) Months since diagnosis: 4.5 (SD 2.4)	120	57/3/120

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Bennett, 1988 United States Fair	Cyclobenzaprine vs Placebo Percentage improvement from baseline at endpoint VAS sleep score: 34.5% vs 17.8% (P<0.02) VAS pain score: 27.8% vs 7.2% (P<0.02) Duration of stiffness: 32.5% vs 18.1% Duration of fatigue: 25.3% vs 6.7% Average score of all tender points: 20.1% vs 12.7% Number of active tender points: 21.4% vs 11.5% Muscle tightness (≥1 categories): 60.5% vs 28.6% Muscle tightness (≥2 categories): 28.1% vs 8.4% Global pain (≥1 categories): 52.4% vs 40.6% Global pain (≥2 categories): 22.2% vs 16.5% Physicians evaluation of global improvement at conclusion of study: Marked: 11 (18%) vs 3 (5.3%) Moderate: 10 (16.4%) vs 6 (10.5%) Mild: 12 (19.7%) vs 26 (19.3%) No change: 24 (39.3%) vs 26 (45.6%) Worse: 4 (6.6%) vs 11 (19.3%)

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Bennett, 1988 United States Fair	Cyclobenzaprine vs Placebo Dry mouth: 57 (91.9%) vs 17 (29.3%); P<0.01 Drowsiness: 34 (54.8%) vs 17 (29.3%); P<0.059 Constipation: 8 (12.9%) vs 2 (3.4%) Dizziness: 7 (11.3%) vs 5 (8.6%) Palpitation: 7 (11.3%) vs 4 (6.9%) Tachycardia: 5 (8.1%) vs 4 (6.9%) Fatigue/tiredness: 5 (8.1%) vs 2 (3.4%) Depression: 5 (8.1%) vs 2 (3.4%) Headache: 3 (4.8%) vs 9 (15.5%) Nausea: 2 (3.2%) vs 7 (12.1%) Generalized pain: 2 (3.2%) vs 4 (6.9%)	Cyclobenzaprine vs Placebo Total withdrawals: 22 (35%) vs 35 (60%); P<0.05 Due to AE: 5 (8%) vs 3 (5%)	NR	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Branco, 2010 France Fair	Outpatients diagnosed with fibromyalgia according to ACR criteria, had a raw score ≥3 on the physical function component of the FIQ, a baseline VAS pain intensity rating between 40 and 90 (0 to 100 scale), and with no severe psychiatric illness including generalized anxiety disorder or current MDD.	A: Milnacipran 200 mg/d B: Placebo For 17 weeks (4-week dose escalation and 12-week stable dose)	<10 mg prednisone equivalent per day	48.8 years (SD 9.8) 94.3% female Ethnicity NR

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Branco, 2010 France Fair	BMI: 26.7 kg/m2 Obese: 22.3% Mean fibromyalgia duration: 9.5 years (SD 8.6)	884	206/NR/876

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Branco, 2010 France Fair	Placebo vs Milnacipran, LS mean change (SEM) FIQ total score: -11.18 (0.99) vs -14.18 (1.03); Difference from Placebo: -3.00 (95% CI, -5.42 to -0.58); P=0.015 PED 24-hour recall pain: -11.97 (1.14) vs -16.50 (1.18); Difference from Placebo: -4.52 (95% CI, -7.29 to -1.76); P=0.001 PED weekly recall pain: -11.60 (1.20) vs -16.34 (1.24); Difference from Placebo: -4.74 (95% CI, -7.64 to -1.83); P=0.001 Paper VAS 24-hour recall pain: -16.09 (1.37) vs -21.90 (1.42); Difference from Placebo: -5.81 (95% CI, -9.15 to -2.47); P=0.0007 Paper VAS weekly recall pain: -15.76 (1.35) vs -21.47 (1.41); Difference from Placebo: -5.71 (95% CI, -9.03, -2.40); P=0.0008 PED current daily morning pain: -10.83 (1.27) vs -17.15 (1.39); Difference from Placebo: -6.32 (95% CI, -9.46 to -3.19); P< 0.0001 PED current daily evening pain: -12.76 (1.28) vs -18.53 (1.40); Difference from Placebo: -5.77 (95% CI, -8.93 to -2.61); P=0.0004 BPI-SF pain intensity: -1.03 (0.10) vs -1.47 (0.11); Difference from Placebo: -0.44 (95% CI, -0.69 to -0.18); P=0.0008 BPI-SF pain interference: -0.93 (0.11) vs -1.26 (0.11); Difference from Placebo: -0.33 (95% CI, -0.60, -0.07); P=0.014 FIQ physical function: -0.22 (0.03) vs -0.31 (0.03); Difference from Placebo: -0.09 (95% CI, -0.16 to -0.01); P=0.021 FIQ pain: -14.60 (1.26) vs -18.68 (1.31); Difference from Placebo: -4.08 (95% CI, -7.14 to -1.02); P=0.009 SF-36 scores: PCS: 3.57 (0.35) vs 4.55 (0.36); Difference from Placebo: 0.98 (95% CI, 0.12 to 1.83); P=0.025 Mental Component Summary: -0.23 (0.43) vs 1.23 (0.45); Difference from Placebo: 1.45 (95% CI, 0.39 to 2.52); P=0.007 Physical functioning: 7.10 (0.88) vs 9.40 (0.92); Difference from Placebo: 2.30 (95% CI, 0.13 to 4.46); P=0.037 Role limitation-physical: 6.25 (1.14) vs 8.85 (1.19); Difference from Placebo: 2.60 (95% CI, -0.20 to 5.39); P=0.068 Bodily pain: 9.79 (1.04) vs 13.34 (1.08); Difference from Placebo: 3.55 (95% CI, 1.01 to 6.09); P=0.006 General health perception: 4.08 (0.83) vs 6.39 (0.87); Difference from Placebo: 2.31 (95% CI, 0.28 to 4.35); P=0.026 Energy/vitality: 5.08 (0.98) vs 7.75 (1.02); Difference from Placebo: 2.67 (95% CI, 0.27 to 5.07); P=0.029 Social functioning: 3.24 (1.15) vs 6.69 (1.20); Difference from Placebo: 3.45 (95% CI, 0.63 to 6.26); P=0.016 Role limit-emotional: -0.47 (1.19) vs 2.57 (1.24); Difference from Placebo: 3.05 (95% CI, 0.13 to 5.96); P=0.041 Mental health: 0.52 (0.84) vs 3.60 (0.87); Difference from Placebo: 3.08 (95% CI, 1.03, 5.13); P=0.003 MFI total score: -3.53 (0.70) vs -5.94 (0.73); Difference from Placebo: -2.41 (95% CI, -4.12 to -0.71); P= 0.006 PED weekly recall fatigue: -10.71 (1.25) vs -15.17 (1.29); Difference from Placebo: -4.47 (95% CI, -7.49 to -1.44); P=0.004 MASQ total score: -3.42 (0.96) vs -5.88 (1.00); Difference from Placebo: -2.45 (95% CI, -4.80 to -0.10); P=0.041 BDI: -0.29 (0.34) vs -0.74 (0.36); Difference from Placebo: -0.44 (95% CI, -1.29 to 0.40); P=0.302 MOS-Sleep Index I: -6.73 (0.95) vs -6.28 (0.99); Difference from Placebo: 0.45 (95% CI, -1.88 to 2.78); P=0.703 MOS-Sleep Index II: -7.40 (0.93) vs -6.93 (0.97); Difference from Placebo: 0.47 (95% CI, -1.81 to 2.75); P=0.685 PED weekly recall sleep: -9.59 (1.28) vs -13.86 (1.32); Difference from Placebo: -4.27 (95% CI, -7.36 to -1.18); P=0.007 STAI-S: 0.01 (0.52) vs -0.96 (0.54); Difference from Placebo: -0.98 (95% CI, -2.26, 0.30); P=0.133

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Branco, 2010 France Fair	Placebo vs Milnacipran At least one treatment emergent AE: 331 (74.2%) vs 363 (84.2%) Nausea: 50 (11.2%) vs 112 (26.0%) Hyperhidrosis: 13 (2.9%) vs 102 (23.7%) Headache: 55 (12.3%) vs 73 (16.9%) Constipation: 10 (2.2%) vs 54 (12.5%) Dizziness: 34 (7.6%) vs 44 (10.2%) Palpitations: 13 (2.9%) vs 34 (7.9%) Insomnia: 24 (5.4%) vs 33 (7.7%) Nasopharyngitis: 33 (7.4%) vs 33 (7.7%) Hot flash: 5 (1.1%) vs 30 (7.0%) Tachycardia: 3 (0.7%) vs 29 (6.7%) Vomiting: 15 (3.4%) vs 22 (5.1%)	Placebo vs Milnacipran Total withdrawals: 79 (17.5%) vs 127 (29.2%) Due to AE: 44 (9.8%) vs 96 (22.1%)	Pierre Fabre Médicament	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Carette, 1986 Canada Fair	Patients with primary fibrositis according to Smythe's criteria: 1) widespread aching of more than 3 months duration, 2) local tenderness at 12 of 14 specified sites, 3) disturbed sleep with morning fatigue and stiffness, 4) absence of traumatic, neurologic, muscular, infectious, osseous, endocrine, or other rheumatic conditions, and 5) normal Westergren erythrocyte sedimation rate, creatine phosphokinase level, latex fixation result, antinuclear antibody factor, and thyroid stimulating hormone level.	A: Amitriptyline 50 mg B: Placebo For 9 weeks Dosing schedule: Week 1: 10 mg/d at bedtime Weeks 2-4: 25 mg/d Weeks 5-9: 50 mg/d	Acetaminophen	40.9 years (SD 10.5) 91.5% female Ethnicity NR

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Carette, 1986 Canada Fair	Duration of fibrositis: 85.1 months (P<0.05 between groups) Duration of morning stiffness: 76.6 minutes Pain analog score: 6.0 (SD 2.4)	70	11/0/59

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Carette, 1986 Canada Fair	Amitriptyline vs Placebo Patient global assessment at 5 weeks: Worse: 0 (0%) vs 4 (12.5%) Unchanged: 6 (22.2%) vs 14 (43.8%) Minimal improvement: 6 (22.2%) vs 7 (21.9%) Moderate improvement: 11 (40.7%) vs 4 (12.5%) Marked improvement: 4 (14.8%) vs 3 (9.4%) Patient global assessment at 9 weeks: Worse: 1 (3.7%) vs 4 (12.5%) Unchanged: 7 (25.9%) vs 12 (37.5%) Minimal improvement: 2 (7.4%) vs 6 (18.8%) Moderate improvement: 11 (40.7%) vs 5 (15.6%) Marked improvement: 6 (22.2%) vs 5 (15.6%) Physician global assessments at 5 weeks: Worse: 0 (0%) vs 5 (15.6%) Unchanged: 8 (29.6%) vs 15 (46.9%) Minimal improvement: 8 (29.6%) vs 7 (21.9%) Moderate improvement: 6 (22.2%) vs 2 (6.3%) Marked improvement: 5 (18.5%) vs 3 (9.4%) Physician global assessments at 9 weeks: Worse: 1 (3.7%) vs 3 (9.4%) Unchanged: 8 (29.6%) vs 15 (46.9%) Minimal improvement: 3 (11.1%) vs 6 (18.8%) Moderate improvement: 8 (29.6%) vs 6 (18.8%) Marked improvement: 7 (25.9%) vs 2 (6.3%) ≥50% improvement in morning stiffness or pain analog scores: 12 (44%) vs 7 (22%); P=0.12 ≥50% improvement in both morning stiffness and pain analog scores: 10 (37%) vs 5 (16%); P=0.12 Patients believing their quality of sleep had improved at endpoint: 70% vs 40%; P=0.02

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Carette, 1986 Canada Fair	Amitriptyline vs Placebo Patients reporting side effects: 19 (70%) vs 4 (12%) Side effects were, for the most part, drowsiness and xerostomia. (Data NR.)	Amitriptyline vs Placebo Total withdrawals: 7 (25.9%) vs 4 (12.5%) Due to AE: 2 (7.4%) vs 2 (6.3%)	Grant from the Arthritis Society	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Carette, 1994 Canada Fair	Patients ≥18 years who met the ACR 1990 criteria for the classification of fibromyalgia, with a score ≥4 on one of the two self-administered 10 cm VAS.	A: Amitriptyline 10 mg/d at bedtime for first week; 25 mg/d at bedtime for weeks 2-12; 50 mg/d at bedtime for last 12 weeks; and placebo (cyclobenzaprine) B: Cyclobenzaprine 10 mg/d at bedtime for first week; 20 mg/d at bedtime for weeks 2-12; 30 mg/d (10 mg in morning, 20 mg at bedtime) for last 12 weeks; and placebo (amitriptyline) C: Placebo (amitriptyline and cyclobenzaprine) For 6 months	Concurrent medications reported by 2 patients: one taking naproxen 500mg BID, one taking triazolam at bedtime	44.6 years 93.8% female Ethnicity NR

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Carette, 1994 Canada Fair	Number of tender points: 15.9 Duration of fibromyalgia: 92.7 months At work: 49% Not at work, because of fibromyalgia: 27.9% Not at work, for other reasons: 23.6%	208	52/24/208

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Carette, 1994 Canada Fair	Amitriptyline vs Cyclobenzaprine vs Placebo Pain intensity on McGill Pain Questionnaire at 6 months, mean (SD): 2.17 (1.02) vs 2.11 (0.93) vs 2.47 (0.97); P<0.001 vs baseline for Amitriptyline and Cyclobenzaprine, P<0.05 vs baseline for placebo Overall SIP score at 6 months, mean (SD): 13.8 (11.9) vs 11.1(10.1) vs 13.6 (12.9); P<0.05 vs baseline for amitriptyline and placebo, P<0.001 vs baseline for cyclobenzaprine AIMS Depression scale score at 6 months, mean (SD): 2.41 (1.86) vs 2.20 (1.59) vs 2.57 (1.84); P<0.001 vs baseline for amitriptyline and placebo, P>0.05 vs baseline for placebo AIMS Anxiety scale score at 6 months, mean (SD): 4.17 (2.22) vs 4.09 (1.85) vs 4.88 (2.24); P<0.001 vs baseline for amitriptyline and cyclobenzaprine HAQ disability index score at 6 months, mean (SD): 0.60 (0.49) vs 0.53 (0.40) vs 0.70 (0.65) Treatment response (improvement) at 6 months: 36% vs 33% vs 19%; P=0.08 for amitriptyline vs placebo, P=0.15 for cyclobenzaprine vs placebo

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Carette, 1994 Canada Fair	Amitriptyline vs Cyclobenzaprine vs Placebo Proportion of patients reporting AE: 95% vs 98% vs 62% Nature of AE did not differ between 2 active groups, with dry mouth, somnolence, dizziness and weight gain being most frequently reported. (Data NR.)	Amitriptyline vs cyclobenzaprine vs placebo Total withdrawals: 16.7% vs 29.3% vs 33.3% Due to AE: 6% vs 5% vs 13%	Canadian Arthritis Society and Merch Frosst Canada	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Carette, 1995 Canada Fair	Patients ≥18 years meeting the ACR 1990 criteria for the classification of fibromyalgia, with a score of > 4 on at least one of two self-administered VAS.	A: Amitriptyline 25 mg/d one hour before bedtime B: Placebo For 2 months	Acetaminophen	43.8 years (SD 8.0) 95.5% female Ethnicity NR

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Carette, 1995 Canada Fair	Duration of fibromyalgia: 82.7 months (SD 75.4) Mean number of tender points: 16.0 (SD 2.17) Symptoms (% patients reporting): Headaches: 77.3% Bowel syndrome: 54.5% Paresthesia: 68.2% Subjective swelling: 77.3%	22	2/NR/22

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Carette, 1995 Canada Fair	Amitriptyline vs Placebo Percent responders: 27.3% vs 0%; P=0.02 Mean (SD) pain score: 5.07 (3.22) vs 7.13 (2.41); P<0.05 for amitriptyline vs baseline and between groups Fatigue score: 5.62 (3.07) vs 7.64 (1.80); P<0.05 for amitriptyline vs baseline and between groups Sleep score: 3.93(3.14) vs 6.51 (2.69); P<0.05 for amitriptyline vs baseline and between groups Patient global evaluation: 5.47 (3.03) vs 7.11 (2.14); P<0.05 for amitriptyline vs baseline and between groups Physician global evaluation: 4.81 (2.81) vs 6.36 (1.59); P<0.05 for amitriptyline vs baseline and between groups Total myalgia score: 3.45 (1.16) vs 3.22 (0.86) Mean (SD) total sleep time, hours: 6.76 (1.2) vs 6.48 (1.1) % stage 1 sleep: 8.14 (4.2) vs 5.55 (2.8); P≤0.05 vs amitriptyline % stage 2 sleep: 51.73 (9.7) vs 47.51 (7.0) % stage 3 sleep: 6.66 (1.9) vs 7.69 (2.4) % stage 4 sleep: 13.75 (7.0) vs 16.44 (6.1) % rapid eye movement: 98.37 (52.3) vs 89.84 (45.3) Sleep latency, minutes: 20.60 (13.1) vs 13.32 (11.9); P≤0.05 vs baseline Latency, stage 3 minutes: 28.60 (23.6) vs 19.32 (8.8) Latency, stage 4 minutes: 98.37 (52.3) vs 89.94 (45.3) Stage 2 alpha rating: 2.47 (0.8) vs 2.20 (1.2) Stage 3 alpha rating: 2.19 (0.9) vs 2.34 (0.7) Stage 4 alpha rating: 1.72 (0.7) vs 1.90 (0.8)

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Carette, 1995 Canada Fair	NR	Amitriptyline vs placebo Total withdrawals: 0 vs 9.1% Due to AE: NR	Canadian Arthritis Society	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Crofford, 2005; Arnold 2007 United States Fair	Patients ≥18 years old who met the ACR criteria for the diagnosis of fibromyalgia, with a score of ≥40 mm on the 100 mm VAS of the SF-MPQ, and a mean score of ≥4 on the 0-10 pain rating scale based on ≥4 daily pain diary entries.	A: Pregabalin 150-450 mg/d B: Placebo For 8 weeks	Acetaminophen, aspirin, symptomatic migraine medication	48.6 years 92% female White: 94%

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Crofford, 2005; Arnold 2007 United States Fair	Mean baseline pain score: 7.0	529	119/NR/varied for efficacy, 529 for safety

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Crofford, 2005; Arnold 2007 United States Fair	Pregabalin 150 mg vs Pregabalin 300 mg vs Pregabalin 450 mg vs Placebo, LS mean at 8 weeks Pain score: 5.74 vs 5.47 vs 4.94 vs placebo 5.88 Total SF-MPQ score: 17.38 vs 16.98 vs 14.05 vs 18.50 FMS intensity score: 5.05 vs 4.65 vs 4.65 vs 5.17 Sleep quality diary: 4.91 vs 4.68 vs 3.99 vs 5.30 MOS-Sleep problems index: 45.66 vs 45.26 vs 40.44 vs 54.16 MAF global fatigue index: 30.67 vs 29.37 vs 29.14 vs 32.85 HAD anxiety: 8.35 vs 8.36 vs 7.56 vs 8.41 HAD depression: 6.82 vs 7.23 vs 6.65 vs 7.41 SF-36 general health score: 53.89 vs 55.28 vs 54.38 vs 49.34

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Crofford, 2005; Arnold 2007 United States Fair	Placebo vs Pregabalin 150mg vs Pregabalin 300mg vs Pregabalin 450mg Any AE: 101 (77%) vs 102 (78%) vs 118 (88%) vs 121 (92%) Dizziness: 14 (10.7%) vs 30 (22.7%)vs 42 (31.3%) vs 65 (49.2%) Somnolence: 6 (4.6%) vs 21 (15.9%) vs 37 (27.6%) vs 37 (28.0%) Headache: 25 (19.1%) vs 16 (12.1%) vs 20 (14.9%) vs 17 (12.9%) Dry mouth: 2 (1.5%) vs 9 (6.8%) vs 8 (6.0%) vs 17 (12.9%) Peripheral edema: 1 (0.8%) vs 7 (5.3%) vs 9 (6.7%) vs 14 (10.6%) Infection: 22 (16.8%) vs 11 (8.3%) vs 13 (9.7%) vs 13 (9.8%) Asthenia: 8 (6.1%) vs 7 (5.3%) vs 12 (9.0%) vs 11 (8.3%) Euphoria: 1 (0.8%) vs 2 (1.5%) vs 11 (8.2%) vs 10 (7.6%) Thinking abnormal: 4 (3.1%) vs 7 (5.3%) vs 5 (3.7%) vs 10 (7.6%) Weight gain: 2 (1.5%) vs 10 (7.6%) vs 13 (9.7%) vs 9 (6.8%) Sinusitis: 3 (2.3%) vs 6 (4.5%) vs 5 (3.7%) vs 9 (6.8%) Pharyngitis: 3 (2.3%) vs 3 (2.3%) vs 2 (1.5%) vs 8 (6.1%) Accidental injury: 4 (3.1%) vs 3 (2.3%) vs 7 (5.2%) vs 7 (5.3%) Confusion: 0 (0.0%)vs 1 (0.8%) vs 5 (3.7%) vs 7 (5.3%) Diarrhea: 8 (6.1%) vs 2 (1.5%) vs 6 (4.5%) vs 7 (5.3%) Flu syndrome: 8 (6.1%) vs 8 (6.1%) vs 8 (6.0%) vs 7 (5.3%) Incoordination: 2 (1.5%) vs 1 (0.8%) vs 7 (5.2%) vs 7 (5.3%)	Pregabalin 150 mg vs Pregabalin 300 mg vs Pregabalin 450 mg vs Placebo Total withdrawals: 29 (22.0%) vs 23 (17.2%) vs 33 (25.0%) vs 34 (26.0%) Due to AE: 11 (8%) vs 10 (7%) vs 17 (13%) vs 10 (8%)	Pfizer Global Research & Development	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Crofford, 2008 United States FREEDOM Fair	Adult patients meeting the ACR criteria for fibromyalgia and had scored their pain over the previous week as ≥40 mm on the 0-100 mm pain VAS at screening and baseline visits. Inclusion in DB phase: ≥50% reduction in pain VAS score from open label baseline and self-rating of overall improvement on the PGIC scale of "much improved" or "very much improved."	A: Pregabalin 300-600 mg/d B: Placebo For 6 week open-label phase followed by a 26 week DB phase Dosing schedule: Open label phase weeks 1-3: escalating doses of pregabalin 150 mg-600 mg Open-label weeks 4-6: optimal fixed doses of 300, 450 or 600 mg/d DB phase: placebo, 300, 450, or 600 mg/d	Acetaminophen up to 4 g/d	Open label: 49.5 years (SD 11.6) 93% female White: 88% Black: 5% Other: 7% DB phase: 49.1 years (SD 11.4) 93.3% female White: 90% Black: 3.4% Other: 6.6%

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Crofford, 2008 United States FREEDOM Fair	Open label: Duration of fibromyalgia: 123.3 months (SD 100.5) Number of painful tender points: 17.1 (SD 1.7) DB phase: Duration of fibromyalgia: 123.7 months (SD 103.2) Number of painful tender points: 17.1 (SD 1.7) Comorbidities: Hypertension: 29% Insomnia: 28% Depression: 26%	Open label: 1051 DB phase: 566	404/NR/566 (all numbers represent DB phase)

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Crofford, 2008	Placebo vs Pregabalin
United States	Patients with LTR by wk 26: 174 (61%) vs 90 (32%)
FREEDOM	Time to LTR for 1st quartile of patients: 7 (95% CI, 5 to 9) vs 34 (95% CI, 21 to 48)
	Median time to LTR: 19 (95% CI, 14 to 36) vs N/A; P<0.0001
Fair	
	PGIC, median time to LTR: 20 days (95% CI, 15 to 35) vs 126 days (95% CI, 7 to no upper limit); P<0.0001
	FIQ, median time to LTR: 14 days vs 19 days (95% CI, 15 to 41); P<0.0001
	MOS, median time to LTR: 14 days vs 42 days (95% CI, 41 to 43); P<0.0001
	MAF, median time to LTR: 27 days (95% CI, 16 to 42) vs 119 (95% CI, 69 to 155); P<0.0001
	SF-36 Physical component, median time to LTR: 15 days (95% CI, 14 to 19) vs 49 days (95% CI, 42 to 71); P<0.0001
	SF-36 Mental component, median time to LTR: 14 days (95% CI, 14 to 15) vs 42 days (95% CI, 41 to 43); P<0.0001

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Crofford, 2008 United States FREEDOM Fair	Placebo vs Pregabalin Open Label: Serious AE: 0.8% DB phase: Serious AE: 1% vs 2.9% Insomnia: 6% vs 6% Nausea: 5% vs 5% Anxiety: 2% vs 5% Arthralgia: 2% vs 5% Sinusitis: 3% vs 5% Influenza 1% vs 5% URTI: 3% vs 4% Weight increased: <1 vs 4% None of the serious AE or deaths were considered treatment related.	Placebo vs Pregabalin DB phase: Total withdrawals: 232 (80.8%) vs 172 (61.6%) Due to AE: 20 (7%) vs 47 (16.8%) Open label phase: Total withdrawals: NA vs 388 (37%) Due to AE: NA vs 196 (19%)	Pfizer Global Research & Development	Actual number of patients with LTR in placebo and pregabalin groups are 171 and 84. The numbers presented in the table 2 of the study are based on Kaplan-Meier analysis captured all patients who experienced an LTR. 3 patients from placebo and 6 from pregabalin who had experienced LTR were discontinued from study for other reasons.

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Ginsberg, 1996 Belgium Fair	Male and female patients meeting ACR 1990 criteria for the classification of primary fibromyalgia, history of widespread pain for 3 months and pain in at least 11 of the 18 specific tender points on digital palpation.	A. Sustained-release amitriptyline qd (Rodomex Difficups, 25 mg per capsule) B. Placebo For 2 months	Paracetamol	46 years 82.6% female Caucasian: 95.7% Black: 2.2% Other: 2.2%

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Ginsberg, 1996 Belgium Fair	Number of positive tender points: 14.6 Duration of fibromyalgia: 3.2 years	46	NR/5/46

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Ginsberg, 1996 Belgium	Sustained-Release Amitriptyline vs Placebo Percent responders at 8 weeks: 58% (95% CI, 36.6 to 77.9) vs 0% (95% CI, 0 to 15.4); P<0.001
Fair	Mean change at 8 weeks from baseline: Patient global evaluation: -3.8 vs -0.2; P<0.001 Physician global evaluation: -3.5 vs -0.3; P<0.001 Evaluation of pain: -3.5 vs -0.1; P<0.001 Number of positive tender point: -4.6 vs -0.4; P<0.001 Sleeping difficulty: -2.6 vs -0.3; P=0.003 Feeling at awakening: -3.1 vs -0.6; P<0.001 Evaluation of fatigue: -3.5 vs -0.8; P=0.001 Morning stiffness: -22.8 vs -5.5; P=0.006 Percentage of patients with improvement in tiredness at awakening: 75% vs 9%; P<0.001 Percentage of patients with improvement in fatigue: 58% vs 18%; P=0.094

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Ginsberg, 1996 Belgium Fair	Sustained-Release Amitriptyline vs Placebo Percent of patients reporting AE: 29% vs 0%; P=0.010 Dryness of mouth: 6.5% vs 0% Digestive symptoms: 4.4% vs 0% Vertigo: 2.2% vs 0% Neuro-psychic symptoms: 4.4% vs 0%	Sustained-Release Amitriptyline vs Placebo Total withdrawals: 4.2% vs 13.6% Due to AE: 4.2% vs 0%	NR	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Giordano, 1999 Italy Fair	Outpatients with fibromyalgia syndrome according to the ARA criteria for ≥6 months.	A. Paroxetine 20 mg/d B. Placebo For 12 weeks	NR	31 years (SD 7.2) 100% female Ethnicity NR

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Giordano, 1999 Italy Fair	NR	40	11/NR/NR

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Giordano, 1999 Italy Fair	Paroxetine vs Placebo Patient's assessment of efficacy: Percent improvement in VAS at endpoint: 70% vs 2.1% Change from baseline in the weighted average tender points score: -2.25% (P<0.001) vs NR (NS) Investigator's assessment of efficacy: Percent much improved or improved: 68% vs 0% Percent slightly improved: 24% vs 4% No change: 8% vs 96% Efficacy of paroxetine correlated with the degree of anxiety (P=0.15), patient's degree of pain (P=0.12), stiffness (P=0.19) and overall condition (P=0.005)

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Giordano, 1999 Italy Fair	Paroxetine vs Placebo Investigator's overall assessment of tolerability, Very good or good: 82% vs 98% Patient's overall assessment of tolerability, Very good or good: 70% vs 18% Incidence of AE reported in Paroxetine treatment group only: Nausea: 50% Diarrhea: 40% Malaise: 30% Dry mouth: 25% Epigastric discomfort/dyspepsia: 25% Headache: 20% Sweating: 20% Insomnia: 10% Palpitation: 10% Drowsiness: 10% Reduced libido: 5% Anxiety: 5%	Paroxetine vs Placebo Total withdrawals: 15% vs 40% Due to AE: 15% vs 0%	NR	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Goldenberg, 1986 United States Fair	Patients who met the proposed clinical criteria for fibromyalgia, modified from those reported by Yunus et al: generalized aches and pain or prominent stiffness involving 3 or more anatomic sites for at least 3 months; absence of underlying causes, e.g. , direct or repetitive trauma or systemic disease; at least 6 typical and consistent moderately or severely tender points; a score of ≥4 on either the initial pain or global assessment analog scale; and at least 3 of the following: modulation of symptoms by physical activity, weather, anxiety, or stress, poor sleep, general fatigue or tiredness, anxiety, chronic headache, irritable bowel syndrome, or subjective swelling and numbness.	A: Naproxen 500 mg bid and amitriptyline 25 mg every night B: Naproxen 500 mg bid and placebo C: Amitriptyline 25 mg every night and placebo D: Double doses of placebo For 6 weeks	Two acetaminophen tablets (650 mg) every 4 hours if needed for severe pain (10% of patients stated they took acetaminophen during the trial)	43.8 years 95% female White: 87.1% Hispanic: 11.3% Black: 1.6%

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Goldenberg, 1986 United States Fair	Mean years of chronic pain: 3.5	62	4/2/1958

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Goldenberg, 1986 United States Fair	Naproxen 500 mg bid/Amitriptyline 25 mg vs Naproxen 500 mg bid vs Amitriptyline 25 mg vs Double Placebo Tender point score at endpoint: 8.3 (vs placebo P<0.05) vs 13.4 vs 11.7 vs 14.2 Patients' pain at endpoint (0 no pain - 10 very severe pain): 4.5 (vs placebo P<0.01) vs 8.2 vs 4.7 (vs placebo P<0.01) vs 7.7 Patient fatigue at endpoint (0 no fatigue - 10 extreme fatigue): 4.7 vs 8.0 vs 4.3 vs 7.5 Sleep difficulty at endpoint (0 no sleep difficulty - 10 severe sleep difficulty): 3.6 (vs placebo P<0.05) vs 8.2 vs 3.0 (vs placebo P<0.05) vs 6.7 Patient global assessment: 4.0 (vs placebo P<0.05) vs 7.8 vs 4.4 (vs placebo P<0.05) vs 8.0 Physician global assessment: 3.3 (vs placebo P<0.01) vs 7.3 vs 4.1 (vs placebo P<0.01) vs 8.7

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Goldenberg, 1986 United States Fair	Naproxen 500 mg bid/Amitriptyline 25 mg vs Naproxen 500 mg bid vs Amitriptyline 25 mg vs Double Placebo Dry mouth: 4 total (groups NR) Dyspepsia: 0 vs 1 vs 0 vs 1 Diarrhea: 0 vs 1 vs 0 vs 1 Total number of patients in each group NR, so percentages could not be calculated.	Naproxen 500 mg bid/Amitriptyline 25 mg vs Naproxen 500 mg bid vs Amitriptyline 25 mg vs Double Placebo Total withdrawals: 1 vs 1 vs 1 vs 1 Due to AE: 1 vs 0 vs 0 vs 1 Total number of patients in each group NR, so percentages could not be calculated.	Grants from the Arthritis Foundation, Multi-purpose Arthritis Center, and Syntex Co.	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Goldenberg, 1996 United States Poor	Patients between 18-60 years old with no concurrent or past history of systemic illness, a VAS score of ≥30 for pain, and a willingness to discontinue all central nervous system active medications, NSAIDs and analgesics at least one week prior to the study.	A: Placebo in the morning, 25 mg amitriptyline at bedtime B: 20 mg fluoxetine in the morning, placebo at bedtime C: 20 mg fluoxetine in the morning, 25 mg amitriptyline at bedtime D: Placebo both morning and bedtime For four 6 week trials each separated by a 2 week washout	NR	43.2 years (SD 9.1) 90.3% female Caucasian: 100%

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Goldenberg, 1996 United States Poor	Mean duration of fibromyalgia: 72.6 months (SD 48.1)	31	12/NR/NR

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Goldenberg, 1996 United States Poor	Amitriptyline vs Fluoxetine vs Amitriptyline/Fluoxetine vs Placebo Mean (SD) outcome measures at 6 weeks: FIQ: 52.3 (22.9) vs 47.6 (19.8) vs 38.0 (21.2) vs 58.5 (17.1); P=0.03 for amitriptyline vs placebo; P=0.006 for fluoxetine vs placebo VAS pain: 64.4 (28.3) vs 57.5 (25.7) vs 42.9 (28.5) vs 81.5 (16.5); P=0.02 for amitriptyline vs placebo; P<0.001 for fluoxetine vs placebo VAS global: 61.6 (29.5) vs 60.9 (24.9) vs 48.2 (29.7) vs 76.8 (24.8); P=0.02 for amitriptyline and fluoxetine vs placebo VAS sleep: 57.0 (34.8) vs 66.0 (26.6) vs 39.9 (29.2) vs 74.6 (23.9); P<0.001 for amitriptyline vs placebo; P=0.04 for fluoxetine vs placebo BDI: 8.7 (6.0) vs 7.8 (4.7) vs 7.4 (4.4) vs 9.3 (6.5); P=NS for fluoxetine and amitriptyline vs placebo Physician VAS: 64.2 (25.2) vs 68.0 (17.8) vs 55.5 (22.1) vs 74.7 (19.9); P=0.04 for amitriptyline vs placebo; P=0.08 for fluoxetine vs placebo VAS fatigue: 67.7 (29.9) vs 68.6 (24.1) vs 57.2 (31.6) vs 73.7 (25.1); P=NS for amitriptyline and fluoxetine vs placebo VAS refreshed: 69.6 (29.1) vs 67.2 (23.3) 59.4 vs vs 75.1 (25.9); P=NS for amitriptyline and fluoxetine vs placebo Tender point score: 18.0 (7.2) vs 20.3 (7.5) vs 16.4 (7.1) vs 19.0 (7.5); P=NS for amitriptyline and fluoxetine vs placebo

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Goldenberg, 1996 United States Poor	NR	Amitriptyline vs Fluoxetine vs Amitriptyline/Fluoxetine vs Placebo Total withdrawals: 1 (3.2%) vs 4 (12.9%) vs 5 (16.1%) vs 1 (3.2%) Due to AE: 0 (0%) vs 1 (3.2%) vs 3 (9.7%) vs 1 (3.2%) Withdrawals are classified by the treatment being taken at time of withdrawal.	NR	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Hannonen, 1998 Finland Fair	Female patients 18-65 years old who fulfilled the ACR 1990 criteria, had a minimum score of 4 on at least 3 of 4 self-administered VAS at baseline, and were not suffering from psychiatric disorders.	A: Moclobemide 150-300 mg bid (maximum dose 450 mg) + amitriptyline placebo B: Amitriptyline 12.5-37.5 mg at night + moclobemide placebo bid C. Placebo For 12 weeks Dosing schedule: If a patient tolerated the baseline treatment, the dose was increase at the 2 week check-up to the target dose of moclobemide 450 mg or amitriptyline 25 mg. If response was still unsatisfactory at the 6 week visit, the dose could be increased to moclobemide 600 mg or amitriptyline 37.5 mg.	Paracetamol 500 mg (up to 4 g/d) supplied by the sponser as escape medication. Use was statistically significantly greater (p=0.012) in placebo group than in other 2 groups. Paracetamol use, mean tablets/patient (SD) consumed during 84 day study period: Moclobemide: 52.6 (62.0) Amitriptyline: 40.0 (33.6) Placebo: 73.1 (53.8)	48.7 years (SD 8.6) 100% female Ethnicity NR

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Hannonen, 1998 Finland Fair	BMI: 27.4 kg/cm2 (SD 4.6) Symptomatic period: 8.2 years	130	38/NR/130

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Hannonen, 1998 Finland Fair	Moclobemide vs Amitriptyline vs Placebo Symptom improvement at 12 weeks: 54% vs 74% vs 49%; P=0.044 for amitriptyline vs moclobemide, P=0.017 for amitriptyline vs placebo, P=NS for moclobemide vs placebo CGIC at 12 weeks, mean (SD): 0.58 (1.40) vs 1.14 (1.05) vs 0.38 (1.42); P=0.046 for amitriptyline vs moclobemide, P=0.003 for amitriptyline vs placebo, P=NS for moclobemide and placebo VAS symptoms and findings, improvement from baseline: General health: 0.9 vs 1.4 vs 0.6; P<0.01 for moclobemide vs baseline, P<0.001 for amitriptyline vs baseline, P<0.05 for placebo vs baseline Pain: 1.2 vs 1.5 vs 0.5; P<0.05 for moclobemide vs baseline, P<0.01 for amitriptyline vs baseline Sleep: 0 vs 2.3 vs 0.7; P<0.001 for amitriptyline vs baseline, P<0.001 for placebo vs baseline Fatigue: 0.4 vs 1.3 vs 1; P<0.01 for amitriptyline vs baseline, P<0.05 for placebo vs baseline Number of tender points: 1.8 vs 1.4 vs 1.3; P<0.001 for all groups vs baseline Physician's CGIS: 0.51 vs 0.55 vs 0.35; P<0.001 for all groups vs baseline Nittingham Health Profile dimensions, improvement from baseline: Mobility: 2.7 vs 2.3 vs -0.7 Energy: 7.7 vs 17 vs 9.1;P<0.001 for amitriptyline vs other groups Pain: 16.4 vs 14.8 vs 4.6; P<0.001 for moclobemide, P<0.01 for amitriptyline Emotions: -1.5 vs 3.8 vs 2.5; P<0.01 for amitriptyline vs other groups Sleep: 2.1 vs 20.1 vs 7.2; P<0.001 for amitriptyline vs other groups Social: 0.2 vs 1.7 vs 0.6 Sheehan's functional scale areas, improvement from baseline: Work: 0.1 vs 1.3 vs 0.1; P<0.001 for amitriptyline vs other groups Social: 0.6 vs 0.9 vs 0.2; P<0.01 for amitriptyline vs other groups Family: 0.4 vs 1 vs 0.1; P<0.01 for amitriptyline vs other groups

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Hannonen, 1998 Finland Fair	Moclobemide vs Amitriptyline vs Placebo Percent of patients with at least 1 AE: 77% vs 74% vs 80% Percent of patients with possible or probable drug related AE: 58% vs 43% vs 53% AEs with possible causal relationship to medication: Moclobemide group: headache, difficulities in falling asleep Amitriptyline group: dry mouth, fatigue Placebo group: fatigue, headache 4 serious AEs reported including one hospitalization due to vasovagal collapse who was taking taking amitriptyline CGI of tolerabilities, mean (SD) (1=poor, 4=very good): 2.72 (1.10) vs 2.90 (1.05) vs 3.64 (1.07); P=NS	Moclobemide vs Amitriptyline vs Placebo Total withdrawals: 13 (30.2%) vs 10 (23.8%) vs 15 (33.3%) Due to AE: 6 (14%) vs 5 (11.9%) vs 5 (11.1%)	Roche Oy, Finland	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Heymann, 2001 Brazil Fair	Female patients >18 years old, meeting the ACR 1990 criteria for fibromyalgia, and not suffering from heart arrhythmia; heart, renal or hepatic impairment; glaucoma, urinary retention, hyperthyroidism or chronic inflammatory diseases.	A: Amitriptyline 25 mg/d B: Nortriptyline 25 mg/d C. Placebo For 8 weeks	Acetaminophen	50.6 years 100% female Caucasian: 61.9% Other: 38.1%

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Heymann, 2001 Brazil Fair	Number of tender points: 16.2	118	12/NR/106

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Heymann, 2001 Brazil Fair	Amitriptyline vs Nortriptyline vs Placebo FIQ scores post treatment, mean (SE): 39.97 (6.54) vs 48.7 (7.28) vs 51.68 (7.98); P<0.05 vs baseline for all groups Percent improvement: 36.5% vs 26.6% vs 24% Number of tender points post treatment, mean (SE): 14.2 (0.7) vs 13.3 (0.9) vs 14.7 (0.6); P<0.05 vs baseline for all groups Percent decrease in number of tender points: 13.9% vs 19.5% vs 8.6% Percentage of patients with improvement in verbal evaluation scale for global improvement: 86.5% vs 72.2% vs 54.5%; Significant difference among study groups P=0.0363, improvement in amitriptyline vs placebo P=0.00981

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Heymann, 2001 Brazil Fair	Amitriptyline vs Nortriptyline vs Placebo % of AE: 40% vs 81.6% vs 62.5% Abdominal pain: 10% vs 18.4% vs 12.5% Sleepiness: 2.5% vs 2.6% vs 5.0% Dizziness: 5.0% vs 10.5% vs 10.0% Nausea: 2.5% vs 2.6% vs 5.0% Weight gain: 2.5% vs 05 vs 0% Palpitation: 0% vs 7.9% vs 5% Apathy: 2.5% vs 5.3% vs 0% Migraine: 0% vs 5.3% vs 5.0%	Amitriptyline vs Nortriptyline vs Placebo Total withdrawals: 7.5% vs 5.3% vs 17.5% Due to AE: 0% vs 5.3% vs 2.5%	NR	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Mease, 2008 United States Fair	Adults meeting ACR criteria for fibromyalgia and had an average pain score of ≥4 on an 11 point numeric rating scale during baseline assessment and reported a score of ≥40 on the 100 mm VAS of the SF-MPQ at both screening and randomization visits. Must have discontinued any use of SMRs, antidepressants, antiepileptic drugs, corticosteroids, benzodiazepines, opioid narcotics, mexiletine, and anti-Parkinson's disease medications ≥7 days before screening visit, tender point injections and fluoxetine ≥30 days before, tramadol, dextromethorphan and NSAID ≥2 days before and zolpidem and diphenhydramine ≥1 day before.	A: Pregabalin 300, 450, or 600 mg/d B: Placebo For 13 weeks Dosing schedule: Pregabalin patients began with 150 mg/day and escalated dosage to fixed dose of 300mg, 450mg and 600mg/day within first week of treatment, administered twice daily.	Aspirin ≤325/d for cardiac prophylaxis, acetaminophen ≤4 g/d as rescue medication	49 years 94% female Caucasian: 90.2% Black: 4.6% Hispanic: 4.4% Other: 0.8%

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Mease, 2008 United States Fair	Postmenopausal women: 58.2% Mean BMI: 30.5 Mean duration of fibromyalgia prior to baseline: 111.7 (SD 94.7) Number of painful tender points mean: 17.1 (SD 1.6)	751	263/25/748

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Mease, 2008 United States Fair	Placebo vs Pregabalin 300 mg vs Pregabalin 450 mg vs Pregabalin 600 mg Pain score, change from baseline: -1.40 vs -1.84 (Difference vs placebo: -0.43, P=0.0449) vs -1.87 (Difference vs placebo: -0.47, P=0.0449) vs -2.06 (Difference vs placebo: -0.66, P=0.0070) PGIC, any improvement: 56.1% vs 70.8% vs 72.2% vs 68.6%; P≤0.05 vs placebo FIQ total score, change from baseline:-13.66 vs -16.15 (Difference vs placebo: -2.48) vs -15.71 (Difference vs placebo: -2.05) vs -14.88 (Difference vs placebo: -1.21) Mean sleep quality score, change from baseline: -1.32 vs -2.19 (Difference vs placebo: -0.86, P=0.0001) vs -2.29 (Difference vs placebo: -0.97, P<0.0001) vs -2.53 (Difference vs placebo: -1.21, P<0.0001)

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Mease, 2008 United States Fair	Placebo vs Pregabalin 300mg vs Pregabalin 450mg vs Pregabalin 600mg Patients reporting AE: 76% vs 89% vs 92% vs 94% Dizziness: 8.4% vs 32.4% vs 43.7% vs 46.3% Somnolence: 5.3% vs 21.1% vs 24.0% vs 27.9% Weight gain: 2.6% vs 8.1% vs 8.7% vs 13.7% Dry mouth: 2.1% vs 7.6% vs 10.4% vs 10.5% Nausea: 5.8% vs 4.9% vs 4.4% vs 10.5% Amblyopia: 1.6% vs 6.5% vs 6.6% vs 8.9% Thinking abnormal: 1.1% vs 8.1% vs 6.6% vs 8.9% Constipation: 0.5% vs 4.9% vs 6.6% vs 8.4% Headache: 6.3% vs 8.1% vs 9.3% vs 7.9% Increased appetite: 1.6% vs 2.2% vs 8.2% vs 7.9% Amnesia: 2.1% vs 2.7% vs 3.8% vs 7.4% Euphoria: 2.6% vs 3.2% vs 6.0% vs 7.4% Ataxia: 0.5% vs 1.6% vs 4.4% vs 6.8% Asthenia: 2.6% vs 7.0% vs 5.5% vs 5.8% Incoordination: 0.0% vs 2.7% vs 3.8% vs 5.3% Nervousness: 1.1% vs 1.1% vs 0.0% vs 5.3% Peripheral edema: 1.1% vs 2.7% vs 2.2% vs 5.3%	Placebo vs Pregabalin 300 mg vs Pregabalin 450 mg vs Pregabalin 600 mg Total withdrawals: 60 (31.6%) vs 62 (33.5%) vs 62 (66.1%) vs 79 (41.6%) Due to AE: 19 (10%) vs 35 (18.9%) vs 41 (22.4%) vs 62 (32.6%)	Pfizer Global Research & Development	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Norregaard, 1995 Denmark Fair	Patients who had fulfilled the ACR criteria for fibromyalgia during the previous year, with no earlier diagnosis of endogenous depression or received antidepressant medication or monoamine oxidase inhibitors.	A: Citalopram 20-40 mg B: Placebo For 8 weeks Dosing schedule: Citalopram patients took 20 mg/d for 4 weeks, and if the subject did not report marked improvement the dosage was increased to 40 mg/d for the next 4 weeks.	Acetaminophen, codeine and NSAIDs	49 years (SD 9) Gender NR Ethnicity NR

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Norregaard, 1995 Denmark Fair	Weight: 72 kg (SD 14) Height: 167.5 cm (SD 6.9) Symptom duration: 10 years (SD 9.5) Concomitant diagnosis: Rheumatic: 11.9% Hypothyroidism tractata: 4.8% Other: 4.8% Daily concomitant medication: Acetaminophen: 23.8% Codeine: 14.3% NSAIDs: 9.5%	43	9/1/42

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Norregaard, 1995 Denmark Fair	Citalopram vs Placebo Self-assessments (0-10), change (SD): Pain: -1 (2.1) vs -0.7 (1.1); 95% CI, -1.6 to 1.0 Fatigue: -0.5 (2.2) vs -0.1 (2.0); 95% CI, -1.8 to 0.9 General condition: -0.9 (2.3) vs -0.6 (2.1); 95% CI, -1.7 to 1.0 Sleep: 1.0 (2.9) vs 0.1 (2.5); 95% CI, -0.8 to 2.7 Tender point count (0-18): 0.1 (1.6) vs - 1.1 (2.1); 95% CI, -0.2 to 2.1 Beck score (0-63): 1.0 (6.1) vs 0.9 (7.9); 95% CI, -5.1 to 5.4 FIQ Physical function (0-3): 0.0 (0.4) vs 0.0 (0.4); 95% CI, -0.3 to 0.3

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Norregaard, 1995 Denmark Fair	Citalopram vs Placebo Dry mouth: 5% vs 10% Nausea/vomiting: 5% vs 5% Fatigue: 0% vs 5% Sleep disturbance: 0% vs 5% Headache: 24% vs 24%	Total withdrawals: unclear (9 total, implied that they were all in the citalopram group) Due to AE: unclear (9 total, implied that they were all in the citalopram group)	H. Lundbeck A/S	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Patkar, 2007; Pae, 2009 United States Fair	Men and women 18-65 years old fulfilling the ACR criteria for fibromyalgia, with a VAS pain score ≥5 and a BDI score of ≤23 at screening and placebo lead-in visits.	A. Paroxetine CR 12.5-62.5 mg/d (mean dose 39.1±8.6 mg/d) B. Placebo For 12 weeks	Acetaminophen up to 4 g/d, ibuprofen up to 1.2 g/day Concomitant medications consumed by 28% of patients in paroxetine CR vs 37% of placebo patients, P=0.31.	48.5 years 94% female Ethnicity NR

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Patkar, 2007; Pae, 2009 United States Fair	Duration of fibromyalgia >5 years: 51%	116	30/11/116

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Patkar, 2007; Pae, 2009 United States Fair	Paroxetine CR vs Placebo Response rates: 56.8% vs 32.7%; χ2 (Breslow)=15.75, P=0.01 ≥50% reduction in FIQ: 25.8% vs 13.7%, χ2 (Breslow)=6.42, P=0.08 Mean treatment difference in FIQ -6.4 in favor of paroxetine CR (95% CI, -11.4 to 0.9; P<0.05; between group difference reached statistical significance (P<0.05) during 6-12 weeks) FIQ subscales, fatigue, anxiety, days felt good: paroxetine CR better than placebo P<0.05 (data NR) Trend favoring paroxetine CR for pain (P=0.07) and depression (P=0.08) (data NR) CGIC scores: Paroxetine CR better than placebo F=13.47, P<0.005 (data NR) CGIC score 1 (very much better) or 2 (much better) considered responders: 56.8% vs 25.8%; χ2=15.11, P<0.01 CGIS scores did not differ significantly between groups, P=0.08 (data NR) Change in VAS from baseline, mean (SD): -12.2 (18.5) vs -8.8 (16.6); P=0.16 Percent of patients with ≥25% or ≥50% reduction in VAS from baseline to endpoint: NSD between groups. Comparison between drug and placebo on tender point counts, the Tender Point Index or the Sheehan Disability Scale Scores: P=NS (data NR) History of depression and/or anxiety as defined by ≥25% reduction in FIQ did not predict a treatment response (OR=0.66; 95% CI, 0.29 to 1.49; Wald=0.97; P=0.32), while paroxetine CR significantly predicted a treatment response (OR 2.57; 95% CI, 1.2 to 5.61; Wald=5.5; P=0.02) No significant interaction between the treatment and history of depression and/or anxiety disorders (P=0.36) NSD in percent of responders with ≥25% reduction in FIQ between subjects with depression (49.1%) and without history of depression and/or anxiety disorders (41%), P=0.22 NSD in proportion of responders by drug group in subjects with or without a history of depression and/or anxiety disorders; responders to paroxetine CR with depression/anxiety history 54.5%, no history 45.5%, P=0.43, responders to placebo with depression/anxiety history 57.8%, no history 42.1%, P=0.018

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Patkar, 2007; Pae, 2009 United States Fair	Paroxetine CR vs Placebo TEAEs: 65.5% vs 58.6% TEAEs occurring in >5% of patients: Drowsiness: 26% vs 7% Dry mouth: 36% vs 9% Female genital disorders*: 9% vs 2% Ejaculatory problems*: 66% vs 2% Impotence*: 33% vs 0% Headaches: 31% vs 26% Sleeplessness: 17% vs 9% Anxiety: 14% vs 7% Nausea: 14% vs 9% Diarrhea: 9% vs 12% Tremors: 5% vs 3% Blurred vision: 5% vs 0% * corrected for gender	Paroxetine CR vs Placebo Total withdrawals: 34.5% vs 17.2% Due to AE: 6.9% vs 1.7%	GlaxoSmithKline	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Pfizer, 2008 (Unpublished) Multiple continents and countries Fair	Males or females aged ≥18 years who met the ACR criteria for fibromyalgia, had a pain VAS score ≥40 mm and at least four pain diaries completed satisfactorily within the previous 7 days with an average pain score ≥4.	A: Pregabalin 150 mg bid (300 mg/d) B: Pregabalin 225 mg bid (450 mg/d) C: Pregabalin 300 mg bid (600 mg/d) D: Placebo For 14 weeks (2-week titration phase plus 12-week fixed-dose phase) Dosing schedule: All pregabalin treatment groups began with a dose of 150 mg/d and titrated to the randomized dose within the first 2 weeks.	NR	48.5 years 91% female White: 76%

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Pfizer, 2008 (Unpublished) Multiple continents and countries Fair	Percent of women post-menopausal: 52%	747	217/7/735

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Pfizer, 2008 (Unpublished) Multiple continents and countries Fair	Placebo vs Pregabalin 300 mg/day vs Pregabalin 450 mg/day vs Pregabalin 600 mg/day Endpoint Mean Pain Scores: 5.93 vs 5.60 vs 5.39 vs 5.70 Endpoint Pain Scores Mean Change: -0.72 vs -1.05 (Difference -0.34; 95% CI, -0.72 to 0.05; P=0.0841) vs -1.26 (Difference -0.54; 95% CI, -0.92 to -0.16; P=0.0055) vs -0.95 (Difference -0.23; 95% CI, -0.61 to 0.15; P=0.2339) Subjects with ≥30% decrease in mean pain score from baseline to endpoint: 19% vs 32% vs 33% vs 26% Subjects with ≥50% decrease in mean pain score from baseline to endpoint: 9% vs 18% vs 18% vs 15% PGIC at Endpoint: Very much improved: 7 (4.1%) vs 13 (8.0%) vs 16 (9.7%) vs 20 (12.9%) Much improved: 43 (25.4%) vs 45 (27.8%) vs 50 (30.3%) vs 46 (29.7%) Minimally improved: 45 (26.6%) vs 50 (30.9%) vs 55 (33.3%) vs 41 (26.5%) No change: 43 (25.4%) vs 27 (16.7%) vs 27 (16.4%) vs 25 (16.1%) Minimally worse: 11 (6.5%) vs 9 (5.6%) vs 7 (4.2%) vs 10 (6.5%) Much worse: 17 (10.1%) vs 13 (8.0%) vs 8 (4.8%) vs 10 (6.5%) Very much worse: 3 (1.8%) vs 5 (3.1%) vs 2 (1.2%) vs 3 (1.9%) Comparison of Pregabalin Treatment Groups to Placebo, p-Values: N/A vs 0.0539 vs 0.0017 vs 0.0227

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Pfizer, 2008 (Unpublished) Multiple continents and countries Fair	Placebo vs Pregabalin 300 mg/day vs Pregabalin 450 mg/day vs Pregabalin 600 mg/day Dizziness: 23 (12.5%) vs 67 (36.6%) vs 70 (38.5%%) vs 90 (48.4%) vs 227 (41.2%) Somnolence: 10 (5.4%) vs 36 (19.7%) vs 23 (12.6%) vs 33 (17.7%) vs 92 (16.7%) Weight Increased: 6 (3.3%) vs 23 (12.6%) vs 23 (12.6%) vs 24 (12.9%) vs 70 (12.7%) Peripheral Edema: 5 (2.7%) vs 16 (8.7%) vs 12 (6.6%) vs 22 (11.8%) vs 50 (9.1%) Dry Mouth: 4 (2.2%) vs 14 (7.7%) vs 19 (10.4%) vs 20 (10.8%) vs 53 (9.6%) Disturbance in Attention: 3 (1.6%) vs 10 (5.5%) vs 11 (6.0%) vs 15 (8.1%) vs 36 (6.5%) Fatigue: 10 (5.4%) vs 11 (6.0%) vs 26 (14.3%) vs 14 (7.5%) vs 51 (9.3%) Vertigo: 3 (1.6%) vs 12 (6.6%) vs 11 (6.0%) vs 14 (7.5%) vs 37 (6.7%) Vision Blurred: 1 (0.5%) vs 5 (2.7%) vs 7 (3.8%) vs 11 (5.9%) vs 23 (4.2%) Constipation: 7 (3.8%) vs 12 (6.6%) vs 9 (4.9%) vs 10 (5.4%) vs 31 (5.6%) Nausea: 12 (6.5%) vs 20 (10.9%) vs 4 (2.2%) vs 10 (5.4%) vs 34 (6.2%) Headache: 22 (12.0%) vs 15 (8.2%) vs 12 (6.6%) vs 9 (4.8%) vs 36 (6.5%) Additionally, there was one report of each of these serious AEs potentially (though unlikely) caused by the study drug: Placebo group: Detached biceps muscle left arm; gastroenteritis salmonella Pregabalin group: Laceration of skin, artery and vein - lower inside right arm; right renal calculus; chest pain; elbow sprain; pneumonia; fall; gallbladder stone; herpes zoster	Placebo vs Pregabalin 300 mg/day vs Pregabalin 450 mg/day vs Pregabalin 600 mg/day Total withdrawals: 43 (23.4%) vs 60 (32.8%) vs 49 (26.9%) vs 65 (35%) Due to AE: 23 (12.5%) vs 36 (19.7%) vs 38 (20.9%) vs 47 (25.3%)	Pfizer	Subjects who demonstrated a high response (≥30% decrease on the pain VAS) to placebo were discontinued from the study at the end of the run-in phase. The primary efficacy measure for the first objective was the endpoint mean pain score derived from the subject's daily pain diary. If the first objective was positive, the PGIC was assessed to meet the second objective.

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Quimby, 1989 United States Fair	Patients who met the following criteria: the presence of aches, pains and stiffness at 3 or more sites for 3 or more months; absence of secondary causes (normal laboratory and radiographic findings); 5 or more tender points by dolorimeter (or 3 or more tender points plus 5 minor criteria); 3 minor criteria (or 5 if 3 tender points, i.e., modulation of symptoms by physical activity, modulation of symptoms by weather factors, aggravation of symptoms by anxiety or stress, poor sleep, general fatigue or tiredness, anxiety, chronic headache, irritable bowel syndrome, subjective swelling, and numbness.	A: Cyclobenzaprine 10-40 mg B: Placebo Dosing schedule: 10 mg before bedtime, to be increased by 10 mg/week to a maximum of 40 mg (30 mg at bedtime and 10 mg in the morning).	NSAIDs and salicylates prescribed for reasons other than fibromyalgia, continued at a steady dose.	45 years 100% female Ethnicity NR

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Quimby, 1989 United States Fair	Duration of pain: 11.4 years Mean number of tender points: 7	45	5/0/40

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Quimby, 1989 United States Fair	Cyclobenzaprine vs Placebo Patient rated overall (P<0.05): Got worse: 1 (4.8%) vs 4 (21.1%) No change: 6 (28.6%) vs 8 (42.1%) Mild improvement: 1 (4.8%) .vs 3 (15.8%) Moderate improvement: 4 (19%) vs 1 (5.3%) Marked improvement: 9 (42.9%) vs 3 (15.8%) Physician rated overall (P<0.01): Got worse: 0 (0%) vs 4 (21.1%) No change: 5 (23.8%) vs 8 (42.1%) Mild improvement: 3 (14.3%) vs 3 (15.8%) Moderate improvement: 8 (38.1%) vs 1 (5.3%) Marked improvement: 5 (23.8%) vs 3 (15.8%) Patient rated stiffness and aching (P<0.05): Got worse: 0 (0%) vs 2 (10.5%) No change: 9 (42.9%) vs 11 (57.9%) Mild improvement: 3 (14.3%) vs 3 (15.8%) Moderate improvement: 4 (19%) vs 1 (5.3%) Marked improvement: 5 (23.8%) vs 2 (10.5%) Patient rated fatigue: Got worse: 3 (14.3%) vs 3 (15.8%) No change: 10 (47.6%) vs 11 (57.9%) Mild improvement: 2 (9.5%) vs 2 (10.5%) Moderate improvement: 5 (23.8%) vs 2 (10.5%) Marked improvement: 1 (4.8%) vs 1 (5.3%) Patient rated muscle pain: Got worse: 1 (4.8%) vs 4 (21.1%) No change: 6 (28.6%) vs 7 (36.8%) Mild improvement: 4 (19%) vs 4 (21.1%) Moderate improvement: 4 (19%) vs 1 (5.3%) Marked improvement: 6 (28.6%) vs 3 (15.8%) Patient rated poor sleep (P<0.05): Got worse: 2 (9.5%) vs 3 (15.8%) No change: 6 (28.6%) vs 10 (52.6%) Mild improvement: 2 (9.5%) vs 4 (21.1%) Moderate improvement: 5 (23.8%) vs 1 (5.3%) Marked improvement: 6 (28.6%) vs 1 (5.3%) Frequency of prescription identification: Physician guess correct: 80.9% vs 73.6% Patient guess correct: 71.4% vs 63.2%

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Quimby, 1989 United States Fair	Cyclobenzaprine vs Placebo Dry mouth: 13 (68.4%) vs 6 (33.3%) 1 patient in cyclobenzaprine group discontinued due to dizziness, and 1 patient in placebo group discontinued due to a believed allergic reaction to study medication. (Data NR.)	Cyclobenzaprine vs Placebo Total withdrawals: 2 (8.7%) vs 3 (13.6%) Due to AE: 1 (4.3%) vs 1 (4.5%)	Merck Sharp & Dohme, and the Maine Chapter of the Arthritis Foundation	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Reynolds, 1991 Canada Fair	Presence of diffuse aching, fatigue and non restorative sleep pattern and the presence of 7 or more of 16 tender fibrositic points in the absence of clinical, biochemical or serological evidence of another underlying disorder.	A. Cyclobenzaprine-start dose 10 mg tid (max dose 10 mg qid) B. Placebo For 8 weeks total (two 4 week treatment periods) and 2 week washout period	None during treatment periods.	43 years 83% female Ethnicity NR

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Reynolds, 1991 Canada Fair	Tender point severity count at baseline (16-80): 38.4 (SD 4.4)	12	3/NR/NR

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Reynolds, 1991	Placebo vs Cyclobenzaprine, mean (SD)
Canada	Evening Dolorimeter: 220.5 (83.4) vs 212.9 (101.6)
	Morning Dolorimeter: 220.7 (71.5) vs 220.8 (89.1)
Fair	Evening Fatigue (1-7): 5.1 (1.3) vs 4.4 (1.1); F=4.7, P<0.05 (for cyclobenzaprine)
	Morning Fatigue: 5.0 (1.2) vs 4.5 (1.4)
	Evening Sleepiness (1-7): 4.2 (1.6) vs 3.7 (1.0)
	Morning Sleepiness: 3.8 (1.2) vs 3.8 (1.4)
	Evening Pain (0-60): 20.3 (15.0) vs 18.0 (12.7)
	Morning Pain: 22.0 (14.9) vs 22.1 (13.8)
	Tender point severity count (16-80): 36.3 (15.1) vs 39.5 (8.8)
	Total sleep time (hours): 7.0 (1.4) vs 7.3 (1.2); F=4.4, P<0.05 (for cyclobenzaprine)
	% stage 1: 7.3 (6.0) vs 5.4 (3.2)
	% stage 2: 51.2 (20.3) vs 56.9 (6.2)
	% slow wave sleep: 17.0 (16.3) vs 13.5 (8.2)
	% REM: 14.8 (8.5) vs 19.1 (5.4)
	Latency stage 2 (mins): 21.1 (15.0) vs 26.4 (24.3)
	Latency REM (mins): 151.9 (101.0) vs 103.8 (54.1)
	Sleep efficiency (%): 87.5 (15.2) vs 92.2 (5.9)

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Reynolds, 1991 Canada Fair	NR (one patient dropped for nocturnal myoclonus found at baseline washout, 1 patient withdrew for taking study medication inconsistently as the patient had sore throat and influenza, third patient withdrew due to excessive sleepiness).	Placebo vs Cyclobenzaprine Total withdrawals: 2 (16.7%) vs 0 (0%); additionally, 1 patient withdrew following baseline washout Due to AE: NR	Merck, Sharpe and Dolme, Canada	

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Scudds, 1989 Canada Fair	Patients with primary fibrositis syndrome according to criteria proposed by Smythe and Moldofsky: 1) widespread muscular aching lasting at least 3 months, 2) a nonrestorative sleep pattern, 4) morning stiffness and fatigue, 5) localized tenderness at 12 or more of 14 specified sites, 6) normal erythrocyte sedimentation rates, thyroid stimulating hormone levels and roentgenograms.	A: Amitriptyline 10-50 mg/d B: Placebo For 10 weeks (two 4-week treatment periods separated by a 2-week washout period) Dosing schedule: Amitriptyline treatment: Week 1: 10 mg/d at bedtime Week 2: 25 mg/d Weeks 3-4: 50 mg/d Double-blind crossover study Group 1: received amitriptyline for the first period of 4 weeks, followed by a 2-week washout period, and then a second period of 4 weeks during which time they received placebo. Group 2: followed the same schedule as group 1 except that they received placebo in the first period and amitriptyline in the second period.	Acetaminophen	39.9 years (SD 10.2) 88.9% female Ethnicity NR

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Other population characteristics	N	Number withdrawn/ lost to fu/analyzed
Scudds, 1989 Canada Fair	Duration of pain: 5.1 years (SD 4.6)	39	3/0/36

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Efficacy/Effectiveness Outcomes
Scudds, 1989 Canada Fair	Amitriptyline vs Placebo Patient ratings of global treatment efficacy: Worse: 3 (8.3%) vs 9 (24.3%) Unchanged: 6 (16.7%) vs 20 (54.1%) Minimally improved: 7 (19.4%) vs 5 (13.5%) Moderately improved: 12 (33.3%) vs 2 (5.4%) Markedly improved: 8 (22.2%) vs 1 (2.7%) Patients reporting improvement, amitriptyline vs placebo p<0.001 For pain rating, pain levels were significantly lower after the amitriptyline period than at any other time (P<0.05) Post hoc contrasts showed that total myalgic score was significantly higher after amitriptyline than at any other time (P<0.01)

Evidence Table 1. Data abstraction of fibromyalgia trials

Author Year Country Trial Name Quality Rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Scudds, 1989 Canada Fair	1 patient in the amitriptyline first group and 1 patient in the placebo first group withdrew due to drowsiness. Otherwise, NR.	Amitriptyline first group vs Placebo first group Total withdrawals: 1 vs 2 Due to AE: 1 vs 1 *Note:* Did not report in which phase of the study participants were in when these withdrawals occurred.	The Arthritis Society Studentship S-198 to R.A. Scudds and NSERC Grant AO 392 to G.B. Rollman	

Evidence Table 2. Quality assessment of fibromyalgia trials

	Internal Validity						
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Anderberg, 2000	Unclear, "randomization was made"	Unclear, "patients were given consecutive codes"	Unclear, only reported comparability on depressive and pain symptoms	Yes	Unclear, described as double-blind	Yes	Yes
Arnold, 2002	Unclear	Unclear	Unclear; more married in fluoxetine group (77% vs 50%, *P*= 0.06)	Yes	Unclear, described as double-blind	Yes	Yes
Arnold, 2004	Yes	Unclear	Yes	Yes	Yes (double blind)	Yes (double blind)	Yes
Arnold, 2005	Unclear	NR	Yes	Yes	Unclear (double blind)	Unclear (double blind)	Unclear
Arnold, 2007	NR	NR	No Drug group had significantly lower average pain interference score & higher SF-36 Bodily pain score	Yes	NR	Implied - double-blind, placebo controlled design	Implied - double-blind, placebo-controlled design
Arnold, 2008	Yes	NR	Yes	Yes	Yes (implied double blind)	Yes (implied double blind)	Yes
Arnold, 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ataoglu, 1997	Unclear	Unclear	Unclear, baseline characteristics only reported for analyzed group (90%)	Yes	Unclear, blinding NR	Unclear, blinding NR	Unclear, blinding NR
Bennett, 1988	Unclear	Unclear	Unclear	Yes	Unclear, described as double-blind	Yes	Yes

Evidence Table 2. Quality assessment of fibromyalgia trials

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality Rating
Anderberg, 2000	Yes	Unclear	NR, NR, NR	Yes (12.5%) Unclear	Fair
Arnold, 2002	No, excluded 15%	Unclear	NR, NR, NR	No=38% Yes=37% for fluoxetine, 40% for placebo	Fair
Arnold, 2004	Yes	Yes	Yes	No	Fair
Arnold, 2005	Yes	Yes	Unclear	No	Fair
Arnold, 2007	Yes	Yes	NR, NR, NR	Yes, Yes	Fair
Arnold, 2008	Yes, LOCF 5/750 excluded from analysis=0.6%	Yes	Unclear, Unclear, Unclear	Yes, Yes	Fair
Arnold, 2010	Yes	Yes	NR	No	Fair
Ataoglu, 1997	No, excluded 10%	Yes	Unclear, Unclear, Unclear	Overall: Yes=10% Between-groups: paroxetine=6%, amitriptyline=15%	Fair
Bennett, 1988	Yes	Yes	Unclear, Unclear, Unclear	Overall: No (47%) Between-group: cyclobenzaprine=35%, placebo=60%, $P<0.05$	Fair

Evidence Table 2. Quality assessment of fibromyalgia trials

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Branco, 2010	Unclear	NR	Yes	Yes	Yes (double blind)	Yes (double blind)	Yes
Carette, 1986	Unclear	NR	NR	Yes	Unclear (double blind)	Unclear (double blind)	Yes
Carette, 1994	Yes	Unclear	Unclear; median duration of fibromyalgia lower in cyclobenzaprine group (36 months) compared to other groups (60 months), but difference not statistically significant	Yes	Unclear, described as double-blind	Yes	Yes
Carette, 1995	Yes	Unclear	Unclear	Yes	Unclear, described as double-blind	Yes	Yes
Chappell, 2008	Yes	NR	Yes	Yes	Yes (double blind)	Yes (double blind)	Unclear
Clauw, 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of fibromyalgia trials

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality Rating
Branco, 2010	Yes, LOCF. 1 excluded from efficacty analysis due to missed baseline data and 7 from safety (4 due to practice concerns at 1 center and 3 as did not receive any study med)	Yes	Yes	No	Fair
Carette, 1986	No	No (placebo had longer duration of fibromyalgia)	Yes	Yes	Fair
Carette, 1994	No, excluded 24/208 (11%)	Unclear	NR, Yes, Yes	No (25%) No; amitriptyline=16.7%, cyclobenzaprine=29.3%, placebo=33.3%	Fair
Carette, 1995	No, excluded 2/22 (9%)	Unclear	Unclear, Yes, Unclear	Yes, Yes	Fair
Chappell, 2008	Yes	Yes	Yes	No	Fair
Clauw, 2008	Yes (LOCF)	Yes	NR	No	Fair

Evidence Table 2. Quality assessment of fibromyalgia trials

	Internal Validity						
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Crofford, 2005; Arnold, 2007	Yes	NR	Yes	Yes	NR	Implied - double blind, placebo-controlled design	Implied - double blind, placebo-controlled design
Crofford, 2008	Unclear, described as telerandomization	NR	Yes	Yes	NR	Implied - double blind, placebo-controlled design	Implied - double blind, placebo-controlled design
Ginsberg, 1996	Unclear	Unclear	Unclear, excluded 5 (11%) who were lost to follow-up	Yes	Unclear, described as double-blind	Yes	Yes
Giordano, 1999	Unclear; "separated into 2 groups according to a randomization list"	Unclear	Unclear, data NR	Yes	Unclear, described as single-blind	Unclear, described as single-blind	Unclear, described as single-blind
Goldenberg, 1986	Unclear	Unclear	Unclear; data NR, but statement of "no significant differences with respect to race, duration of fibromyalgia symptoms, prevalence of sleep disturbances, or morning tirednes", "neither the tender point score nor any other outcome measure differed significant between groups at study onset"	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of fibromyalgia trials

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality Rating
Crofford, 2005; Arnold, 2007	Yes	Yes	Unclear, Unclear, Unclear	Yes, Yes	Fair
Crofford, 2008	Yes	Yes	Yes, Unclear, Unclear	Overall=Yes Between-groups=No, Pregabalin 300mg/day:52%, 450mg/day: 67%, 600mg/day: 63%, placebo: 81%	Fair
Ginsberg, 1996	No, excluded 5/51 (11%)	Yes	NR, Yes, Yes	Yes, Yes	Fair
Giordano, 1999	Yes	Unclear	NR, NR, NR	No=27.5% No=15% for paroxetine and 40% for placebo	Fair
Goldenberg, 1986	Unclear	Yes, excluded 3%	NR, Yes, NR	Yes, Yes	Fair

Evidence Table 2. Quality assessment of fibromyalgia trials

	Internal Validity						
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Goldenberg, 1996	Yes	Yes	Unclear, crossover study but characteristics only reported for overall group	Yes	Unclear, described as double-blind	Yes	Yes
Hannonen, 1998	Yes	Yes	Yes	Yes	Yes (implied double blind)	Tes (implied double blind)	Yes
Heymann, 2001	Yes	Unclear	Unclear, no statistical differences, but fewer Caucasians in nortriptyline group (55%) vs amitriptyline and placebo groups (65% in both) and duration of illness NR	Yes	Unclear, described as double-blind	Yes	Yes
Mease, 2008	Unclear	NR	Yes	Yes	Yes (implied double blind)	Yes (implied double blind)	Yes (implied double blind)
Mease, 2009	Unclear	NR	Yes	Yes	Unclear	Unclear	Yes
Norregaard, 1995	Unclear	Unclear	Yes	Yes	Unclear, described as double-blind	Yes	Yes
Patkar, 2007; Pae, 2009	Yes	Yes	Yes	Yes	Unclear, described as double-blind	Yes	Yes

Evidence Table 2. Quality assessment of fibromyalgia trials

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality Rating
Goldenberg, 1996	No, excluded 29% to 39%, depending on outcome	Unclear	NR, NR, NR	No=39% No=4 while receiving fluoxetine, 1 while receiving amitriptyline, 5 while receiving both, and 1 with placebo	Poor
Hannonen, 1998	Yes	Unclear	Yes, Yes, Yes	Overall - NO (29%) Between grous - Yes (moclobemid 30%, amitriptyline 23%, Placebo 33%)	Fair
Heymann, 2001	No, excluded 12/118 (10%)	Unclear	NR, NR, NR	Yes (14%) No; placebo=17.5%, amitriptyline=7.5%, nortriptyline=5.3%	Fair
Mease, 2008	Yes, LOCF 3/751 excluded from analysis=0.4%	Yes	Unclear, Unclear, Unclear	Overall=Yes Between-groups=No; 41.6%,450mg/day: 33.9%, 300mg/day: 33.5%, placebo 31.6%, difference between groups (600mg/day and placebo): 10%, p value between groups p=0.044	Fair
Mease, 2009	Yes (LOCF)	Yes	Yes	No	Fair
Norregaard, 1995	Yes, included 42/43 (98%)	Yes	NR, NR, NR	No (10/43=23%) Unclear; attrition not stratified by treatment group	Fair
Patkar, 2007; Pae, 2009	Yes	Unclear	NR, NR, NR	No=26% No=34% for paroxetine, 17% for placebo	Fair

Evidence Table 2. Quality assessment of fibromyalgia trials

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Pfizer, 2008	Unclear	NR	Reported as similar but data NR	Yes	Yes (implied double blind)	Yes (implied double blind)	Yes
Quimby, 1989	Unclear	Unclear	Unclear, statement of "nonsignificant differences", but data NR	Yes	Unclear, described as double-blind	Yes	Yes
Reynolds, 1991	Unclear	Unclear	Unclear; NR based on order of randomization	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double-blind
Russell, 2008; Hunter 2009	Yes	NR	Yes	Yes	Unclear (double blind)	Unclear (double blind)	Unclear
Scudds, 1989	Unclear	Unclear	Unclear, crossover study but characteristics only reported for overall group	Yes	Unclear, described as double-blind	Yes	Yes
Vitton, 2004; Gendreau, 2005	Yes	Yes	Yes except for MDD	Yes	Yes	Yes	Yes
Wolfe, 1994	Yes	Unclear	No; more high school graduates (90.5% vs 61.9%, $P = 0.03$) and longer disease duration (16.1 vs 9.6 years; $P = 0.05$) in fluoxetine group	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double-blind

Evidence Table 2. Quality assessment of fibromyalgia trials

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality Rating
Pfizer, 2008	Yes - those randomized and took study med	NR	NR	Yes	Fair
Quimby, 1989	Unclear, numbers analyzed NR	Unclear	Unclear, Unclear, Unclear	Overall: Yes (11%) Between-groups: Yes	Fair
Reynolds, 1991	Unclear, numbers analyzed NR	Unclear	Unclear, Unclear, Unclear	Overall: No (25%) Between-groups: Yes	Fair
Russell, 2008; Hunter 2009	Yes	Yes	Unclear	No	Fair
Scudds, 1989	No, excluded 8%	Unclear	Unclear, Unclear, Unclear	Overall: Yes=8% Between-groups: Yes	Fair
Vitton, 2004; Gendreau, 2005	Yes	Unclear	NR	No	Fair
Wolfe, 1994	No; excluded 18/42 (43%)	Unclear	Unclear, Unclear, Unclear	Overall=No (43%) Between-groups=No (fluoxetine=29%, placebo=57%)	Poor

Evidence Table 3. Data abstraction of systematic reviews

Author Year Country	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Hauser, 2010 Germany	To give physicians and patients an orientation on FDA approved pharmacological treatment options of fibromyalgia syndrome	Through May 2009	1. An RCT design with a head-to-head comparison of at least 2 drugs or an RCT design with duloxetine, milnacipran or pregabalin with a pharmacological placebo control group or uncontrolled open label extension studies with these drugs 2. Outcomes of at least 1 key domain of fibromyalgia syndrome (pain, sleep, fatigue, depressed mood, health related quality of life and data on harms) 3. Data published as full paper or data on file in the public databases All studies included patients diagnosed with fibromyalgia according to 1990 ACR criteria	6388	Duloxetine: 4 RCTs, 2 uncontrolled open label extension studies, and 1 open label/double blind study Milnacipran: 5 RCTs and 1 uncontrolled open-label extension study Pregabalin: 5 RCTs and 3 uncontrolled open label extension studies

Evidence Table 3. Data abstraction of systematic reviews

Author Year Country	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results
Hauser, 2010 Germany	All studies included patients with Fibromyalgia according to ACR 1990 criteria, patients recruited from America, Europe, Australia, Asia with Americans in the majority. 4508 on active drug, 1880 on placebo Median duration of randomized phase of trials: 24 weeks Median age: 49 years (range 47-51) Median % women: 95% (range 88-100%) Caucasians: 90% (range 76-94%)	Pregabalin, Milnacipran, Duloxetine	Standardized mean difference [95% CI], p of test for overall effect, I^2 (%): Duloxetine Pain -0.33 (-0.43 to -0.23), p<0.0001, I^2: 15 Fatigue: -0.10 (-0.21 to 0.01), p=0.06, I^2: 0 Sleep: -0.31 (-0.50 to -0.13, p=0.0007, I^2:0 Depressed mood: -0.27 (-0.39 to -0.16)p<0.0001, I^2: 0 HRQOL: -0.25 (-0.42, -0.08), p=0.05, I^2:69 Milnacipran Pain: -0.19 (-0.26 to -0.11), p<0.0001, I^2:0 Fatigue: -0.13 (-0.21 to -0.06), p=0.006, I^2: 0 Sleep: -0.05 (-0.12 to .03), p=0.23, I^2:0 Depressed mood: -0.11(-0.19 to -0.04), p=0.003, I^2:0 HRQOL: -0.17(-0.25 to -0.10), p<0.0001, I^2:0 Pregabalin Pain: -0.27 (-0.35 to -0.19), p<0.0001, I^2: 36 Fatigue: -0.16 (-0.23 to -0.09), p<0.0001, I^2:26 Sleep: -0.37 (-0.46 to -0.28), p<0.0001, I^2: 0 Depressed mood: 0.01 (-0.07 to 0.10), p=0.75, I^2=0 HRQOL:-0.25 (-0.36 to -0.13), p<0.0001, I^2=0 NNTs for 30% pain reduction: Duloxetine 7.2 (95% CI 5.2 to 11.4), Milnacipran 19 (95% CI 7.4 to 20.5) and Pregabalin 8.6 (95% CI 6.4 to 12.9) NNHs for dropout due to lack of efficacy: Duloxetine 14.9 (95% CI 9.1 to 41.4), Milnacipran 7.6 (95% CI 6.2 to 9.9) and Pregabalin 7.6 (95% CI 6.3 to 9.4)

Evidence Table 3. Data abstraction of systematic reviews

Author Year Country	Subgroups	Adverse events
Hauser, 2010 Germany	NR	NNH (95% CI), RR (95% CI, I2 (%), p-value: Nausea: Duloxetine: 5.6 (4.5 to 7.2), 2.54 (1.92 to 3.37), 0%, p<0.0001, Milnacipran: 5.1 (4.3 to 6.3), 1.84 (1.55 to 2.18), 0%, p<0.0001, Pregabalin: -96.3 (-24.4 to 49.6), 0.97 (0.64 to 1.48), 0%, p=0.89 Headache: Duloxetine: 12.5 (8.4 to 23.8), 1.61 (1.20 to 2.17), 0%, p=0.01, Milnacipran: 25.0 (19.7 to 144), 1.30 (1.04 to 1.64), 0%, p=0.02, Duloxetine: 17.7(-32.1 to 11.6), 0.72 (0.57 to 0.91), 0%, p=0.007 Dry mouth: Duloxetine:7.9 (6.3 to 10.5), 3.16 (2.11 to 4.72), 0%, p<0.001, Milnacipran: 25.5 (14.8 to 92.3), 2.46 (1.06 to 5.69), 0%, p=0.04, Pregabalin: 15.3 (12.4 to 19.9), 4.98 (2.72 to 9.10), 0%, p<0.0001 Insomnia: Duloxetine:18.7 (11.5 to 51.0), 2.47 (0.57 to 10.71), 40%, p=0.23, Milnacipran: 38.8 (18.8 to 45.3), 1.35 (1.01 to 1.79), 0% p=0.04 Constipation: duloxetine:10.1 (7.9 to 13.9 , 3.50 (2.23 to 5.79), 0%, p<0.0001, Milnacipran: 8.1 (6.8 to 10.0), 4.47 (2.91 to 6.86), 0%, p=0.04, Pregabalin: 24.3 (14.1 to 83.6), 3.94 (0.50 to 30.74), 74%, 0.19 Hyperhidrosis: Duloxetine 11.8 (9.4 to 15.8), 5.71 (2.34 to 13.95), 0%, p=0.0001, Milnacipran: 14.4 (11.5 to 19.2), 5.00 (2.64 to 9.47), 0%, p<0.0001 Dizziness: Duloxetine:23.6 (13.9 to 79.0), 2.62 (1.53 to 4.50), 27%; p=0.004, Milnacipran: 19.4 (13.4 to 35.5), 1.94 (1.34 to 2.81), 0%, p=0.0004, Pregabalin: 3.5 (3.2 to 3.9), 3.87 (3.06 to 4.89), 0%, p<0.0001 Diarrhea: Duloxetine:26.6 (14.5 to 147), 1.59 (1.11 to 2.29), 8%, p=0.01, Milnacipran: -5.7 (-25.3 to 29.1), 0.72 (0.49 to 1.05), Pregabalin: -64.6 (-117 to 26.9), 0.79 (0.42 to 1.48), 40%, p=0.46 Fatigue: Duloxetine: 13.5 (9.4 to 23.8), 2.07 (1.47 to 2.91), 0%, p<0.0001, Milnacipran: NR, Pregabalin(fatigue/asthenia): 32.1 (19.8 to 84.8), 1.67 (1.15 to 2.43), 0%,p<0.0001 Somnolence: Duloxetine: 14.7 (10.9 to 22.8), 2.66 (1.78 to 3.96), 0%,p<0.0001, Milnacipran: NR, Pregabalin: 6.4 (5.5 to 7.5), 4.21 (2.96 to 5.94), 0%, p<0.0001 Weight gain: Pregabalin: 11.5 (9.9 to 14.5), 4.58 (2.44 to 6.82), 0%,p<0.0001, peripheral edema:20.5 (15.5 to 30.1), 3.52 (2.01 to 6.18),0%,p<0.0001

Evidence Table 3. Data abstraction of systematic reviews

Author Year Country	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Moore 2010 U.K.	To assess the analgesic efficacy and associated adverse events of pregabalin in acute and chronic pain	1990 through May 2009	Adults aged ≥18 years who reported pain in acute pain setting or were studied in situations where pain was anticpated, had one or more of a wide range of chronic or neuropathic pains including diabetic neuropathy, post herpetic neuralgia, phantom limb pain, Guillain barre and spinal cord injury and had any other chronic painful condition.	2294 patients in 4 trials 1 trial had 1051 patients analyzed seperately as it used complete EERW design.	5 PCTs of fibromyalgia

Evidence Table 3. Data abstraction of systematic reviews

Author Year Country	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results
Moore 2010 U.K.	NR	Pregabalin in any dose and by any route Placebo or any active control	Proportion of patients with at least 30% pain relief (Results from 4 studies) Pregabalin 150mg vs placebo: 31% vs 27%, Relative benefit 1.1 , 95%CI (0.8 to 1.7), NNT not calculated Pregabalin 300mg vs placebo: 39% vs 28%, Relative benefit 1.4 , 95% CI (1.2 to 1.6), NNT 9.2 , 95% CI (6.3 to 17) Pregabalin 450mg vs placebo: 43% vs 28%, Relative benefit 1.5, 95% CI (1.3 to 1.8), NNT 6.6 (5.0 to 9.8) Pregabalin 600mg vs placebo: 39% vs 28%, Relative benefit 1.4 , 95% CI (1.2 to 1.6), NNT 9.1 (6.1 to 18) Proportion of patients with atleast 50% pain relief (Results from 4 studies) Pregabalin 150mg vs placebo: 13% vs 13%, Relative benefit 1.0 , 95% CI (0.5 to 1.9), NNT not calculated Pregabalin 300mg vs placebo: 21% vs 14%, Relative benefit 1.5, 95% CI (1.2 to 1.9), NNT 14, 95% CI (9.0 to 33) Pregabalin 450mg vs placebo:25% vs 14%, Relative benefit 1.7, 95% CI (1.4 to 2.1), NNT 9.8, 95% CI (7.0 to 16) Pregabalin 600mg vs placebo: 24% vs 15%, Relative benefit 1.6, 95% CI (1.3 to 2.1), NNT 11, 95% CI (7.1 to 21) Proportion of patients with PGIC much or very much improved (Results from 4 studies) Pregabalin 150mg vs placebo: 32% vs 27%, Relative benefit 1.2, 95% CI (0.8 to 1.8), NNT not calculated Pregabalin 300mg vs placebo: 36% vs 28%, Relative benefit 1.5, 95% CI (1.2 to 1.9), NNT 11, 95% CI (7.3 to 26) Pregabalin 450mg vs placebo: 42% vs 28%, Relative benefit 1.5, 95% CI (1.3 to 1.8), NNT 6.8, 95% CI (6.1 to 1.0) Pregabalin 600mg vs placebo: 41% vs 28%, Relative benefit 1.5, 95% CI (1.2 to 1.7), NNT 7.7, 95% CI (5.4 to 13) Effficacy results from 1 EERW study : DB phase % of patients experiencing loss of therapeutic response: Pregabalin vs placebo: 32% vs 61%, NNT 3.5, 95% CI (2.8 to 4.9)

Evidence Table 3. Data abstraction of systematic reviews

Author Year Country	Subgroups	Adverse events
Moore 2010 U.K.	NR	% of patients with AE discontinuation Pregabalin 150mg vs placebo: 8% vs 8%, RR 1.1, 95% CI(0.5 to 2.5), NNH not calculated Pregabalin 300mg vs placebo: 16% vs 10%, RR 1.6, 95% CI (1.2 to 2.1), NNH 17, 95% CI (11 to 43) Pregabalin 450mg vs placebo: 20%vs 10%, RR 1.9, 95% CI 1.5 to 2.5), NNH 11, 95% CI (7.6 to 18) Pregabalin 600mg vs placebo: 28% vs 11%, RR 2.5, 95% CI (1.9 to 3.3), NNH 5.9, 95% CI (4.6 to 8.0) % of patients with Somnolence Pregabalin 150 mg vs placebo: 16% vs 5%, RR 3.5, 95% CI (1.5 to 8.3), NNH 8.8, 95 % CI (5.4 to 24) Pregabalin 300mg vs placebo: 32% vs 10%, RR 3.1, 95% CI 2.8 to 5.8), NNH 6.7, 95% CI (5.5 to 8.7) Pregabalin 450mg vs placebo: 21% vs 5%, RR 4.2, 95% CI 2.9 to 6.0), NNH 6.4, 95% CI (5.2 to 8.1) Pregabalin 600mg vs placebo: 23% vs 5%, RR 4.5, 95% CI 3.1 to 6.7), NNH 5.7, 95% CI (4.6 to 7.3) % of patients with dizziness Pregabalin 150mg vs placebo: 13% vs 10%, RR 1.3, 95% CI (0.8 to 2.1), NNH not calculated Pregabalin 300mg vs placebo: 32% vs 10%, RR 3.1, 95% CI (2.4 to 3.9), NNH 4.6, 95% CI 3.9 to 5.7) Pregabalin 450mg vs placebo 43% vs 10%, RR 4.1, 95% CI (3.2 to 5.2), NNH 3.1, 95% CI (2.8 to 3.6) Pregabalin 600mg vs placebo 46% vs 10%, RR 4.4 , 95% CI (3.4 to 5.8), NNH 2.8, 95% CI (2.5 to 3.2) Results from EERW study DB phase % of patients with any adverse event placebo 45%, pregabalin 300mg 59% vs pregabalin 600mg 62%

Evidence Table 4. Quality assessment of systematic reviews

Author Year	Report clear review question, state inclusion and exclusion criteria of primary studies?	Substantial effort to find relevant research?	Adequate assessment of validity of included studies?	Sufficient detail of individual studies presented?	Primary studies summarized appropriately?	Quality
Hauser 2009	Yes	Yes	Yes	Yes	Yes	Good
Moore, 2009	Yes	Yes	Yes	Yes	Yes	Good