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More ubiquitous effects from non-pharmacologic than from pharmacologic treatments for fibromyalgia syndrome: A meta-analysis examining six core symptoms

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Abstract

This study aimed to characterize and compare the efficacy profile on six fibromyalgia syndrome (FM) core symptoms associated with pharmacologic and non-pharmacologic treatments. We screened PubMed, Embase and the Cochrane Library for FM articles from 1990 to September 2012 to analyse randomized controlled trials comparing pharmacologic or non-pharmacologic treatments to placebo or sham. Papers including assessments of at least 2 of the 6 main FM symptom domains – pain, sleep disturbance, fatigue, affective symptoms (depression/anxiety), functional deficit and cognitive impairment – were selected for analysis. Studies exploring pharmacologic approaches ($n = 21$) were mainly dedicated to treating a small number of dimensions, mostly pain. They were of good quality but were not prospectively designed to simultaneously document efficacy for the management of multiple core FM symptom domains. Only amitriptyline demonstrated a significant effect on as many as three core FM symptoms, but it exhibited many adverse effects and was subject to early tachyphylaxis. Studies involving non-pharmacologic approaches ($n = 64$) were typically of poorer quality but were more often dedicated to multidimensional targets. Pool therapy demonstrated significant effects on five symptom domains, repetitive transcranial magnetic stimulation on four domains, balneotherapy on three domains and exercise, cognitive behaviour therapy and massage on two domains each. Differences between pharmacologic and non-pharmacologic approaches may be related to different modes of action, tolerability profiles and study designs. Very few drugs in well-designed clinical trials have demonstrated significant relief for multiple FM symptom domains, whereas non-pharmacologic treatments with weaker study designs have demonstrated multidimensional effects. Future therapeutic trials for FM should prospectively examine each of the core domains and should attempt to combine pharmacologic and non-pharmacologic therapies in well-designed clinical trials.

1. Introduction

Among the major challenges in designing randomized clinical trials (RCTs) for fibromyalgia syndrome (FM) is the task of determining which clinical outcomes should be assessed. Classically, most trials and meta-analyses have evaluated pain and physical function (Fibromyalgia Impact Questionnaire) as the primary outcome measures. To provide a complete assessment of a treatment for FM, the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group defined core symptomatic domains that should be

What's already known about this topic?
- Most trials and meta-analyses in fibromyalgia syndrome (FM) have evaluated pain and physical function as the primary outcome measures. But FM includes a broader constellation of core symptoms, including pain, sleep dysfunction, fatigue, depression, physical dysfunction and cognitive dysfunction.

What does this study add?
- This analysis lends insight into the effects of multiple pharmacologic and non-pharmacologic treatments on six core symptom domains in FM.

measured in all FM RCTs (Mease et al., 2009, 2011). These core domains included pain, sleep dysfunction, fatigue, depression and multidimensional function. Second-level outcome domains to be measured in some but not necessarily all clinical trials included cognitive dysfunction, anxiety and tenderness.

Discrepancies between the US Food and Drug Administration (FDA)'s approval of three medications for the treatment of FM and the European Medicines Agency's rejection of the same dossier have suggested that that there is no single intervention for the management of the FM symptom complex that can be considered fully effective. Several meta-analyses have been performed on pharmacologic and non-pharmacologic treatments for FM, and the results have shown that treatments may be effective at managing a few core FM symptoms (Glombiewski et al., 2010; Häuser et al., 2010, 2013; Choy et al., 2011; Kelley and Kelley, 2011; Nüesch et al., 2013). Some combination of multicomponent therapy, consisting of pharmacologic and non-pharmacologic treatments, has been recommended to improve the efficacy of FM treatment (Häuser et al., 2010). A recent meta-analysis identified a combination of a pharmacologic treatment – such as pregabalin or a serotonin–norepinephrine reuptake inhibitor (SNRI) – and a non-pharmacologic intervention – such as aerobic exercise and/or cognitive behaviour therapy (CBT) – as prime candidates for use in a combination therapy programme (Nüesch et al., 2013). Despite the obvious appeal of such regimens, objective clinical trial evidence for additive or synergistic benefit derivable from combining pharmacologic and non-pharmacologic therapies in FM is still lacking.

Guidelines used by patients and physicians to determine effective treatment for the management of FM have been created, based on secondary research, including meta-analyses and reviews. The first level of treatment recommended by the American Pain Society (Burckhardt, et al., 2005) includes cognitive–behavioural therapy, aerobic exercise, amitriptyline and multicomponent therapy. By contrast, the European League Against Rheumatism (Carville et al., 2008) recommends only pharmacologic treatment – such as amitriptyline, tramadol, fluoxetine, duloxetine, milnacipran, moclobemide, pirlindole, tropisetron, pramipexole or pregabalin – as first line of treatment for FM.

The aim of the current meta-analysis is to characterize the efficacy profiles of pharmacologic and non-pharmacologic interventions for the management of the six core FM clinical domains as defined by OMERACT (Mease et al., 2009, 2011; pain, sleep dysfunction, fatigue, depression, physical dysfunction, cognitive dysfunction). An additional goal was to identify potential combinations of interventions that may prove to be complementary in treating patients with multisymptomatic FM.

2. Materials and methods

2.1 Data sources and searches

The meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Liberati et al., 2009) and the recommendations of the Cochrane Collaboration (Higgins and Green, 2011). The electronic bibliographic databases screened, from 1990 to September 2012, included PubMed, Embase and Cochrane Library. The keywords for initial inclusion were 'fibromyalgia', 'human', 'randomized clinical trial' and 'adult'.

2.2 Study selection

To be included in the meta-analysis, studies were required to meet the following criteria:
(1) The diagnosis of FM was based on the ACR 1990 criteria;
(2) Clinical trials in which a pharmacologic or a non-pharmacologic treatment was used as an active treatment for FM;
(3) Assessment of at least two of the following six domains: pain, sleep disturbance, fatigue, affective symptoms (depression/anxiety), functional deficit and cognitive impairment;
(4) A placebo-controlled study design for pharmacologic treatments and a controlled study design for non-pharmacologic treatment, in which the control group received sham treatment, usual care, no treatment or a lesser intensity of the active treatment;
(5) Studies that were available as a full-text English-language publication in a peer-reviewed science journal.

(6) Studies in which the data were appropriate for meta-analysis.

Studies were excluded if:

(1) Some or all of the patients in the study had been diagnosed with separate medical conditions co-morbid with FM, e.g., inflammatory or psychiatric disorders;

(2) They were pilot or extension studies.

The authors of the original reports were contacted for additional information as needed.

2.3 Data abstraction

Two clinical reviewers independently screened the titles and abstracts of potentially eligible studies identified by the search strategy detailed above. The full-text articles were then examined independently by two contributors to confirm that they met the inclusion criteria, and then each article was scored based on study quality. Discrepancies were resolved by discussion and, when needed, an author reviewed and adjudicated the articles in question.

2.4 Quality assessment

The methodological quality of the studies was assessed using a scoring method adapting the Jadad criteria for pharmacologic trials (Jadad et al., 1996), assessing for randomization, blinding and explanations for study dropouts. For each study, quality was assessed independently by two reviewers. Disagreements were resolved through discussion.

2.5 Data synthesis and analysis

If the study included more than one measure to assess an outcome within a symptom domain (e.g., if pain is measured in multiple ways), only one outcome measure per domain was included. If an outcome measure was specified as a primary variable, then that outcome measure was used. For outcome measures that were not identified as a primary variable, the order of preference for the outcome measures developed by the authors was used. When a study contained a measure assessing both depression and anxiety, the depression outcome measure was included in the meta-analysis.

The meta-analyses were conducted using RevMan software version 5.2 (The Nordic Cochrane Centre, Copenhagen, Denmark). Individual effect sizes for each domain that were assessed in more than one study were calculated using pre- and post-treatment differences. The overall effect size for each domain was computed based on all of the studies with individual effect sizes for that particular domain. The standard mean difference was calculated using mean, standard deviation (SD) or standard error (SE), and N at baseline and end point mean or postbaseline and SD or SE and N for change from baseline.

To measure heterogeneity between the RCTs, I^2 statistics was used. When $I^2 = 0\%$, an inverse variance, fixed-effect model was used. When $I^2 > 0\%$, the DerSimonian and Laird random effect model was used (DerSimonian and Kacker, 2007).

The magnitude of the overall effect size was evaluated using Cohen's categories, where >0.2–0.5 indicates a small effect size, >0.5–0.8 indicates a medium effect size and >0.8 indicates a large effect size (Cohen, 1992).

3. Results

3.1 Selection of studies

The literature search yielded 1516 citations that were potentially relevant for pharmacologic and non-pharmacologic treatments for FM. Of these, 754 citations were excluded due to duplication. Of the 762 potential studies that remained, 266 articles were excluded because they were about diseases other than FM or included diseases other than FM ($n = 115$), because they were not studies of treatments for symptoms of interest ($n = 105$), or for other reasons ($n = 46$). After screening the remaining 496 abstracts, 229 articles were excluded for reasons presented in Fig. 1.

After a detailed review of the selected reports, 79 more articles were excluded, because they did not present results for at least 2 of the 6 FM-specific domains. Therefore, 188 studies remained that could potentially be included in the meta-analysis: 69 studies assessed pharmacologic treatment for FM and 119 studies assessed non-pharmacologic treatment for FM. Of the 69 studies assessing pharmacologic treatment, 44 were excluded due to insufficient data. Of the 119 studies assessing non-pharmacologic treatment, 52 were excluded due to insufficient data. In both cases, insufficient data referred primarily to missing data on several FM core symptoms. Finally, 25 articles assessing pharmacologic treatment and 67 assessing non-pharmacologic treatment for FM were included in the meta-analysis.

3.2 Study design

3.2.1 Pharmacologic studies

All studies were conducted in an outpatient setting. Six were conducted in Europe, one was conducted in Brazil and eight were conducted in the United States.

3.2.2 Non-pharmacologic studies

The non-pharmacologic studies were conducted in Brazil, Canada, Finland, France, Germany, Italy, the Netherlands, Spain, Switzerland, Tunisia, Turkey, the United Kingdom and the United States.

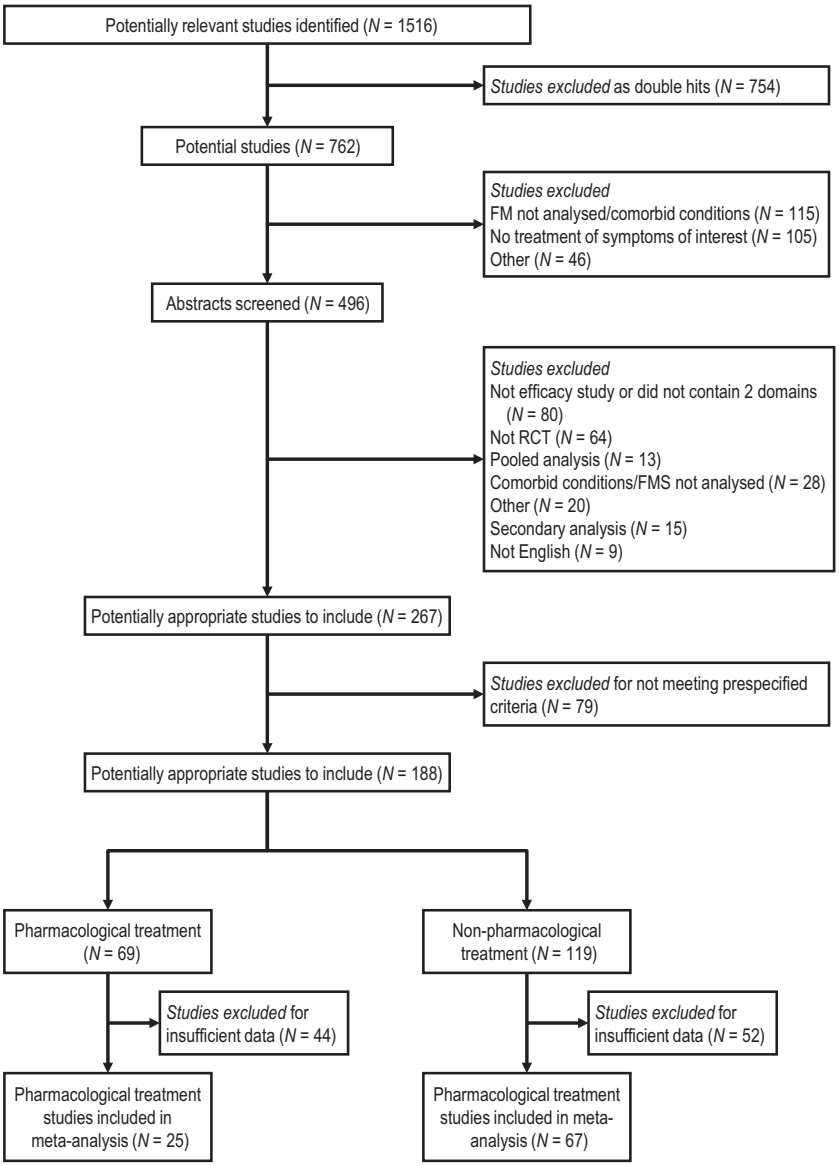

Figure 1 Study flow chart.

3.3 Studies' populations

3.3.1 Pharmacologic studies

Studies contributing data to the pharmacologic agent analysis are characterized in Supporting Information Table S1. Fifteen studies reported the percentage of screened and randomized patients. Approximately 68% (2855/4229) of patients in all the pharmacologic treatment groups completed their study compared with approximately 73% (2258/3090) of placebo patients. The mean age across all studies was about 50 years. There were nine studies that involved only women; for the remaining studies, the proportion of subjects who were women ranged from 83% to 97%. Ten studies reported patients' ethnicities. White patients represented 65–100% of the studies' populations.

3.3.2 Non-pharmacologic treatment

Studies contributing data to the non-pharmacologic analysis are characterized in Supporting Information Table S2. Thirty-eight studies reported the number of subjects screened (7049 subjects) and randomized [3371 (47.8%)]. Approximately 81% (999/1239) of patients in all the non-pharmacologic treatment groups completed their study versus approximately 64.6% (779/1205) of control patients. The mean age range across the studies was 30–59 years. Twenty studies had inclusion criteria calling for inclusion of

women only. For the remaining studies, the proportion of women ranged from 77.1% to 100.0%. Of the studies reporting race, white patients represented 80–100% of the studies' populations.

3.4 Methodological quality

For the pharmacologic treatment studies, the overall average quality score was 5.1 (range 0–6). Pharmacologic treatment studies included studies of good methodology, developed for the approval of new drugs, with many clinical centres, large numbers of subjects and low variance. For the non-pharmacologic treatment studies, the overall average quality score was 3.4 (range 0–6). The non-pharmacologic treatment studies tended to be performed at single centres, having smaller sample sizes, less rigidly controlled study designs and high variances.

3.5 Meta-analyses

3.5.1 Pharmacologic treatment

The overall effect sizes compared with placebo for each domain assessed in more than one study are summarized by treatment in Table 1 and are detailed, by symptom domain and treatment, in Supporting Information Figs. S1–S7. The effect size of a pharmacologic treatment was presented for a domain only if data from more than one study were available. Due to a lack of data availability in many studies, the effect of pharmacologic treatment on cognitive impairment was assessed only for treatment with duloxetine and milnacipran.

Amitriptyline (Carette et al., 1995; Ginsberg, 1996; Goldenberg et al., 1996; Hannonen et al., 1998; Heymann et al., 2001) was effective at reducing pain [effect size 0.83; 95% confidence intervals (95% CIs) 0.36, 1.29; $p = 0.0005$] and sleep disturbance (effect size 0.70; 95% CI 0.40, 0.99; $p < 0.00001$) and for improving fatigue (effect size 0.59; 95% CI 0.07, 1.12; $p < 0.03$). The effect size on pain was large, whereas the effects on sleep disturbance and fatigue were medium. Curiously, for an antidepressant drug, there was no influence on affective symptoms (effect size 0.08; 95% CI −0.31, 0.47; $p = 0.69$). However, interpretation of these data must be balanced by two considerations: first, the burden of amitriptyline side effects has been demonstrated to be greater than that of other antidepressants, with only one-third of patients benefiting from amitriptyline (Moore et al., 2012); second, findings from a negative study on pain due to tachyphylaxis at 12 weeks (Carette et al., 1994) that was not included in our meta-analysis, because of insufficient data in several domains.

Citalopram (Nørregaard et al., 1995; Anderberg et al., 2000) produced a non-significant weak effect size on sleep disturbance (effect size 0.29; 95% CI −0.16, 0.74; $p = 0.21$). There were no significant effects on pain, fatigue or affective symptoms.

Duloxetine studies provided data to analyse across all domains (Arnold et al., 2004, 2005, 2010). A statistically significant improvement in reducing pain, sleep disturbance, fatigue, affective symptoms, functional deficit and cognitive impairment was noted for duloxetine treatment. The effect sizes across these domains ranged from 0.22 (95% CI 0.07, 0.36; $p = 0.003$) to 0.37 (95% CI 0.22, 0.51; $p < 0.00001$), indicating small treatment effects.

Fluoxetine treatment demonstrated a medium effect for pain (effect size 0.67; 95% CI 0.01, 1.34; $p = 0.05$) (Wolfe et al., 1994; Goldenberg et al., 1996; Arnold et al., 2002). Small effects on sleep disturbance (effect size 0.28; 95% CI −0.09, 0.65; $p = 0.14$), fatigue (effect size 0.30; 95% CI −0.07, 0.67; $p = 0.11$), affective symptoms (effect size 0.45; 95% CI 0.07, 0.82;

Table 1 Effect sizes of pharmacologic treatments on FMS symptom domains.

Treatment	Pain effect size (95% CI)	Sleep disturbance effect size (95% CI)	Fatigue effect size (95% CI)	Affective symptoms effect size (95% CI)	Functional deficit effect size (95% CI)	Cognitive impairment effect size (95% CI)
Amitriptyline	**0.82** (0.36, 1.28)	**0.69** (0.41, 0.96)	**0.58** (0.05, 1.11)	0.08 (–0.27, 0.43)	0.37 (–0.01, 0.74)	–
Citalopram	0.12 (–0.49, 0.72)	0.29 (–0.16, 0.74)	–0.03 (–0.48, 0.41)	0.15 (–0.30, 0.60)	–	–
Duloxetine	0.36 (0.19, 0.53)	0.24 (0.06, 0.43)	0.22 (0.07, 0.36)	0.23 (0.10, 0.35)	0.34 (0.18, 0.49)	0.37 (0.22, 0.51)
Fluoxetine	**0.67** (0.01, 1.34)	0.28 (–0.09, 0.65)	0.30 (–0.07, 0.67)	0.48 (0.10, 0.85)	0.31 (–0.06, 0.69)	–
Growth hormone	**1.35** (0.50, 2.20)	–	–	–	**1.24** (–0.36, 2.84)	–
Milnacipran	0.22 (0.15, 0.30)	0.11 (0.00, 0.21)	0.13 (0.06, 0.21)	0.12 (0.04, 0.19)	0.15 (0.08, 0.23)	0.17 (0.09, 0.24)
Pregabalin	0.31 (–0.06, 0.67)	0.57 (0.42, 0.71)	–	–	0.19 (–0.02, 0.39)	–
Sodium oxybate	0.44 (0.31, 0.58)	**0.47** (0.28, 0.66)	**0.48** (0.35, 0.60)	*	*	*

Bolded values indicate effect sizes >0.5. CI, confidence interval; FMS, fibromyalgia syndrome.

– The domain was not measured in the study or not enough information was provided to calculate effect size.

*The effect size for the domain was not calculated, data available from only one study.

$p = 0.02$) and functional deficit (effect size 0.31; 95% CI −0.06, 0.68; $p = 0.10$) were also noted with fluoxetine treatment. The dosage of fluoxetine was up to 80 mg/day in one study (Arnold et al., 2002) and 20 mg in the other two studies (Wolfe et al., 1994; Goldenberg et al., 1996). When used at a standard dosage, fluoxetine is not effective for FM pain, while at very high dosages, it may act non-specifically, in the manner of an SNRI or a tricyclic antidepressant.

Milnacipran demonstrated a small but significant effect on pain (effect size 0.22; 95% CI 0.15, 0.30; $p < 0.00001$) (Vitton et al., 2004; Clauw et al., 2008; Branco et al., 2010), while there were no effects on sleep disturbance, fatigue, affective symptoms, functional deficit or cognitive impairment.

Growth hormone induced a very substantial reduction in pain (effect size 1.36; 95% CI 0.01, 1.34; $p = 0.05$) and a similar magnitude of improvement in functional deficit (effect size 1.24; 95% CI −0.36, 2.84; $p = 0.13$) (Bennett et al., 1998; Cuatrecasas et al., 2007). Both outcomes achieved large effect sizes with this biological intervention.

Pregabalin induced a small but significant effect on pain (effect size 0.31; 95% CI −0.06, 0.67; $p = 0.10$). Its effect on sleep disturbance was larger but still in the small-effect range (effect size 0.49; 95% CI 0.34, 0.63; $p < 0.00001$) (Arnold et al., 2008; Pauer et al., 2011). No effect (effect size 0.19; 95% CI −0.02, 0.39; $p = 0.08$) was evident on functional deficit. Due to unavailability of data, the effects of pregabalin on fatigue, affective symptoms and cognitive impairment were not analysed.

Sodium oxybate reduced sleep disturbance (effect size 0.6; 95% CI 0.32, 0.91; $p < 0.00001$) and fatigue (effect size 0.59, 95% CI 0.25, 0.92; $p = 0.0005$) with a medium effect size (Scharf et al., 2003; Russell et al., 2009, 2011; Moldofsky et al., 2010). The effect on pain (effect size 0.42; 95% CI 0.11, 0.73; $p = 0.008$) was small but significant (Russell et al., 2009; Moldofsky et al., 2010; Spaeth et al., 2012).

3.5.2 Non-pharmacologic treatment

The individual effect sizes for each domain assessed in more than one study are shown in Supporting Information Figs. S8–S19. The effect size of a non-pharmacologic treatment was presented for a domain only if data from more than one study were available.

Table 2 presents the overall effect size per non-pharmacologic treatment compared with control groups. Due to limitations in data availability, the effect of non-pharmacologic treatment on cognitive impairment was assessed only for CBT, exercise, neurotherapy and pool/water treatment groups. Pool/water, CBT, exercise and neurotherapy were the non-pharmacologic treatments with data available to analyse across all domains.

Acupuncture (Deluze et al., 1992; Harris et al., 2005; Martin et al., 2006) produced a small non-significant effect on sleep disturbance (effect size 0.49; 95% CI −0.17, 1.15; $p = 0.15$) but did not have an effect on pain, fatigue or functional deficit.

Balneotherapy (Ardiç et al., 2007; Brockow et al., 2007; Fioravanti et al., 2007; Evcik et al., 2008) was an effective treatment for all the domains assessed, which included large effects on pain (effect size 1.02; 95% CI 0.34, 1.70; $p = 0.003$) and affective symptoms (effect size 1.65; 95% CI 1.06, 2.23; $p < 0.00001$) and

Table 2 Effect sizes of non-pharmacologic treatments on FM symptom domains.

Treatment	Pain effect size (95% CI)	Sleep disturbance effect size (95% CI)	Fatigue effect size (95% CI)	Affective symptoms effect size (95% CI)	Functional deficit effect size (95% CI)	Cognitive impairment effect size (95% CI)
Acupuncture	0.18 (–0.13, 0.49)	0.49 (–0.17, 1.15)	0.02 (–0.43, 0.46)	–	0.14 (–0.24, 0.53)	–
Balneotherapy	**1.02** (0.34, 1.70)	–	–	**1.65** (1.06, 2.23)	**0.67** (0.39, 0.96)	–
Cognitive behaviour	**0.53** (0.29, 0.77)	0.42 (0.12, 0.71)	**0.96** (0.47, 1.45)	0.16 (–0.04, 0.36)	0.48 (0.24, 0.73)	0.40 (0.03, 0.77)
Exercise	0.50 (0.26, 0.74)	0.46 (0.22, 0.70)	0.45 (0.16, 0.74)	0.48 (0.26, 0.69)	**0.52** (0.36, 0.69)	0.49 (0.16, 0.82)
Education	0.50 (0.12, 0.89)	0.14 (–0.29, 0.58)	0.36 (0.13, 0.59)	0.43 (0.10, 0.77)	0.36 (–0.00, 0.72)	–
Education/exercise combined	0.19 (–0.06, 0.44)	0.23 (–0.08, 0.54)	0.40 (0.20, 0.61)	0.07 (–0.32, 0.46)	0.20 (–0.13, 0.52)	–
Homeopathic	**0.54** (0.26, 0.83)	–	0.38 (–0.08, 0.85)	0.25 (–0.03, 0.53)	0.37 (0.05, 0.69)	–
Magnetic cerebral stimulation	**1.30** (0.11, 2.48)	**0.53** (–0.02, 1.07)	**1.19** (0.77, 1.62)	0.23 (–0.13, 0.59)	**1.04** (0.23, 1.84)	–
Massage	**0.53** (0.08, 0.98)	0.20 (–0.27, 0.68)	–	**0.70** (0.31, 1.09)	0.39 (–0.10, 0.87)	–
Neurotherapy	0.44 (0.03, 0.86)	0.03 (–0.39, 0.44)	0.17 (–0.25, 0.58)	0.05 (–0.36, 0.46)	–0.03 (–0.45, 0.38)	0.14 (–0.27, 0.55)
Pool/water	**0.79** (0.14, 1.44)	**1.06** (0.15, 1.96)	**1.05** (0.19, 1.90)	**0.89** (0.37, 1.41)	**0.69** (0.39, 0.99)	**0.64** (–0.10, 1.39)
UV/bright light	0.50 (–0.10, 1.10)	0.48 (–0.02, 0.97)	0.39 (–0.21, 0.99)	0.11 (–1.05, 1.26)	0.39 (–0.45, 1.23)	–

Bolded values indicate effect sizes >0.5. CI, confidence interval; FM, fibromyalgia; UV, ultraviolet.

– The domain was not measured in the study or not enough information was provided to calculate effect size.

a medium effect on functional deficit (effect size 0.67; 95% CI 0.39, 0.96; $p < 0.00001$).

CBT treatment was effective at improving all symptom domains except affective symptoms (Soares, 2002; Edinger et al., 2005; Thieme et al., 2006; Grossman et al., 2007; Falcao, 2008; Lera et al., 2009; Ang et al., 2010; Hsu et al., 2010; van Koulil et al., 2010; Carleton et al., 2011; Miró, 2011; Schmidt et al., 2011). The effect size on fatigue was large (effect size 0.96; 95% CI 0.47, 1.45; $p = 0.0001$), whereas the effect on pain was medium (effect size 0.53; 95% CI 0.29, 0.77; $p < 0.00001$). Effects on sleep disturbance, functional deficit and cognitive impairment were small.

Exercise had a medium effect size on functional deficit (effect size 0.52; 95% CI 0.36, 0.69; $p < 0.00001$), a small effect on pain (effect size 0.50; 95% CI 0.26, 0.74; $p < 0.0001$) and small effects (range, 0.45–0.49) on the other four symptom domains (Martin et al., 1996; Gowans et al., 2001; Häkkinen et al., 2001; Jones et al., 2002; King et al., 2002; Schachter et al., 2003; Valim et al., 2003; Sencan, 2004; Lemstra and Olszynski, 2005; Rooks et al., 2007; Altan et al., 2009; Carson et al., 2010; Fontaine et al., 2010; Mannerkorpi et al., 2010; Sañudo et al., 2011; García-Martínez, 2012).

Education as treatment for FM had a small effect on pain (effect size 0.50; 95% CI 0.12, 0.89; $p = 0.01$) (Luciano et al., 2011). Small effects (effect sizes ranging from 0.43 to 0.36) were also noted for fatigue, affective symptoms and functional deficit. There was no effect of education on sleep disturbance.

The combination therapy of exercise and education had a small effect on fatigue (effect size 0.40; 95% CI 0.20, 0.61; $p < 0.00001$) and on sleep disturbance (effect size 0.23; 95% CI −0.08, 0.54; $p = 0.15$) but did not have an effect on pain, affective symptoms or functional deficit (Cedraschi et al., 2004; Zijlstra et al., 2005; Hammond and Freeman, 2006).

Homeopathic treatment had a medium effect on pain (effect size 0.54; 95% CI 0.26, 0.83; $p = 0.0002$) and small effects (effect sizes ranging from 0.38 to 0.25) on fatigue, affective symptoms and functional deficit (Merchant, 2001; Bell et al., 2004; Ali et al., 2009; Relton et al., 2009).

Repetitive transcranial magnetic stimulation (rTMS) was effective on all five domains with data available, providing large effects on pain (effect size 1.30; 95% CI 0.11, 2.48; $p = 0.03$), fatigue (effect size 1.19; 95% CI 0.77, 1.62; $p < 0.00001$) and functional deficit (effect size 1.04; 95% CI 0.23, 1.84; $p = 0.01$); a medium effect on sleep disturbance (effect size 0.53; 95% CI −0.02, 1.07; $p = 0.06$); and a small effect on affective symptoms (effect size 0.23; 95% CI −0.13, 0.59; $p = 0.21$) (Passard et al., 2007; Sutbeyaz et al., 2009; Mhalla et al., 2011).

Massage showed medium effects on affective symptoms (effect size 0.70; 95% CI 0.31, 1.09; $p = 0.0005$) and pain (effect size 0.53; 95% CI 0.08, 0.98; $p = 0.02$) (Blunt et al., 1997; Brattberg, 1999; Field, 2002, 2003). A small effect was seen on functional deficit (effect size 0.39; 95% CI −0.10, 0.87; $p = 0.12$), but no effect was apparent on sleep disturbance.

Neurotherapy (Kravitz, 2006; Nelson et al., 2010) produced a small effect on pain (effect size 0.44; 95% CI 0.03, 0.86; $p < 0.04$). There were no effects on sleep disturbance, fatigue, affective symptoms, functional deficit or cognitive impairment.

Treatments in a pool/water (Mannerkorpi et al., 2000; Altan et al., 2004; Assis et al., 2006; Tomas-Carus et al., 2007, 2008; Ide, 2008; Cuesta-Vargas, 2011) were effective for pain (effect size 0.79; 95% CI 0.14, 1.44; $p = 0.02$), sleep disturbance (effect size 1.06; 95% CI 0.15, 1.96; $p = 0.02$), fatigue (effect size 1.05; 95% CI 0.19, 1.90; $p = 0.02$), affective symptoms (effect size 0.89; 95% CI 0.37, 1.41; $p = 0.0008$), functional deficit (effect size 0.69; 95% CI 0.39, 0.99; $p < 0.00001$) and cognitive impairment (effect size 0.64; 95% CI −0.10, 1.39; $p = 0.09$). Based on Cohen's categories, effects were medium (pain, functional deficit, cognitive impairment) to large (sleep disturbance, fatigue, affective symptoms).

Finally, ultraviolet/bright light treatments (Pearl et al., 1996; Gür et al., 2002; Almeida, 2003; Armagan, 2006; Matsutani et al., 2007; Taylor et al., 2009) showed a small effect on pain (effect size 0.50; 95% CI −0.10, 1.10; $p = 0.008$), small effects on sleep disturbance, fatigue and functional deficit (effect sizes ranging from 0.39 to 0.48), but no influence on affective symptoms.

4. Discussion

The current meta-analysis has documented that amitriptyline, growth hormone and sodium oxybate demonstrated significant effects on at least two of the core symptom domains of FM. Amitriptyline was found to have exhibited significant effects on three symptom domains: pain, sleep disturbance and fatigue, whereas growth hormone exhibited significant effect on pain and function. As observed in previous meta-analyses, pain was relieved by most treatments studied, but only growth hormone demonstrated a large effect size for pain. The rationale for using growth hormone is based on the fact that human growth production occurs mainly with aerobic exercise and slow wave sleep.

Both of these are in low in FM. This has been confirmed in FM where production of growth hormone and levels of insulin-like growth factor-1 are low (Cuatrecasas et al., 2014). Fluoxetine showed no effect at normal dosages and a medium effect size in quadruple the antidepressant dosage. Duloxetine, milnacipran, pregabalin and sodium oxybate showed small effects on pain, whereas citalopram showed no effect on pain. None of the pharmacologic treatments showed a large effect on sleep disturbance: amitriptyline, sodium oxybate and pregabalin showed medium effect sizes, whereas all other treatments with available data, except for milnacipran, showed small effects. Among the remaining four domains (fatigue, affective symptoms, functional deficit, cognitive impairment), effects, if present at all, were typically small. The only large effect was shown by growth hormone for functional deficit and the only medium effect size was associated with amitriptyline and sodium oxybate on fatigue.

Among non-pharmacologic interventions, this meta-analysis has shown that pain was the symptom that was most frequently relieved: balneotherapy and rTMS demonstrated large effects on pain. Pool/water exercise, CBT, homeopathy and massage all showed medium effect sizes on pain. For the other domains, the effects were variable. Pool/water exercise showed consistent medium-to-large effects on all six domains. Large effects were also shown by rTMS (fatigue and functional deficit), balneotherapy (affective symptoms) and CBT (fatigue). Balneotherapy and exercise had medium effect sizes on functional deficit, as did massage on affective symptoms and magnetic therapy on sleep disturbance. All other therapeutic effects for treatments with data available were small, if present at all. Somewhat surprisingly, the combination of exercise and education showed smaller effect size changes overall than either exercise or education alone.

Meta-analyses are commonly used to assess outcomes in pain conditions and to compare treatments for one or two clinical domains, e.g., most commonly pain and function, consistent with EULAR's FM recommendations (Carville et al., 2008). However, in a complex condition like FM, in which symptom severity and illness burden are associated with six quite different core OMERACT FM domains (Perrot et al., 2012), it seems inappropriate to limit any comparison with pain only. Our meta-analysis has tried to examine responses in each of the six core clinical domains to therapies that have been studied by two or more research groups. The findings have demonstrated that very few pharmacologic interventions induce significant relief on more than one FM symptom domain, whereas non-pharmacologic treatments seemed to demonstrate more potential to concomitantly treat multiple FM symptoms.

Among the pharmacologic treatments, amitriptyline looked very good for such an old and inexpensive drug. It exhibited at least a medium effect on three symptom domains (pain, sleep dysfunction and fatigue). From one viewpoint, comparison seems legitimate because all three of those manifestations (co-morbidities) are highly prevalent among people with FM. The problem with amitriptyline that our meta-analysis cannot easily address is that most of those benefits attributable to amitriptyline were short-term effects: efficacy on pain and sleep compared with placebo was demonstrated in studies of no more than 3 months in length. At 3 months, the perceived benefit was no greater than with placebo. Moreover, effects of amitriptyline strongly depend on the dose: analgesic between 25 and 50 mg, and antidepressant above 75 mg/day. The amitriptyline story may be a unique case, because the studies were conducted so long ago that they may not be directly comparable with more contemporary studies. Indeed, the tachyphylaxis experience with amitriptyline may have prompted the regulatory requirement of newer drugs to show persistent benefit against placebo for 6–12 months. The tachyphylaxis of amitriptyline after 1–2 months in patients with FM was so well recognized in the years from 1970 to 2000 that many clinicians would treat patients on 4-month cycles; amitriptyline 10 mg at bedtime for 2 months, 20–25 mg at bedtime for 1 month, off amitriptyline for 1 month and then repeat the cycle three times per year. This programme was, of course, off-label for FM, but there were no FDA-approved drugs for FM at the time. A recent meta-analysis from Moore et al. (2012) has demonstrated that in FM and neuropathic pain, only about 38% of participants benefited from amitriptyline, whereas 64% of participants who took amitriptyline experienced at least one adverse event.

Interestingly, pool/water therapy showed broad efficacy across all domains. When a facility is available, pool exercise can be quite economical. Patients can be trained on how to do 20 min of aerobic walk-in-place therapy on alternate days (in about 4 feet of water) without any need for the involvement of trained therapists. Aside from their objections to the cold sensation associated with initially entering the water, patients typically tolerate this therapy very well. It can be very helpful for FM patients who are overweight because the support of the water reduces the risk of mechanical injury to weight-bearing joints. But as with any exercise regimen in FM, compliance tends to be poor.

Our findings for rTMS therapy and balneotherapy should inspire additional study of these modalities.

It was very difficult to know how to interpret the substantial differences observed between meta-analyses of pharmacotherapies and non-pharmacotherapies for FM. There are many recognized differences between pharmacologic and non-pharmacologic research studies as they apply to FM therapy. The methodological quality of pharmacologic clinical trials was typically better than the quality of the non-pharmacologic trials. The pharmacologic studies were typically well-funded by pharmaceutical company sponsors; were multicentre; were, by law, heavily regulated; and involved large numbers of patients whose outcome data were assessed by professional statisticians. Whether legitimate or not, some suspicion regarding bias in favour of sponsors has been considered. In contrast, non-pharmacologic studies tended to be poorly funded, were typically from single centres and were challenged by poor patient compliance, leading to variability in outcomes and concerns regarding the validity of the statistical analyses. Readers of such studies must wonder about the potential differences in quality of the available data and about the conclusions derived from these two rather different types of investigations.

Some of the differences between the apparent effectiveness of pharmacologic and non-pharmacologic therapies for selected symptomatic domains of FM may relate to the historical development of diagnostic criteria for FM. With the advent of the 1990 ACR Research Classification Criteria, pain quickly became the gatekeeper for the diagnosis of this central pain amplification syndrome. Logically, pain also became the measure of note for regulatory evaluation of medications to treat FM. It became common knowledge that for a medication to gain FDA approval for FM, the medication would have to control FM pain. As a result, pain became the primary outcome variable for preclinical animal studies and for phase II screening of pharmacologic agents to treat FM. Non-pharmacologic interventions did not have the same mandatory focus on improving a single-symptom domain, so they were typically empirically tested for multidimensional effects. In addition, pharmacologic and non-pharmacologic studies may select FM patients differently. The specter of rigorous monitoring of pharmacotherapy studies included regimented adherence to a specific form of diagnostic criteria, whereas it is clear that non-pharmacologic studies were not so rigidly adherent to a specific diagnostic criteria (Katz et al., 2006). With pharmacotherapy trials, formal start-up investigators' meetings typically focus on training investigators how to apply specific diagnostic criteria and how to systematically document outcomes. At intervals, monitors review the case report forms at each study site to ensure quality data. In contrast, non-pharmacotherapy studies may rely more on regional patterns of FM recognition and diagnosis. While patients with co-morbidities such as anxiety, depression, severe sleep disturbance or cognitive dysfunction have often been excluded from pharmacologic studies, they became the focus of or are at least were less likely to have been excluded from enrolment in a non-pharmacologic study.

4.1 Study limitations

There were several potential limitations to our meta-analysis. First, although we included cognitive impairment as one of the OMERACT core domains of clinical interest, few studies included assessed cognition as an outcome measure, so minimal results were available to assess. Second, we did not include domains of global assessment or overall quality of life for FM patients. Third, studies were excluded if the appropriate data (mean, *n*, SD/SE) were not included in the paper and not provided by the authors upon request. Fourth, for some treatments and domains, the results were based on only two or three applicable studies.

Another potential problem concerns the prevalence of individual symptom domains relative to each other in FM study populations. Pain is a universal and nearly constant symptom, whereas other manifestations tend to be less prevalent and can vary in severity over time (Bennett et al., 2007). In our meta-analysis, all selected patients had pain as required by the 1990 ACR criteria, which was an entry criterion for this meta-analysis. Most studies gave a similar prevalence of sleep dysfunction and fatigue, but depression occurs in only about 34% of FM patients (Ahles et al., 1991) and dyscognition can be quite difficult to document (Glass, 2009). This problem may compromise the ability of meta-analyses to directly compare the responsiveness of different co-morbidities with very different prevalence rates in the same populations, because meta-analysis assumes the same denominator for change despite differences in prevalence within the group. For example, assume that only one-third of FM patients in a study are depressed at study entry; assume also that all patients in the same study have pain, by virtue of study inclusion criteria. Imagine then that the absolute effect size for improvement of depressive symptoms is only one-third that of the effect size on pain in the same study. In reality, the change in each of these symptoms is similar, because it

is inappropriate to apply a portion of the improvement in depressive symptoms to the two-thirds of the study participants who were not depressed during the study period. In future studies, it might be possible to correct the meta-analysis results for low prevalence manifestations using the prevalence as a correction factor.

Our meta-analysis raises questions about interrelationships between the efficacies for each different symptoms. It would be of interest to analyse the links between all symptom domains in FM. Improvement on pain may induce improvement on other symptoms. For example, a patient who is in less pain because of treatment will also probably sleep better. In pharmacologic studies, in which pain was typically the primary target, and efficacy on pain was not necessarily associated with improvement in sleep dysfunction or physical impairment in function. Non-pharmacologic approaches may have better effects, as they are simultaneously directly acting on several symptoms, and as they include a lot of attention, with several activities performed at the same time, compared with drug intake. It is possible to consider FM as a heterogeneous disorder with what might realistically result from several very different pathophysiological mechanisms, some being more related to sleep disorders, some more to affective symptoms and others more to pain dysfunction (Perrot, 2008). Along this line, classification according to main pathophysiological mechanisms should also be discussed. The current subclassification of patients with FM according to the symptom severity score (Wolfe et al., 2011) may lead the way to a future approach likely to provide more adequate treatment according to the types of symptoms and their relative severity.

Meta-analyses do not capture tolerability issues, and there are probably differences between drugs and non-pharmacologic treatments in terms of tolerability and side effects experienced. In FM, drugs are often poorly tolerated, especially with regard to cognitive dysfunction that can be modulated by pharmacotherapies, such as sedating anticonvulsants or antidepressants.

4.2 Future studies

We propose that future studies begin with well-characterized pharmacologic and non-pharmacologic interventions that have already shown clinical promise and analyse the effects of combining them on the many co-morbid manifestations of FM. This approach would require viable sham or placebo controls, large numbers of compliant patients and sophisticated multivariate statistical analyses that addresses domains of different prevalence.

Our study clearly emphasizes the need for combination therapy in FM involving both pharmacologic and non-pharmacologic interventions. Only a few studies have investigated the efficacy of multiple drug approaches (Calandre et al., 2012), but to our knowledge there is no study that has formally investigated the effects of combinations of pharmacologic and non-pharmacologic interventions. Thus, when polytherapy is considered, therapeutic decisions are based on data from monotherapy trials and a sound knowledge of the pharmacologic profile of each drug. Well-designed clinical trials exploring specific drug combinations selected on the basis of potential additive or synergistic effects should be performed.

4.3 Conclusions

Overall, the results of this meta-analysis reinforce the still unmet need for better pharmacologic and non-pharmacologic treatments for FM. Further, they underscore how modest expectations for treatment success must be with current therapies, especially for the relief of affective symptoms, functional deficit and cognitive impairment associated with FM. Not many studies to date have placed an emphasis on the core FM OMERACT domains as future studies are likely to do. Moving forward, the results of our analysis provide evidence suggesting that combination therapy incorporating one or more non-pharmacologic treatment approaches augmented by a pharmacologic treatment could potentially contribute to better management of the multisymptomatic domains associated with FM.

Author contributions

S.P. and I.J. were equally involved in data search, data analyses and manuscript writing.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Amitriptyline.
Figure S2. Citalopram & Duloxetine.
Figure S3. Fluoxetine.
Figure S4. Growth Hormone.
Figure S5. Milnacipran.
Figure S6. Pregabalin.
Figure S7. Sodium oxybate.
Figure S8. Acupuncture.
Figure S9. Balneotherapy.
Figure S10. Cognitive Behavior.
Figure S11. Exercise.
Figure S12. Education.
Figure S13. Education/Exercise Combined.
Figure S14. Homeopathic.
Figure S15. Magnetic.
Figure S16. Massage.
Figure S17. Neurotherapy.
Figure S18. Pool Water.
Figure S19. UV/Bright Light.
Table S1. Summary of pharmacologic treatment studies contributing data to this analysis.
Table S2. Summary of nonpharmacologic treatment studies contributing to this analysis.
Table S3. Effect Size Tables by Domain and Study for Each Treatment.
Table S4. Overall Effect Size per domain for each Treatment.
Table S5. Effect Size Tables by Domain and Study for Each Treatment.
Table S6. Overall Effect Size Table per domain for each Treatment.