Review

Efficacy of Cognitive-Behavioral Therapies in Fibromyalgia Syndrome — A Systematic Review and Metaanalysis of Randomized Controlled Trials

KATHRIN BERNARDY, NICOLE FÜBER, VOLKER KÖLLNER, and WINFRIED HÄUSER

ABSTRACT. ***Objective.*** We performed the first systematic review with metaanalysis of the efficacy of cognitive-behavioral therapies (CBT) in fibromyalgia syndrome (FM).

Methods. We screened Cochrane Library, Medline, PsychINFO, and Scopus (through June 2009) and the reference sections of original studies and systematic reviews for CBT in FM. Randomized controlled trials (RCT) comparing CBT to controls were analyzed. Primary outcomes were pain, sleep, fatigue, and health-related quality of life (HRQOL). Secondary outcomes were depressed mood, self-efficacy pain, and healthcare-seeking behavior. Effects were summarized using standardized mean differences (SMD).

Results. A total of 14 out of 27 RCT with 910 subjects with a median treatment time of 27 hours (range 6–75) over a median of 9 weeks (range 5–15) were included. CBT reduced depressed mood (SMD –0.24, 95% CI –0.40, –0.08; p = 0.004) at posttreatment. Sensitivity analyses showed that the positive effect on depressed mood could not be distinguished from some risks of bias. There was no significant effect on pain, fatigue, sleep, and HRQOL at posttreatment and at followup. There was a significant effect on self-efficacy pain posttreatment (SMD 0.85, 95% CI 0.25, 1.46; p = 0.006) and at followup (SMD 0.90, 95% CI 0.14, 1.66; p = 0.02). Operant behavioral therapy significantly reduced the number of physician visits at followup (SMD –1.57, 95% CI –2.00, –1.14; p < 0.001).

Conclusion. CBT can be considered to improve coping with pain and to reduce depressed mood and healthcare-seeking behavior in FM. (First Release August 1 2010; J Rheumatol 2010;37:1991–205; doi:10.3899/jrheum.100104)

Key Indexing Terms:
FIBROMYALGIA SYNDROME
COGNITIVE BEHAVIORAL THERAPY
SYSTEMATIC REVIEW
COGNITIVE THERAPY
OPERANT BEHAVIORAL THERAPY
METAANALYSIS

The key symptoms of fibromyalgia syndrome (FM) are chronic widespread pain, fatigue, nonrestorative sleep, and psychological distress[1,2]. The estimated prevalence of FM in Western European countries ranges from 2.2% to 6.6%[3]. Comorbidities with affective or anxiety disorders are common[4].

Patients with FM use a lot of pharmacological and nonpharmacological therapies, resulting in high costs for health services[5]. Pharmacological and physical therapies are used more frequently than psychotherapeutic treatments. In an Internet survey, only 8% of respondents reported use of cognitive-behavioral therapies (CBT), but over 80% named emotional distress as an aggravating factor[6].

CBT include interventions that are based on the basic premise that chronic pain is maintained by cognitive and behavioral factors, and that psychological treatment leads to changes in these factors through cognitive (e.g., cognitive restructuring) and/or behavioral (e.g., relaxation training, social skills training) techniques. Different types of CBT can be differentiated by the techniques applied. Mindfulness-based stress reduction (MBSR) is a cognitive therapy that helps individuals to self-manage and reframe worrisome and intrusive thoughts by mindfulness meditation, that is, the nonjudgmental awareness of one's present experience

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(thoughts, emotions, bodily sensations)[7]. Operant behavioral treatment (OBT) focuses on the modification of pain behavior by increasing activity levels, and on reducing healthcare-seeking behavior, as well as on including significant others to reduce reinforcement of pain behaviors[8]. The main therapeutic techniques employed in CBT are the modification of dysfunctional thoughts and behavioral modification[9].

Systematic reviews and evidence-based guidelines intend to provide a guide through the variety of pharmacological and nonpharmacological treatment options for healthcare professionals and patients. The 3 existing evidence-based guidelines available for management of FM gave different grades of recommendation for CBT. Whereas the American Pain Society[10] and the Association of the Scientific Medical Societies in Germany[11] gave the highest grade of recommendation to CBT based on qualitative systematic reviews, the European League Against Rheumatism gave only a weak (expert opinion) recommendation for CBT[12]. The conclusions of narrative systematic reviews on CBT in FM were inconclusive as well. Koulil, *et al*[13] concluded from 6 randomized controlled trials (RCT) that the effects on pain, disability, and mood were limited and that mostly CBT within a multicomponent approach yielded improvements. Bennett and Nelson concluded from 6 RCT that CBT as a single treatment modality did not offer any distinct advantage over well planned group programs of education or exercise, or both[9]. Thieme and coworkers concluded from 14 studies that CBT were superior to controls in most key domains of FM at posttreatment and followup[14]. A metaanalysis of the results of RCT with CBT in FM had not been conducted until now. A recent Cochrane Review on the efficacy of CBT in chronic pain syndromes included only 5 studies with FM patients[15].

Because of these inconsistent results we saw the need to reexamine the literature and to perform the first quantitative analysis of the outcomes of CBT in FM. The aims of this systematic review were to assess if CBT have beneficial effects at posttreatment and at followup on symptoms of FM compared with controls.

MATERIALS AND METHODS

The review was performed according to the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses[16]) and the recommendations of the Cochrane Collaboration[17].

Study protocol. Methods of analysis and inclusion criteria were specified in advance. We used the review protocol of our systematic review on balneotherapy in FM[18].

Eligibility criteria. *Types of studies*. This was a RCT design comparing CBT with no treatment, treatment as usual, attention control (unspecific elements of CBT such as education, group discussion, or emotional support), or active therapy (any defined pharmacological or nonpharmacological therapy other than CBT). Studies without randomization were excluded.

Types of participants. Patients diagnosed with FM on recognized criteria, of any age, were included.

Types of interventions. RCT with face to face cognitive, operant behavioral, or cognitive-behavioral therapies with defined psychotherapeutic content as an active treatment of primary interest were included. Studies with education only (information on the symptoms and management of FM and/or discussion and/or emotional support) or relaxation and/or biofeedback only were excluded. Studies in which CBT were part of multicomponent therapy were excluded because it would not be possible to separate the effects of CBT from aerobic exercise.

Types of outcomes measures. Studies should assess at least one key domain of FM [pain, sleep, fatigue, patient global multidimensional function, i.e., health related quality of life (HRQOL)][1]. Depressed mood, self-efficacy pain (SE Pain, i.e., subjects' perceived ability to manage and cope with pain and its emotional and behavioral consequences), and healthcare-seeking behavior were chosen for secondary outcomes because emotional status, increasing activity, and coping with pain are the main targets of all types of CBT[8,9]. Reducing healthcare-seeking behavior is a major goal of operant behavioral therapy[8]. From each trial we selected the measure considered most appropriate for each of the 7 outcomes. When there was more than one measure for an outcome we gave preference to measures recommended by OMERACT[1].

Data sources and searches. The electronic bibliographic databases screened included the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, Medline, and PsycINFO (through June 30, 2009). The search strategy for Medline is detailed in Table 1. The search strategy was adapted for each database if necessary. No language restrictions were applied. Only fully published reports were reviewed. In addition, reference sections of original studies, systematic reviews[9,13,14], and evidence-based guidelines on the management of FM[10,11,12] were screened manually.

Study selection. Two authors (KB, NF) independently screened the titles and abstracts of potentially eligible studies identified by the search strategy as above. The full-text articles were then examined independently by 2 authors (VK, WH) to determine if they met the inclusion criteria.

Data collection process. Two authors (KB, NF) independently extracted the data using standard extraction forms[18]. Discrepancies were rechecked and consensus achieved by discussion. If needed, a third author (WH) reviewed the data to reach a consensus.

Where means or standard deviations were missing, attempts were made to obtain these data by contacting 5 trial authors. Additional data were provided by 2 authors (Table 2). Where standard deviations were not available from trial authors, they were calculated from t values, confidence intervals, or standard errors, as reported in articles[17]. If these data were not available, the standard deviation was substituted by the mean of the standard deviations of studies that used the same outcome scale[17]. In case of different directions of scales the mean from one set of the studies was multiplied by –1[17].

Data items. Data for study settings, participants, exclusion criteria, interventions, cotherapies, attendance rates, reported side effects, and outcomes sought are listed in Table 2.

Table 1. Search strategy for Medline.

To locate Fibromyalgia
1. fibromyalgia [MeSH]
2. fibromyal* [tw]
3. fibromyalgia syndrome [tw]
4. RCT [tw]
5. or/1-4
To locate CBT
6. cognitive therapy [MeSH]
7. meditation [MeSH]
8. behavior therapy [MeSH]
9. aversive therapy [MeSH]
10. desensitization [MeSH]
11. implosive therapy [MeSH]
12. sleep phase chronotherapy [MeSH]
13. mindfulness based stress reduction
14. or/6-13
15. 5 and 14

Table 2. Characteristics of studies with cognitive-behavioral therapies in fibromyalgia syndrome (FM). Studies are arranged in alphabetical order by author.

Study; Setting; Referral	Mean age, yrs; Women, Race	Exclusion Criteria	Diagnosis of FM; Comorbidities Assessed and Reported	Population		Treatment Group		Control Group		Outcomes Usable for Metaanalysis; Latest Followup
				N Screened Randomized (%)	N Completing End of Therapy (%)	N Completing End of Therapy (%)	Treatment (duration)	Treatment (duration) N Completing End of Therapy (%)	Comedication Allowed; Other Cotherapies; Attendance Rates (all sessions); Side effects	
Astin USA 2003: university outpatient based; radio/newspaper advertisement and local physicians	48; 99% women, 91% White	Internal disease, major mental disorder, pending litigation	ACR; Yes	NR	128/65 (51)	64/32 (50)	Cognitive (MBSR) group: mindfulness meditation (1 × 1.5 h/8 wks) plus Qi-gong (1 × 1 h/8 wks) Total: 20 h	Attention control: education and support; (8 × 2.5 h) Total 20 h 63/33 (51)	NR NR IR NR	Pain SF-36 Pain Sleep NP Fatigue NP Depression BDI total HRQOL FIQ total SE Pain CSQ NP HCSB NA; 6 mo
Burckhardt Sweden 1994; regional hospital outpatient based; Clinic register	46.5; 100% women, 99% White	Rheumatic disease	ACR; no	120/99 (83)	99/86 (87)	31/28 (90)	CBT group: education, relaxation, assertiveness training, coping strategies, problem solving techniques (1 × 1.5 h/6 wks) Total 9 h	Delayed treatment control — 35/30 (86) Study arm CBT plus physical therapy not used for comparison	Yes, not controlled for NR NR NR	Pain VAS 0–10* Sleep VAS 0–10 NA Fatigue VAS 0–10* Depression 0–10* HRQOL FIQ total* SE Pain SES NP HCSB NA; 3 and 6 mo but not control group
Edinger USA 2005; university outpatient based; newspaper advertisement	48.6; 92% women, 90% White	Somatic diseases associated with sleep disorder, mental disorder except dysthymia	ACR; Yes	106/47 (44)	47/41 (87)	16/15 (94)	CBT group: insomnia therapy with education and stimulus control (1 × 1 h/6 wks) Total 6 h	Usual care — 11/9 (82) Treatment arm sleep hygiene not used for comparison	Yes NR IR NR	Pain: MPQ total Sleep: ISQ total Fatigue NA Depression NA HRQOL NA SE Pain NA HCSB NA; 6 mo
Garcia Spain 2006; university outpatient based; pain and rheumatology department	49.9; 96% women, NR	No medication, request or lawsuit for disability	ACR, No	NR	28/28 (100)	7/7 (100)	CBT group: Education, relaxation, cognitive techniques, self-instructions (1 × 1.5 h/9 wks) Total 13.5 h	Nontreatment 7/7 (100) Treatment arms pharmacological therapy and pharmacological therapy plus CBT not used for comparison	No medication used for FM NR NR NR	Pain NP Sleep NP Fatigue NP Depression NP HRQOL: FIQ total SE Pain NA HCSB NA; 3 mo
Grossman Switzerland 2007; university outpatient based; local physician; self-help group	54.4; 100% women, NR	Life-threatening disease, mental disorder that could interfere with adherence	ACR; 26% suggestive of a mental disorder	NR	58/52 (90)	43/39 (91)	Cognitive (MBSR) group: formal mindfulness practice, mindful awareness during yoga, stressful situations and social interactions (1 × 2.5 h/8 wks plus one day) Total 27 h	Attention control group: nonspecific elements of MBSR: progressive relaxation, gentle stretching, group discussion (8 wks, 27 h) 15/13 (87)	NR NR IR NR	Pain VAS 0–100 Sleep NA Fatigue NA Depression HADS HRQOL QoL** SE Pain IPR HCSB NA; 36 mo, but not control group

Table 2. Continued.

Study; Setting; Referral	Mean age, yrs; Women, Race	Exclusion Criteria	Diagnosis of FM; Comorbidities Assessed and Reported	Population		Treatment Group		Control Group		Outcomes Usable for Metaanalysis; Latest Followup
				N Screened Randomized (%)	N Completing End of Therapy (%)	N Completing End of Therapy (%)	Treatment (duration)	Treatment (duration) N Completing End of Therapy (%)	Comedication Allowed; Other Cotherapies; Attendance Rates (all sessions); Side effects	
Kashikar-Zuck USA 2005; university outpatient based; pediatric rheumatology clinic	15.8; 100% women, 93% White	Rheumatic disease, depressive disorder	JPFM; No	44/30 (68)	30/27 (90)	15/14 (93)	CBT single. Group and with parents: relaxation, distraction; activity pacing, cognitive and problem-solving techniques (1 × 1.5 h/8 wks) Total 12 h	Active control; Single: self-monitoring with diary 15/13 (87)	NR NR 90% NR	Pain VAS 0–10 Sleep NA Fatigue NA Depression CDI HRQOL NA SE Pain PCQ HCSB NA; No followup
Nicassio USA 1997; university outpatient-based; community, private and hospital rheumatologists, FMS support groups	53.1; 89% women, 86% White	Rheumatic disease, other serious illness, psychosis or bipolar disorder	ACR; No	94/86 (92)	86/71 (82)	48/36 (75)	CBT group: education, relaxation, activity pacing, pain coping, involvement of support person reinforcing adherence to protocol (1 × 1.5 h/10 wks) Total 15 h	Attention control, Group: lectures, group discussion, support (10 wks, 1.5 h/wk) Total 15 h 38/35 (92)	Yes, not controlled for NR NR NR	Pain Index Sleep NA Fatigue NA Depression CES-D HRQOL QWB SE Pain RAI HCSB NA; 6 mo
Redondo Spain 2004; university general practitioners	NR; 100% women, NR	Serious concomitant diseases	ACR; No	56/40 (71)	40/31 (77)	21/16 (76)	CBT group: education, relaxation, coping with pain and daily activities, problem solving, prevention of relapses (1 × 2.5 h/8 wks) Total 20 h	Active control: pool and cycle ergometer (5 × wk 0.45 h; 8 wks) Total 30 h 19/15 (79)	Flexible medication with NSAID, amitriptyline and acetaminophen allowed NR 72% NR	Pain VAS 0–10 Fatigue VAS 0–10 Sleep VAS 0–10 Depression BDI total HRQOL FIQ total SE Pain CPSS HCSB NA; 12 mo
Sephton USA 2007; university outpatient based; television broadcast and newspaper advertisement	48; 100% women, 94% White	Severe mental illness	ACR; Yes	282/91 (32)	91/78 (86)	51/41 (80)	Cognitive (MBSR) group: stress reduction by sitting meditation, hatha yoga and body scan; meditation retreat (1 × 2.5 h/8 wks plus one day; daily home practice of 30–45min encouraged) Total 28 h	Delayed treatment control 40/27 (68)	Flexible comedication allowed NR 69% NR	Pain NA Sleep NA Fatigue NA Depression BDI total HRQOL NA SE Pain NA HCSB NA; 2 mo

Table 2. Continued.

Study; Setting; Referral	Mean age, yrs; Women, Race	Exclusion Criteria	Diagnosis of FM; Comorbidities Assessed and Reported	Population		Treatment Group		Control Group		Outcomes Usable for Metaanalysis; Latest Followup
				N Screened Randomized (%)	N Completing End of Therapy (%)	N Completing End of Therapy (%)	Treatment (duration)	Treatment (duration) N Completing End of Therapy (%)	Comedication Allowed; Other Cotherapies; Attendance Rates (all sessions); Side effects	
Soares Sweden 2002; university outpatient based; practitioners	45; 100% women, NR	Serious somatic diseases, substance abuse, other therapies	ACR; No	85/53 (62)	60/53 (88)	20/18 (90)	CBT single and group: education, problem solving, pain- and self-management [10 wks (2x2 h individual, 15 × 2 h group)] Total 34 h	Attention control, Group: education, discussion (10 wks, total 102 h) 20/18 (90) Waiting list control not used for comparison because of lack of followup assessment	No other therapy No other therapy NR NR	Pain MPQ total Sleep KSQ Sleep Quality Fatigue NA Depression NA HRQOL FIQ total SE Pain ASES Pain HCSB NA; 6 mo
Thieme Germany 2003; inpatient-based; district hospital, district hospital for rheumatic diseases	46.6; 100% women, NR	Serious somatic diseases, major psychiatric disorder	ACR; No	NR	61/61 (100)	40/40 (100)	Behavior group: education; structured time-contingent exercises, reduction of medication, increase of bodily activity, reduction of interference of pain with daily activities; reduction of healthcare utilization; assertiveness training 5 wks DNR Total 75 h	Active control: Group: education, antidepressants, passive physical therapy 21/21 (100) (5 wks, 5 days a wk) Total 75 h	Reduction of medication NR NR NR	Pain MPI 0–6 Sleep NA Fatigue NA Depression NA HRQOL MPI Total Activity Scale SE Pain MPI HCSB, number of physician visits; 15 mo
Thieme Germany 2006; university outpatient based; rheumatology clinics	45; 100% women, NR	Serious somatic diseases	ACR; NR	131/125 (95)	125/100 (80)	OBT 43/40 (93) CBT 42/40 (95)	Behavior group: education; structured time-contingent exercises; reduction of medication, increase of bodily activity, reduction of interference of pain with daily activities; reduction of healthcare utilization; assertiveness training CBT group: relaxation, problem-solving, stress and pain coping (Both groups: 1 × 2 h/15 wks) Total 30 h	Attention control, Group: discussion (h NR) 40/20 (50)	NR NR NR 2 dropouts because of depression in behavior and CBT each	Pain VAS 0–10** Sleep NA Fatigue VAS 0–10** Depression VAS 0–10** HRQOL FIQ total SE Pain PRSS** HCSB, number of physician visits; 12 mo

Table 2. Continued.

Study; Setting; Referral	Mean age, yrs; Women, Race	Exclusion Criteria	Diagnosis of FM; Comorbidities Assessed and Reported	Population		Treatment Group		Control Group		Outcomes Usable for Metaanalysis; Latest Followup
				N Screened Randomized (%)	N Completing End of Therapy (%)	N Completing End of Therapy (%)	Treatment (duration)	Treatment (duration) N Completing End of Therapy (%)	Comedication Allowed; Other Cotherapies; Attendance Rates (all sessions); Side effects	
Vlaeyen Netherlands 1996; university outpatient based; regional general hospital	44; 88% women, NR	Somatic diseases, substance abuse, disability litigation	ACR; No	290/131 (45)	125/112 (90)	49/39 (80)	CBT group: education (24 h), imagination, EMG-supported relaxation; training to use relaxation skills in case of stimuli of muscle tension (1 × 2 h/12 wks) Total 48 h	Active control: group education and low intensity physical exercise (12 wks, 2 h) Total 24 h 39/30 (77) Waiting list control not used for comparison because of lack of followup assessment	NR NR 78% 1 dropout in CBT and 2 in control because of increase of symptoms	Pain Index Sleep NA Fatigue NA Depression BDI HRQOL*** SE Pain CSQ HCSB***; 12 mo
Wigers Norway 1996; university outpatient; local patient association and outpatient department	43; 90% women, NR	NR	ACR; NR	76/60 (79)	60/48 (80)	20/16 (80)	CBT group: relaxation, stress management skills (1 × 1-1.5 h/14 wks) Total 21 h	Usual care — 20/17 (85) Study arm aerobic exercise not used for comparison	Baseline treatment unchanged Exclusion from analysis if new therapies were initiated IR No treatment related side effects	Pain VAS 0–100 Fatigue VAS 0–100 Sleep VAS 0–100 Depression VAS 0–100 HRQOL NA SE Pain NA HCSB NA; 48 mo

* SD substituted by the mean of SD of other trials on the same scale; ** data provided on request: *** HRQOL utilities as reported[32] not suited for metaanalysis: HCSB-data as reported[32]. Reasons for exclusion from metaanalysis: see Discussion. ACR: American College of Rheumatology; ASES: Arthritis Self-Efficacy Scale; BDI: Beck Depression Inventory; CBT: cognitive-behavioral therapy; CDI: Children's Depression Inventory; CES-D: Center for Epidemiological Studies Depression Scale; CSQ: Coping Strategies Questionnaire; DNR: details not reported; EMG: electromyography; FIQ: Fibromyalgia Impact Questionnaire; HADS: Hospital Anxiety and Depression Scale; HRQOL: health-related quality of life; HCSB: healthcare-seeking behavior; IPR: Inventory of Pain Regulation; IR: insufficiently reported; ISQ: Insomnia Symptom Questionnaire; JPMF: juvenile primary fibromyalgia; MMQ: Mild Motion Questionnaire; MPI: Multidimensional Pain Inventory; MPQ: McGill Pain Questionnaire; NA: not assessed; NP: not provided on request; NR: not reported; OBT: operant behavioral therapy; PCQ: Pain Coping Questionnaire; PRSS: Pain-related self-statement scale; QoL: Quality of life profile for the Chronically Ill; RAI: Rheumatology Attitude Index, subscale helplessness; SCL 90-R: Symptom Check List 90-revised; SE: self-efficacy; SES: Self-Efficacy Scale; SF-36: Short Form Health Survey; VAS: visual analog scale.

If studies had 2 or more potential control groups we used the following order to select for control group: attention placebo, treatment as usual, and active control.

Risk of bias in individual studies. To ascertain the internal validity of the eligible RCT, 2 pairs of reviewers (KB, NF; VK, WH) working independently determined the adequacy of randomization, concealment of allocation, blinding of outcome assessors, and adequacy of data analysis (was intention-to-treat analysis performed?). The quality of the treatment was assessed by the 5 items (treatment content/setting, treatment duration, manualization of the treatment, adherence of the therapist to the manual, therapist training and client engagement) of a quality rating scale designed specifically for application to psychological treatment studies in pain. The maximum score is 9[19]. Based on the classification of Yates and coworkers[19] we defined scores 0–2 to indicate poor, scores 3–5 average, and scores 6–9 excellent treatment quality. The same pairs of reviewers checked the settings of the studies, the means of referral to the RCT, the inclusion and exclusion criteria, and the sociodemographic data of the study samples and if patients with affective or anxiety disorders were included to assess the representativeness of study samples for FM patients of clinical practice (external validity).

Summary measures. Metaanalyses were conducted using RevMan Analysis software (RevMan 5.0.17) of the Cochrane Collaboration[20]. Standardized mean differences (SMD) were calculated by means and SD or change scores for each intervention. Examination of the combined results was performed by a random-effects model (inverse variance method), because this model is more conservative than the fixed-effects model and incorporates both within-study and between-study variance[21]. The SMD used in Cochrane reviews is the effect size known as Hedges (adjusted) g. We used Cohen's categories to evaluate the magnitude of the effect size, calculated by SMD, with g > 0.2–0.5 = small effect size, g > 0.5–0.8 = medium effect size, and g > 0.8 = large effect size[22].

Planned methods of analysis. Heterogeneity was tested using the I^2 statistic, with I^2 values over 50% indicating strong heterogeneity. Tau-squared was used to determine how much heterogeneity was explained by subgroup differences[17].

Risk of bias across studies. Potential publication bias (i.e., the association of publication probability with the statistical significance of study results) was investigated by visual assessment of the funnel plot (plots of effect estimates against its standard error) calculated by RevMan Analysis software if appropriate (at least 10 studies available). Publication bias may lead to asymmetrical funnel plots[17].

Additional analyses. *Subgroup analysis*. If there were at least 2 studies available, subgroup analyses were prespecified for type (cognitive, cognitive-behavioral, operant behavioral), duration of total CBT (< 10 h, 10–20 h, ≥ 20 h), type of control group (attention control, no therapy or treatment as usual, active therapy). These subgroup analyses were also used to examine potential sources of clinical heterogeneity.

Sensitivity analyses. When at least 2 studies were available, the following sensitivity analyses were prespecified: (1) studies with inadequate or unclear versus studies with adequate sequence generation; (2) studies with inadequate or unclear versus studies with adequate concealment of allocation; (3) studies with no or unclear versus studies with adequate blinding of the outcome assessor; (3) studies without versus studies with intention-to-treat analysis; (4) studies that excluded (or did not report exclusion criteria) versus studies that included patients with affective or anxiety disorders; (5) studies with poor versus average and versus high treatment quality; and (6) because we assumed a growing acceptance of active therapies such as CBT in FM by patients over the years, an analysis with publication of studies before 2000 and then 2000–2005 and 2006–2009 was conducted. These sensitivity analyses were also used to examine potential sources of methodological heterogeneity.

RESULTS

Search results. The literature search produced 298 citations; 167 were "double hits" (study found in at least 2 data sources). By screening, 104 records were excluded: 37 did not evaluate CBT in FM, 52 were review articles, and 15 were case reports, conference papers or commentaries. Twenty-seven full-text articles assessed for eligibility; 13 full-text articles were excluded for the following reasons: one lacking a control group[23], 2 lacking randomization[24,25], one because CBT was only Internet-based[26], 5 because CBT were combined with aerobic exercise[27,28,29,30,31], one because the data presented in the report were not suited for the predefined outcomes of this metaanalysis and necessary data for metaanalysis were not provided on request[32], and 3 because of secondary (e.g., economic) analysis[33,34,35] of 2 RCT included in metaanalysis[36,37]. Finally, 14 studies with 15 study arms were included[36,37,38,39,40,41,42,43,44,45,46,47,48,49] (Figure 1).

Study characteristics. *Setting, referral, and exclusion criteria*. Five studies were conducted in North America and 9 in North and Middle Europe. Patients were recruited by registers of hospitals, referral (general practitioner, rheumatologist, departments of hospitals), local self-help groups, and newspaper advertisements. Twelve studies were conducted within the setting of a university, 2 within district hospitals. All studies were single-center based. One study did not report the inclusion and exclusion criteria. Thirteen studies excluded patients with somatic diseases. Seven studies excluded patients with mental disorders. The exclusion criteria of mental disorders were clearly defined in only 5 studies. Three studies excluded patients with unresolved litigation. FM was diagnosed in 14 studies by the criteria of the American College of Rheumatology[50] and in one study with adolescents by the Juvenile Primary Fibromyalgia criteria[51]. Three studies reported somatic comorbidities of the patients. No study performed a psychiatric interview or reported the frequency of mental disorders.

Participants. The median of the mean age of participants was 47 years (range 16–54 yrs). The median percentage of women was 100% (range 88%-100%). The median percentage of Caucasians was 91% (range 86%–94%).

Interventions. Ten studies reported the number of persons screened and randomized with a median of 69% (range 32%–95%). The median number of patients with CBT was 40 (range 7–64) and controls 40 (range 7–63). We found 426/527 (81%) patients in the CBT groups and 288/383 (75%) in the control groups completed therapy ($z = -0.9$, $p = 0.4$).

Three studies offered cognitive (MBSR), 2 studies operant behavioral, and 10 studies cognitive-behavioral therapy. All studies but one were outpatient-based. In all studies, CBT were performed as group therapy. Four studies reported the attendance rates with a median of 75% (range 69%–90%).

In 5 studies the controls received treatment as usual or no therapy and in 4 studies they were treated by another active therapy (self-monitoring, aerobic exercise, antidepressants and passive physical therapy, education and low-intensity physical activity). In 6 studies an attention control was used (education, relaxation, and group support and discussion; Table 2).

The length of the interventions, excluding followup, ranged from 5 to 15 weeks (median 9 weeks). The median total treatment time was 27 hours (range 6–75 hours). Twelve studies performed followups. The median of the latest followup was 6 months (range 2–48 months).

Outcomes. The underlying rationale for applying CBT to predefined outcomes was reported by 10 studies. The 3 studies with MBSR aimed to reduce stress and to train mindfulness to reduce the negative effects of thoughts and sensation associated with pain. Primary outcomes were coping with pain and depression. The 2 studies with operant behavioral therapy were intended to increase the physical activity levels at home and at work, to reduce healthcare-seeking behavior, and to include significant others to reduce reinforcement of pain behaviors. The primary outcomes were disability, pain, affective distress, and number of physician visits. The rationale reported by 4 studies with CBT was to teach patients the skills needed to control pain and disability and to enhance self-efficacy pain. The primary outcomes used most frequently by these studies were pain, disability, and self-efficacy pain. One CBT study focused on improvement of sleep to interrupt the pain/distress cycle. Outcomes of this study were pain, sleep quality, depressed mood, and HRQOL.

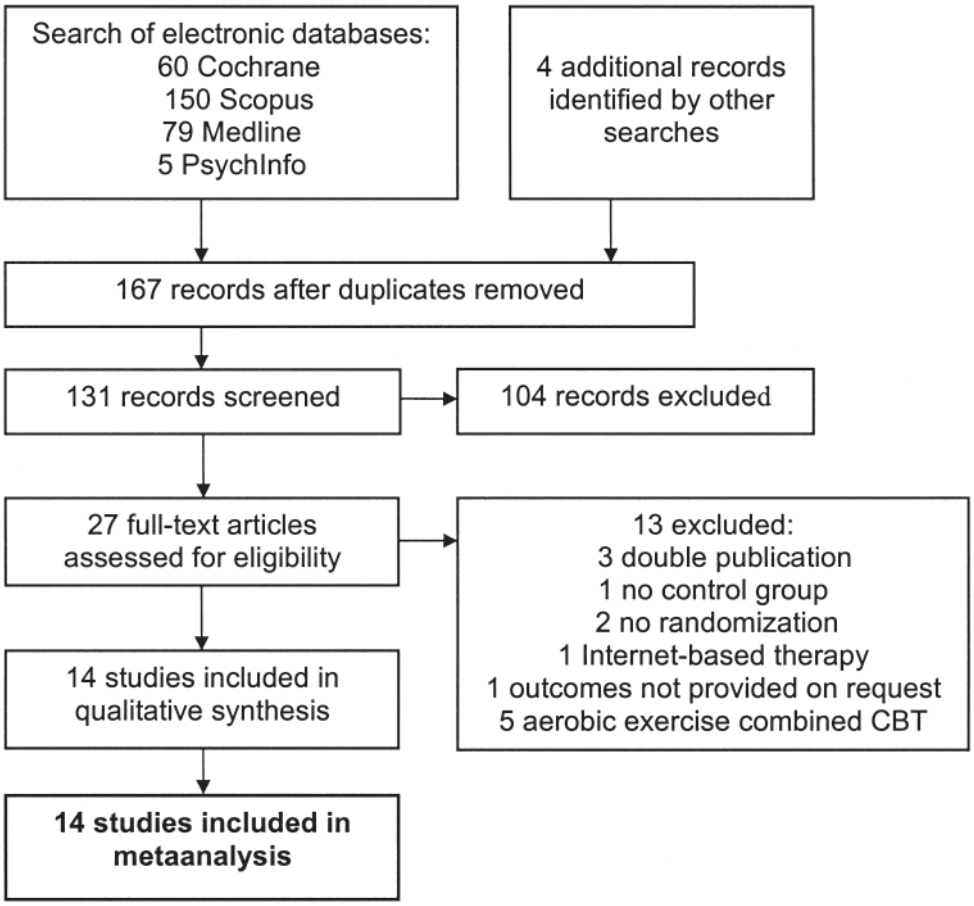


Figure 1. The selection of articles for review. CBT: cognitive-behavioral therapies.

There was a great variety of most outcomes measures. Some studies did not assess all outcomes of the review. The subscales of the Fibromyalgia Impact Questionnaire were not reported by 2 studies and were not provided on request (Table 2). No study assessed predefined response rates (e.g., percentage of patients with 30% pain reduction). Other potential outcomes of interest, e.g., anxiety or physical function, were used by only a minority of studies.

Four studies reported on side effects. Three studies reported dropouts because of increase of symptoms in the CBT group (5/129 patients) and one study in the control group (2/39 patients). One study reported that no treatment-related side effects occurred.

Risk of bias within studies. One study fulfilled all predefined criteria for methodological quality (Table 3). The reported quality of treatment was low in most studies (Table 4). Seven studies included patients with mental disorders.

Results of individual studies. The means, SD, sample sizes, and effect estimates at posttreatment of each study can be seen in the forest plots (Figure 2).

Synthesis of results. Data are reported as follows: standardized mean difference, 95% confidence interval; p value of test for overall effect.

CBT reduced depressed mood (0.24, 95% CI –0.40, –0.08; p = 0.004) and improved self-efficacy pain (0.85, 95% CI 0.25, 1.46; p = 0.006) compared to controls at posttreatment. There was no significant effect on fatigue (–0.09, 95% CI –0.27, 0.51; p = 0.61), sleep (–0.15, 95% CI –0.60, 0.29; p = 0.50), and HRQOL (–0.13, 95% CI –0.40, 0.15; p = 0.37). Based on Cohen's categories the effects were small for depression and high for self-efficacy pain.

CBT improved self-efficacy pain (0.90, 95% CI 0.14, 1.66; p = 0.02), and operant behavioral therapy reduced the number of physician visits (–1.57, 95% CI –2.00, –1.14; p < 0.001) compared to controls at the latest followup. These effects were high. There were no significant effects on pain (–0.20, 95% CI –0.57, 0.16; p = 0.28), fatigue (–0.33, 95% CI –0.87, 0.21; p = 0.23), sleep (–0.30, 95% CI –1.04, 0.44; p = 0.44), and depressed mood (–0.16, 95% CI –0.35, 0.02; p = 0.07) at latest followup (Table 5).

Risk of bias across studies. There was substantial heterogeneity in all comparisons of outcomes at posttreatment and at latest followup, except for fatigue and depressed mood at posttreatment and for depressed mood at followup (Table 5).

On visual inspection, the funnel plots of the outcomes pain, depressed mood, and HRQOL did not indicate publication bias (data available on request).

Table 3. Risk of bias summary (methodological quality) of the randomized controlled trials analysis.

Study	Adequate Randomization	Adequate Allocation Concealment	Blinding of Assessor	Intention to Treat Analysis
Astin 2003[38]	No	Yes	Yes	No
Burckhardt 1994[39]	No	No	No	No
Edinger 2005[40]	No	No	No	Yes
Garcia 2006[41]	No	No	No	Yes
Grossman 2007[42]	No	No	No	Yes
Kashikar-Zuck 2005[43]	Yes	Yes	Yes	Yes
Nicassio 1997[44]	Yes	No	No	No
Redondo 2004[45]	Yes	No	No	Yes
Sephton 2007[36]	Yes	No	No	Yes
Soares 2002[46]	No	No	No	Yes
Thieme 2003[47]	No	No	No	Yes
Thieme 2006[48]	No	No	No	Yes
Vlaeyen 1996[37]	No	No	No	Yes
Wigers 1996[49]	Yes	No	Yes	No

No: not performed or not reported (unclear).

Table 4. Risk of bias summary (treatment quality) of the randomized controlled trials analysis.

Study	Treatment Content and Setting	Treatment Duration	Manualization	Adherence to Manual	Therapist Training	Client Engagement	Sum
Astin 2003[38]	2	1	2	0	1	0	6
Burckhardt 1994[39]	1	1	0	0	1	0	3
Edinger 2005[40]	1	1	2	0	1	0	5
Garcia 2006[41]	1	1	0	0	0	0	2
Grossman 2007[42]	2	1	0	0	1	0	4
Kashikar-Zuck 2005[43]	2	1	2	1	2	0	8
Nicassio 1997[44]	1	1	0	0	0	0	2
Redondo 2004[45]	2	1	0	0	0	0	2
Sephton 2007[36]	2	1	2	0	2	0	5
Soares 2002[46]	1	1	0	0	1	0	3
Thieme 2003[47]	2	1	2	0	0	0	5
Thieme 2006[48]	2	1	1	0	2	0	6
Vlaeyen 1996[37]	1	1	0	0	0	0	2
Wigers 1996[49]	1	1	0	0	1	1	4

0: inadequate or not reported; 1: partially adequate; 2: adequate.

Additional analysis. *Subgroup analysis*. None of the comparisons of subgroup analyses yielded a significant test for overall effect for the outcome of pain. Statistical heterogeneity of analysis was substantially reduced in case of MBSR and CBT, in case of duration < 10 and 10–20 hours, and if attention placebo and therapy as usual/no therapy were used for controls. Heterogeneity was due to cases of operant therapy, therapies > 20 hours, and active therapies as controls (Table 6).

Sensitivity analysis. Stratification according to potential risks of methodological bias for the outcome with a significant test for overall effect, namely depressed mood at posttreatment, confirmed only partially the robustness of the results: the test for overall effect was significant only in studies without adequate allocation concealment, without intention-to-treat analysis, with moderate treatment quality, without inclusion of patients with affective and anxiety disorders, and with adequate randomization. Only studies published in the period 2006–2009 had a significant test for overall effect on depressed mood. Statistical heterogeneity of analysis was substantially reduced in all comparisons (Table 7).

DISCUSSION

Summary of evidence. There was evidence of the efficacy of CBT to reduce depressed mood at posttreatment and to improve self-efficacy pain at posttreatment and at followup. The positive effect on depressed mood cannot be clearly distinguished from biases. There was evidence of the efficacy of operant behavioral therapy to reduce the number of physician

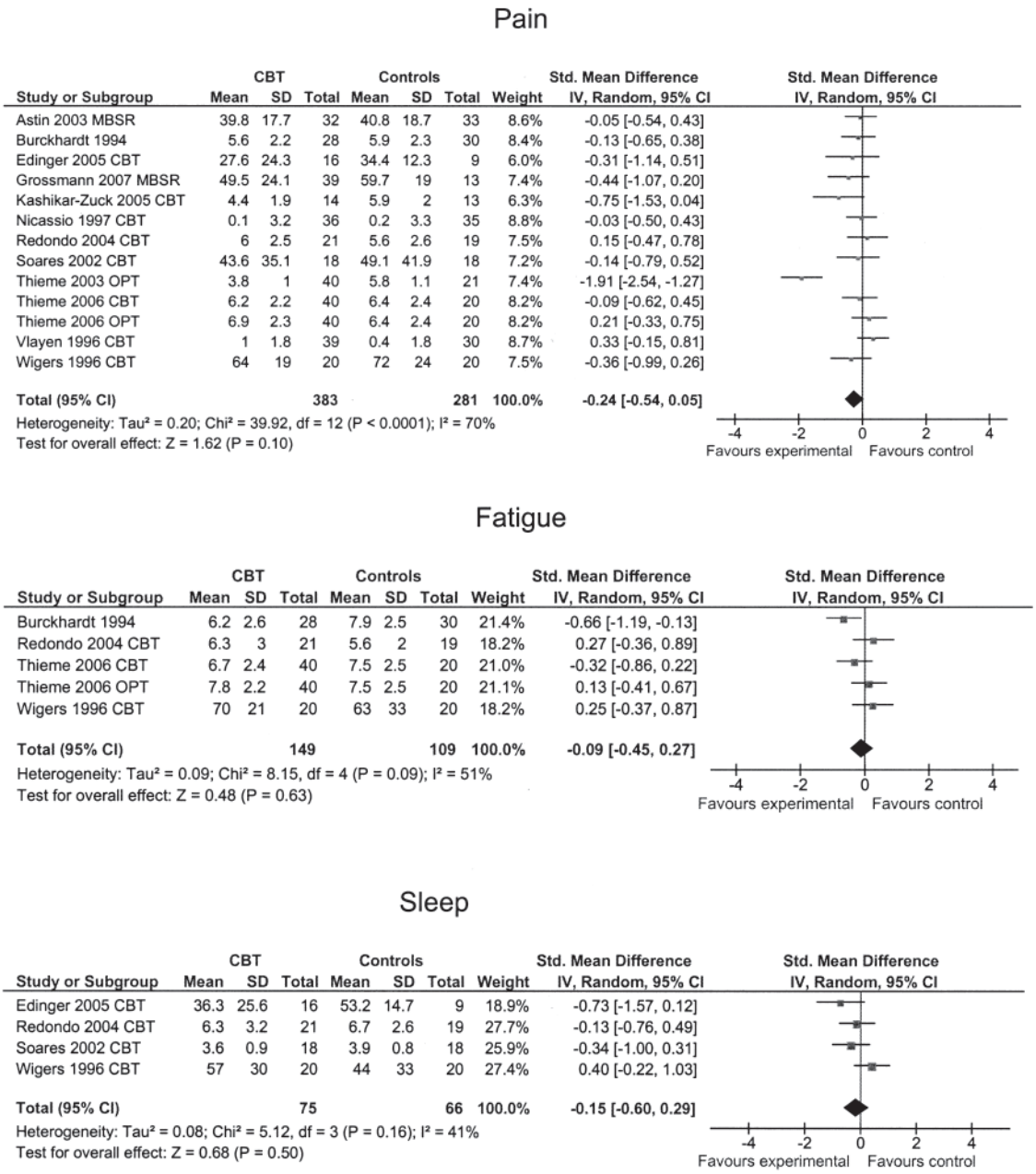


Figure 2. Forest plots of the effect estimates (standardized mean differences) of cognitive behavioral therapies versus controls on primary and secondary outcomes at posttreatment. CBT: cognitive-behavioral therapies; MBSR: mindfulness-based stress reduction.

visits at followup. There was no evidence of the efficacy of CBT to reduce pain, fatigue, sleep disturbances, and limitations of HRQOL at posttreatment and at followup.

Applicability of evidence. The study settings of secondary and tertiary care centers and the study samples, with a preponderance of middle-aged women, are representative for populations with clinical FM in the USA and Northern and Middle Europe.

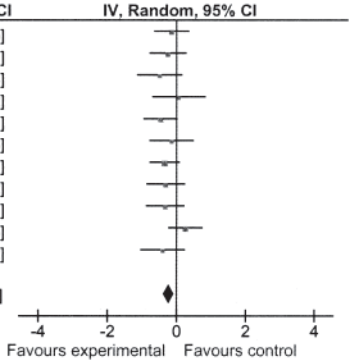
Limitations. Although every effort was made to obtain missing data from authors, it was not possible in every case to do so. Therefore some studies are not represented fully in our metaanalysis. We decided to substitute missing data by means of other studies using the same outcome scale despite the small sample sizes and substantial heterogeneity in some outcomes because we intended to include all available studies into this metaanalysis.

The methodological quality of the studies varied. Considerable heterogeneity existed for the outcomes of pain, sleep, fatigue, HRQOL, and self-efficacy pain posttreatment and at followup, and this could mainly be explained by clinical and methodological differences between the studies.

Depressed mood

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Controls Mean	Controls SD	Controls Total	Weight	Std. Mean Difference IV, Random, 95% CI
Astin 2003 MBSR	13.1	7.9	31	14.3	8.4	33	10.7%	-0.15 [-0.64, 0.35]
Burckhardt 1994	3	3	30	3.8	3.3	28	9.7%	-0.25 [-0.77, 0.27]
Grossmann 2007 MBSR	6.1	3.6	39	8	4.4	13	6.4%	-0.49 [-1.13, 0.14]
Kashikar-Zuck 2005 CBT	49.6	17.6	14	48.5	12.9	13	4.5%	0.07 [-0.69, 0.82]
Nicassio 1997 CBT	15.5	12.1	36	20.7	9.8	35	11.6%	-0.47 [-0.94, 0.01]
Redondo 2004 CBT	15.4	8.8	21	16.8	10.2	19	6.7%	-0.14 [-0.77, 0.48]
Sephton 2007 MBSR	12.4	7.4	51	15.1	8.1	39	14.7%	-0.35 [-0.77, 0.07]
Thieme 2006 CBT	4.5	3.1	40	5.5	3.2	20	8.9%	-0.32 [-0.85, 0.22]
Thieme 2006 OPT	4.3	3.8	40	5.5	3.2	20	8.9%	-0.33 [-0.87, 0.21]
Vlayen 1996 CBT	13.4	5.8	39	11.9	5.8	30	11.3%	0.26 [-0.22, 0.73]
Wigers 1996 CBT	24	22	20	36	35	20	6.6%	-0.40 [-1.03, 0.22]
Total (95% CI)			**361**			**270**	**100.0%**	**-0.24 [-0.40, -0.08]**

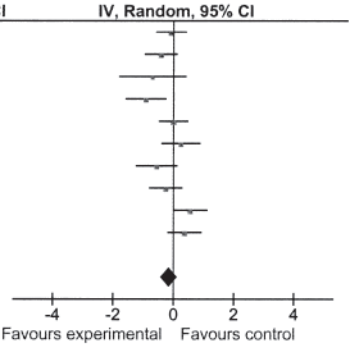
Heterogeneity: Tau² = 0.00; Chi² = 7.18, df = 10 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.89 (P = 0.004)



Health-related quality of life

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Controls Mean	Controls SD	Controls Total	Weight	Std. Mean Difference IV, Random, 95% CI
Astin 2003 MBSR	48.8	15.4	32	50.1	18.3	33	11.8%	-0.08 [-0.56, 0.41]
Burckhardt 1994	43.7	18.3	28	50.8	15.3	30	11.2%	-0.42 [-0.94, 0.10]
Garcia 2006 CBT	42	25.1	7	57	14	7	4.8%	-0.69 [-1.78, 0.40]
Grossmann 2007 MBSR	-17	5.6	39	-12.2	3.6	13	9.1%	-0.91 [-1.56, -0.26]
Nicassio 1997 CBT	-0.6	0.1	36	-0.6	0.1	35	12.1%	0.00 [-0.47, 0.47]
Redondo 2004 CBT	44.3	14.5	21	40.8	13.7	19	9.5%	0.24 [-0.38, 0.87]
Soares 2002 CBT	2.3	0.7	18	2.7	0.7	18	8.9%	-0.56 [-1.23, 0.11]
Thieme 2003 OPT	2.7	0.7	40	2.9	0.9	21	11.0%	-0.26 [-0.79, 0.28]
Thieme 2006 CBT	6.6	2.2	40	5.4	2	20	10.7%	0.55 [0.01, 1.10]
Thieme 2006 OPT	6.3	2.6	40	5.4	2	20	10.8%	0.37 [-0.17, 0.91]
Total (95% CI)			**301**			**216**	**100.0%**	**-0.13 [-0.40, 0.15]**

Heterogeneity: Tau² = 0.11; Chi² = 20.32, df = 9 (P = 0.02); I² = 56%
Test for overall effect: Z = 0.90 (P = 0.37)



Self efficacy pain

Study or Subgroup	CBTs Mean	CBTs SD	CBTs Total	Controls Mean	Controls SD	Controls Total	Weight	Std. Mean Difference IV, Random, 95% CI
Grossmann 2007 MBSR	36.8	9	39	34.7	7	13	11.1%	0.24 [-0.39, 0.87]
Kashikar-Zuck 2005 CBT	3.7	0.7	14	3.1	0.4	13	10.3%	1.01 [0.20, 1.82]
Nicassio 1997 CBT	23.4	4.3	36	24.1	4.4	35	11.7%	-0.16 [-0.63, 0.31]
Redondo 2004 CBT	5.5	2.3	21	4.7	2.2	19	11.1%	0.35 [-0.28, 0.97]
Soares 2002 CBT	52.4	22	18	35.1	17.7	18	10.9%	0.85 [0.16, 1.53]
Thieme 2003 OPT	3.7	0.7	40	1.8	1.1	21	11.0%	2.19 [1.53, 2.85]
Thieme 2006 CBT	3.9	0.5	40	2.2	1	20	10.8%	2.38 [1.69, 3.08]
Thieme 2006 OPT	3.4	1.1	40	2.2	1	20	11.3%	1.11 [0.53, 1.68]
Vlayen 1996 CBT	0.6	1.7	39	0.8	1.7	30	11.7%	-0.12 [-0.59, 0.36]
Total (95% CI)			**287**			**189**	**100.0%**	**0.85 [0.25, 1.46]**

Heterogeneity: Tau² = 0.76; Chi² = 72.10, df = 8 (P < 0.00001); I² = 89%
Test for overall effect: Z = 2.76 (P = 0.006)

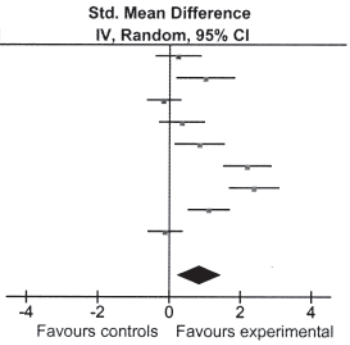


Figure 2. Continued.

Formal blinding of participants and clinicians to treatment arm is not possible in psychotherapy trials. Therefore underestimation of the extent to which clinicians' and participants' knowledge of group assignation influenced the true effect could be possible.

The reliability of the results of some sensitivity and subgroup analyses is limited because the analyses were underpowered due to the small number of included studies.

Responses in studies in patients with chronic pain are frequently not Gaussian, but with a split between responders and

Table 5. Effect sizes of cognitive-behavioral therapies on selected outcome variables.

Outcome	No. Study Arms	No. Patients	Effect Size, SMD (95% CI)	Test for Overall Effect, p	Heterogeneity, I^2 (%); Tau^2
Posttreatment					
1. Pain	13	664	–0.24 (–0.54, 0.05)	0.10	70; 0.2
2. Fatigue	4	200	0.05 (–0.23, 0.34)	0.71	0; 0
3. Sleep	4	141	–0.15 (–0.60, 0.29)	0.50	41; 0.08
4. Depressed mood	12	631	–0.24 (–0.40, –0.08)	0.004	0; 0
5. HRQOL	10	517	–0.13 (–0.40, 0.15)	0.37	56; 0.11
6. Self-efficacy pain	9	476	0.85 (0.25, 1.46)	0.006	89; 0.76
Latest followup					
1. Pain	10	527	–0.20 (–0.57, 0.16)	0.28	76; 0.26
2. Fatigue	4	200	–0.33 (–0.87, 0.21)	0.23	70; 0.21
3. Sleep	4	141	–0.30 (–1.04, 0.44)	0.44	78; 0.43
4. Depressed mood	8	494	–0.16 (–0.35, 0.02)	0.07	0; 0
5. HRQOL	7	393	0.04 (–0.21, 0.28)	0.77	31; 0.03
6. Self-efficacy pain	7	396	0.90 (0.14, 1.66)	0.02	92; 0.06
7. No. physician visits	2	121	–1.57 (–2.00, –1.14)	< 0.001	0; 0

HRQOL: Health-related quality of life; SMD: Standardized mean difference.

Table 6. Subgroup analysis of the effect size on pain at posttreatment.

Outcome	No. Study Arms	No. Patients	Effect Size, SMD (95% CI)	Test for Overall Effect, p	Heterogeneity, I^2 (%); Tau^2
Type of CBT					
Cognitive (MBSR)	2	117	–0.20 (–0.58, 0.32)	0.32	0; 0
Operant behavioral	2	121	–0.84 (–2.92, 1.24)	0.43	96; 2.16
Cognitive-behavioral	9	426	–0.08 (–0.27, 0.12)	0.44	0; 0
Duration, h					
< 10	2	87	–0.18 (–0.62, 0.25)	0.41	0; 0
10–20	4	203	–0.10 (–0.39, 0.20)	0.53	0; 0
> 20	7	374	–0.33 (–0.86, 0.21)	0.23	83; 0.43
Type of control group					
Attention placebo	6	364	–0.06 (–0.30, 0.18)	0.62	0; 0
Therapy as usual or no therapy	3	123	–0.24 (–0.60, 0.12)	0.19	0; 0
Active therapy	4	177	–0.53 (–1.58, 0.51)	0.32	91; 1.03

CBT: cognitive-behavioral therapy; MBSR: mindfulness-based stress reduction; SMD: Standardized mean difference.

nonresponders. No study assessed predefined response rates (e.g., 30% pain reduction). Therefore the IMMPACT response outcomes (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials[52]) could not be calculated.

There is no "gold standard" for the methods of a meta-analysis, e.g., for combining results and assessing risks of bias within and between studies. We followed a recent recommendation on the methods of a systematic review with metaanalysis[16]. We used the same outcomes and statistical methods as a recent Cochrane Review on psychological therapies in chronic pain[15] and other systematic reviews of the German guideline group on pharmacological and nonpharmacological therapies in FM[18,53,54,55] to allow indirect comparisons of the results of systematic reviews.

Conclusions. Agreements with other systematic reviews. Our metaanalysis does not confirm the conclusion of a qualitative systematic review of the German FM guideline group that CBT are superior to controls in most key domains of FM at the end of therapy and at followup[14]. Our results are partially in agreement with a recent Cochrane Review on CBT and behavioral therapies in chronic pain syndromes, which found that both were effective in altering mood outcomes at the end of treatment. In contrast, we previously could not find a weak effect on pain in patients with FM[15]. Therefore the high grade of recommendation given to CBT in the American and German guidelines on FM[10,11] needs to be reconsidered.

Agreement with excluded studies. The lack of efficacy of CBT on most key symptoms of FM is mainly confirmed by the studies we excluded. One RCT found no differences between CBT and treatment as usual on pain[32]. One RCT with the Internet-based arthritis self-management program found it was not superior to usual care on pain, fatigue, and disability

Table 7. Sensitivity analysis of the effect size on depressed mood at posttreatment.

Outcome	No. Study Arms	No. Patients	Effect Size, SMD (95% CI)	Test for Overall Effect, p	Heterogeneity, I^2 (%); Tau^2
Sequence generation					
Adequate	5	268	–0.31 (–0.56, –0.07)	0.01	0; 0
Unclear or inadequate	6	363	–0.18 (–0.39, 0.04)	0.11	0; 0
Concealment of allocation					
Adequate	2	91	–0.08 (–0.49, 0.33)	0.70	0; 0
Unclear or inadequate	9	540	–0.26 (–0.44, –0.07)	0.006	0; 0
Intent-to-treat analysis					
Yes	7	398	–0.19 (–0.40, 0.01)	0.07	0; 0
No	4	233	–0.31 (–0.57, –0.05)	0.02	0; 0
Treatment quality					
Poor	3	180	–0.12 (–0.56, 0.33)	0.33	55; 0.05
Average	4	240	–0.36 (–0.62, –0.09)	0.008	0; 0
Excellent	4	211	–0.21 (–0.49, 0.07)	0.14	0; 0
Patients with affective and anxiety disorders included					
Yes	6	358	–0.20 (–0.42, 0.01)	0.07	3; 0
No	5	273	–0.28 (–0.53, –0.04)	0.02	0; 0
Public period					
Until 2000	4	238	–0.20 (–0.54, 0.14)	0.124	42; 0.05
2000–2005	3	131	–0.10 (–0.44, 0.24)	0.56	0; 0
2006–2009	4	262	–0.36 (–0.62, –0.10)	0.006	0; 0

SMD: Standardized mean difference.

at the 1-year followup[26]. One controlled study found CBT was superior to waiting list on pain, fatigue, and HRQOL, but not on sleep[25]. Another controlled study found no differences between CBT and nontreated patients on sleep and depressed mood at posttreatment[24]. One CBT study[37] reported the effects on healthcare use at followup in a second publication[32]; CBT was not superior to education alone. We excluded this study from our metaanalysis because no specific interventions for healthcare use were delivered and pain behavior was not expected to be affected by the program[37].

Agreement with other studies on psychological therapies in FM. An increase in self-efficacy pain predicted the reduction of pain intensity and disability at followup by multicomponent therapy including CBT[56]. In contrast, the large effect size of CBT on self-efficacy pain in this metaanalysis was in contrast to the lack of effects of CBT on pain and HRQOL measures (which included items of disability).

Implications for clinical practice. CBT cannot be recommended for therapy of the key symptoms of FM, namely pain, fatigue, sleep disturbances, and HRQOL. The lower rate of side effects and dropouts in the studies of CBT compared to antidepressants[53] can be a major argument for CBT as a treatment option for depressive symptoms. Operant behavioral therapy can be considered to reduce healthcare-seeking behavior of patients with FM.

Implications for research. The methodological quality of further studies could be improved by consideration of the following issues. The use of a core set of outcome measures including response rates would improve the internal validity of a metaanalysis[52]. Recommendations on the quality of the treatment delivered, study design, and statistical methods should be followed[19]. Potential side effects, such as worsening of symptoms or increase of interpersonal conflicts, should be documented to allow indirect comparisons of the safety of CBT versus pharmacological therapies. More studies with adolescents and separate studies or subgroup analyses of male patients are needed to clarify the effects of CBT in these patients. Predictors of positive treatment outcomes, e.g., improved self-efficacy pain, should be investigated. Further studies are required to determine if CBT tailored to subgroups of patients with FM (e.g., with and without affective disorder) will improve the key symptoms of FM.

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