

EXTENDED REPORT

EULAR revised recommendations for the management of fibromyalgia

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ABSTRACT

Objective The original European League Against Rheumatism recommendations for managing fibromyalgia assessed evidence up to 2005. The paucity of studies meant that most recommendations were 'expert opinion'.

Methods A multidisciplinary group from 12 countries assessed evidence with a focus on systematic reviews and meta-analyses concerned with pharmacological/non-pharmacological management for fibromyalgia. A review, in May 2015, identified eligible publications and key outcomes assessed were pain, fatigue, sleep and daily functioning. The Grading of Recommendations Assessment, Development and Evaluation system was used for making recommendations.

Results 2979 titles were identified: from these 275 full papers were selected for review and 107 reviews (and/or meta-analyses) evaluated as eligible. Based on meta-analyses, the only 'strong for' therapy-based recommendation in the guidelines was exercise. Based on expert opinion, a graduated approach, the following four main stages are suggested underpinned by shared decision-making with patients. Initial management should involve patient education and focus on non-pharmacological therapies. In case of non-response, further therapies (all of which were evaluated as 'weak for' based on meta-analyses) should be tailored to the specific needs of the individual and may involve psychological therapies (for mood disorders and unhelpful coping strategies), pharmacotherapy (for severe pain or sleep disturbance) and/or a multimodal rehabilitation programme (for severe disability).

Conclusions These recommendations are underpinned by high-quality reviews and meta-analyses. The size of effect for most treatments is relatively modest. We propose research priorities clarifying who will benefit from specific interventions, their effect in combination and organisation of healthcare systems to optimise outcome.

INTRODUCTION

Fibromyalgia is common with a prevalence of 2% in the general population.^{1,2} However, its diagnosis and management remain a challenge for patients and healthcare professionals. It often takes >2 years for a diagnosis to be made with an average of 3.7 consultations with different physicians.³ Referral to specialists and investigations results in high healthcare use, for up to 10 years prior to diagnosis, compared with persons who do not have fibromyalgia.⁴

Although pain is the dominant symptom in fibromyalgia, other symptoms such as fatigue, non-refreshed sleep, mood disturbance and cognitive impairment are common, but not universal, have an important influence on quality of life and emphasise that it is a heterogeneous and complex condition.^{5,6}

The original European League Against Rheumatism (EULAR) recommendations for the management of fibromyalgia assessed evidence up to and including 2005.⁷ Given the paucity of information and poor quality of the studies available, it was recommended that the guidelines be revised after a period of 4 years. However, no subsequent revision took place and thus a decade later we revisit the recommendations with the aim of making them more evidence based. In the time since the original recommendations, there have been a considerable number of individual trials examining pharmacological and non-pharmacological interventions and, moreover, there have been systematic reviews conducted for nearly all of the commonly used management strategies. Our aim therefore was, using the systematic reviews conducted and taking into account their quality, to make evidence-based recommendations for the use of individual pharmacological and non-pharmacological approaches, and how these could be combined. Further, we aimed to identify priority areas for future research.

METHODS**Working group membership**

The working group included 18 members from 12 European countries: clinicians (representing rheumatology, internal medicine, pain medicine and epidemiology), non-clinical scientists (occupational health, epidemiology), patient representatives and the allied health professions (nursing).

Eligibility, search strategy and quality assessment

We focused on systematic reviews (with or without meta-analysis) concerned with the management of fibromyalgia. Details of eligibility, review and quality assessment are provided in online supplementary text.

Evaluating evidence

We retained pain as one of the key outcomes of interest, from the original guidelines, but also included fatigue, sleep and daily functioning. The committee considered the following in making a



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recommendation: number of trials, number of patients, outcomes assessed, quality of reviews and the trials included within the reviews, effect size (and 95% CI), adverse events and cost. We used the Grading of Recommendations Assessment, Development and Evaluation system for making recommendations.¹⁰ This is a four-point scale: strong for/weak for/weak against/strong against; or allowing a recommendation 'use only for research'. The strength of recommendation is based on the balance between desirable and undesirable effects (considering values and preferences), confidence in the magnitude of effects and resource use. A strong recommendation implies that, if presented with the evidence, all or almost all informed persons would make the recommendation for or against the therapy, while a weak recommendation would imply that most people would, although a substantial minority would not.¹¹

Two subgroups considered the evidence for pharmacological and non-pharmacological therapies and proposed a recommendation. At a face-to-face meeting, after presentation of the evidence and the preliminary recommendation, discussion resulted in a 'final recommendation'. In addition to the evidence on efficacy/effectiveness, the committee also took into account safety. All participants then voted on their level of agreement with the recommendation on a scale from 0, 'completely disagree', to 10, 'completely agree'. The percentage of the committee scoring at least 7 was taken to indicate level of agreement.

RESULTS

In total, 2979 titles were identified. From these, 571 abstracts and then 275 full papers were selected for review, and 107 reviews evaluated as eligible for consideration in making recommendations for management (figure 1).

Information on the reviews informing these recommendations on pharmacological therapy and on non-pharmacological and complementary and alternative medicines/therapies is collated in online supplementary tables A and B, respectively, while information from one review, for each medicine/therapy, selected based on recency and quality is provided in tables 1 and 2, respectively.

Evaluation of pharmacological medicines

Amitriptyline

Five reviews included up to 13 trials and a maximum of 919 subjects. Häuser *et al*¹² reported that patients receiving amitriptyline were more likely to achieve 30% pain reduction (risk ratio (RR) 1.60, 95% CI 1.15 to 2.24), equivalent to a 'number needed to treat' (NNT) of 3.54, 95% CI 2.74 to 5.01. There was a moderate effect on sleep (standardised mean difference (SMD) -0.56, 95% CI -0.78, to -0.34)ⁱ and small effect on fatigue (-0.44; -0.71 to -0.16). There was no difference in discontinuation rates compared with patients receiving placebo. Nishishinya *et al*¹³ in their high-quality review concluded that 25 mg/day improved pain, sleep and fatigue at 6–8 weeks of treatment but not at 12 weeks while 50 mg/day did not demonstrate efficacy. *Amitriptyline evaluation: weak for, at low dose (100% agreement)*.

Anticonvulsants

Nine reviews of pregabalin included up to seven studies and a maximum of 3344 patients. A recent Cochrane review²⁴ reported patients receiving active treatment were more likely to

have 30% pain reduction, RR 1.37, 95% CI 1.22 to 1.53, with a 'number needed to benefit' (NNTB) over placebo of 9, 95% CI 7 to 13. There was a very small effect on fatigue (-0.17; -0.25 to -0.09) and small effect on sleep (-0.35; -0.43 to -0.27) but no effect on disability (-0.01; -0.11 to 0.09). A single, moderate quality, study of gabapentin in 150 subjects (eg, in ref. 104) showed a significant effect on 30% pain reduction (RR 1.65, 95% CI 1.10 to 2.48), a small effect on sleep (-0.71; -1.08 to -0.24) and a large effect on disability (-0.94; -1.32 to -0.56). *Anticonvulsant evaluation: pregabalin—weak for (94% agreement); gabapentin—research only (100% agreement)*.

Cyclobenzaprine

A single systematic review of five studies involving 312 patients reported that of those taking cyclobenzaprine 85% experienced side effects and only 71% completed the studies. They were more likely to report themselves as 'improved' (NNT 4.8, 95% CI 3.0 to 11.0). Only two studies reported an 'intention-to-treat' (ITT) analysis. Sleep, but not pain, showed a significant, very small, improvement relative to baseline at the longest outcome considered (12 weeks: SMD 0.34) and patients on placebo showed similar improvement (SMD 0.52).²⁵ *Cyclobenzaprine evaluation: weak for (75% agreement)*.

Growth hormone

A single systematic review of two studies involving 74 patients reported an effect size on pain of 1.36 (0.01 to 1.34).¹⁶ The improvement in functional deficit was not statistically significant (1.24; -0.36 to 2.84). There are concerns on safety (sleep apnoea, carpal tunnel syndrome). The drug is not approved for fibromyalgia (FM) or related disorders in Europe. *Growth hormone evaluation: strong against (94% agreement)*.

Monoamine oxidase inhibitors

Four reviews identified up to three studies and 241 patients. Häuser *et al*²⁶ reported a moderate effect on pain across the studies (-0.54; -1.02, to -0.07), but the single studies that evaluated fatigue and sleep showed no effect. There were no differences in dropouts or adverse events compared with placebo. There was no comparison between compounds. Life-threatening interactions have been documented. *Monoamine oxidase inhibitors (MAOIs) evaluation: weak against (81% agreement)*.

NSAIDs

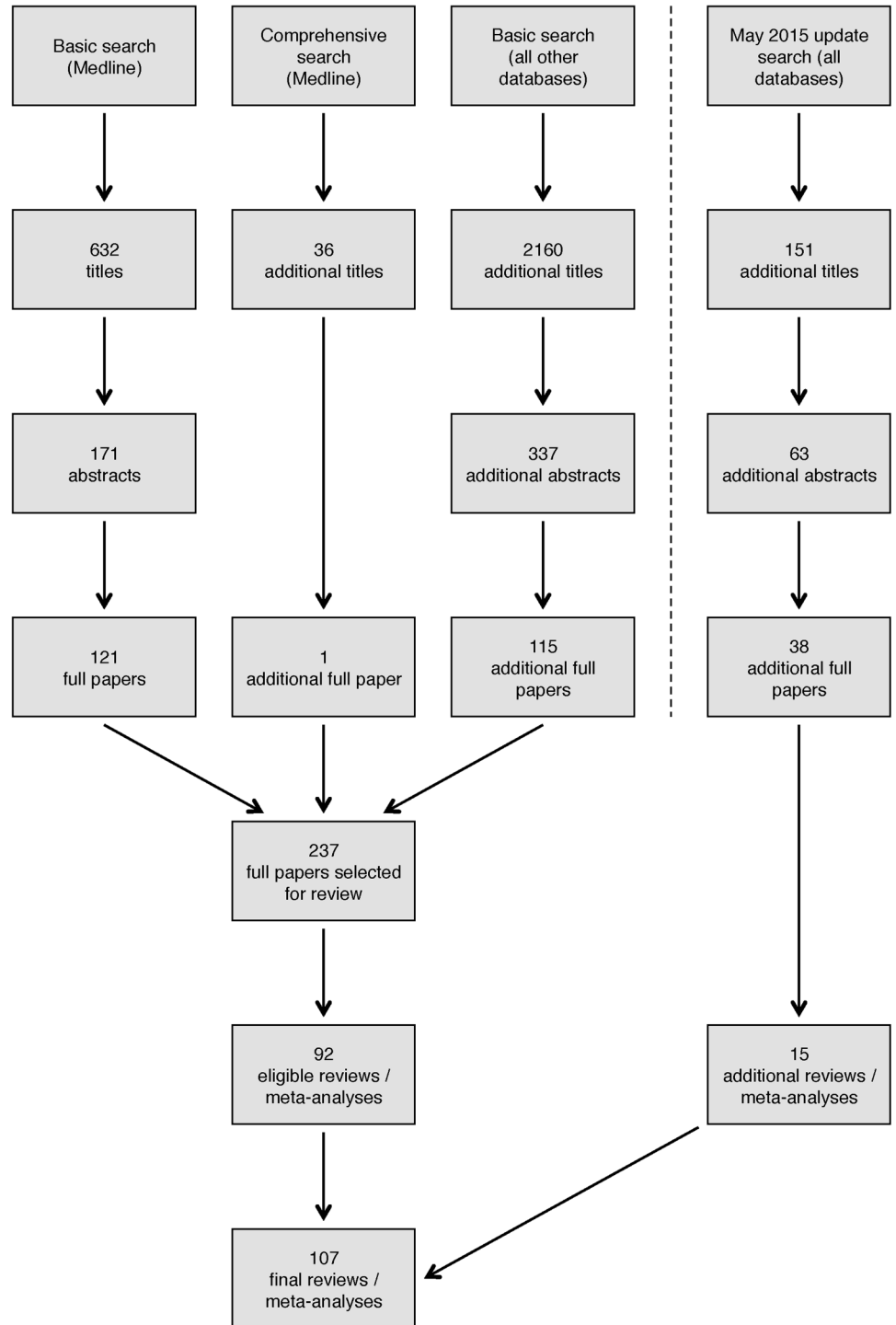
A single review²¹ identified two small trials with no evidence of improved outcome compared with placebo. One low-quality review was not considered. *Non-steroidal anti-inflammatory drugs (NSAIDs) evaluation: weak against (100% agreement)*.

Serotonin-noradrenalin reuptake inhibitors

Eight systematic reviews were identified, which presented data separately for duloxetine. The largest review of 2249 subjects³² reported duloxetine, short term (up to 12 weeks) and long term (up to 28 weeks), was more effective than placebo at reducing pain (RR >30% pain, RR 1.38, 95% CI 1.22 to 1.56), although there was no significant effect at 20–30 mg/day and no difference between doses of 60 and 120 mg/day. NNTB, based on 60 mg/day up to 12 weeks, was 6, 95% CI 3 to 12. A previous review reported small effects on sleep (-0.24; -0.37, to -0.12) and disability (-0.33; -0.43, to -0.24) but no effect on fatigue.³⁰ Seven systematic reviews were identified of milnacipran, a recent one of which evaluated five trials.³⁰ Patients taking milnacipran were more likely, at the end of treatment, to

ⁱAll effect sizes are expressed as SMD with 95% CI unless otherwise stated.

Figure 1 Flow chart identifying eligible reviews.



have 30% pain reduction (RR 1.38, 95% CI 1.25 to 1.51) but there was only a small benefit on fatigue (−0.14; −0.19 to −0.08), disability (−0.16; −0.23 to −0.10) and no effect on sleep. *Duloxetine and milnacipran evaluation: weak for (100% agreement).*

Selective serotonin reuptake inhibitors

Seven systematic reviews included up to 11 trials and a maximum of 521 subjects. Given that reviews have not focused on specific drugs or comparisons, drugs within this class were considered together. A recent review of medium quality included seven trials and reported a moderate effect on pain (−0.40;

−0.73, to −0.07), sleep (−0.31; −0.60 to −0.02) and no effect on fatigue (−0.17; −0.46 to 0.11).³⁶ *Selective serotonin reuptake inhibitor (SSRI) evaluation: weak against (94% agreement).*

Sodium oxybate

A single systematic review of five studies including 1535 patients reported small effects sizes on pain (0.44; 0.31 to 0.58), sleep problems (0.47; 0.28 to 0.66) and fatigue (0.48; 0.35 to 0.60). The European Medicines Agency and the US Food and Drug Administration refused the approval for FM because of safety concerns.¹⁶ The drug is only approved for narcolepsy. *Sodium oxybate evaluation: strong against (94% agreement).*

Table 1 Overview of results from selected systematic reviews of placebo-controlled pharmacological trials

| Treatment (review reference) | No. of trials (no. of participants) Review quality | Dosages; durations of treatment | Overall trial quality* | Safety and comments |
|--|--|---|------------------------|--|
| Amitriptyline ¹² | 10 (767) AMSTAR=6 | 10–50 mg/day; 8–24 weeks | Low | There was no analysis of safety but no difference in discontinuation rates compared with patients on placebo was reported. |
| Anticonvulsants—pregabalin ²⁴ | 5 (3256) AMSTAR=10 | Three studies with fixed doses of 300, 450 and 600 mg/day; one with fixed doses of 150, 300 or 450 mg/day; one flexible dosing study of 300 or 450 mg/day; 8–14 weeks | High | Increased likelihood of withdrawal due to adverse events, RR 1.68, 95% CI 1.36 to 2.07; NNH 12 95% CI 9 to 17. No difference in likelihood of serious adverse events. |
| Cyclobenzaprine ²⁵ | 5 (312) AMSTAR=7 | 10–40 mg; 2–24 weeks | Moderate | There was no analysis of adverse outcomes in the trials reviewed although dropout across trials was large (cyclobenzaprine 29%, placebo 43%). Only two studies conducted ITT. |
| Growth hormone ¹⁶ | 2 (74) AMSTAR=5 | 0.0125 mg/kg/day; adjusted to maintain IGF-1 level of 250 ng/mL after first month, 0.0125 mg/kg/day; 9 months to 1 year | NE | Safety concerns include sleep apnoea and carpal tunnel syndrome. |
| MAOIs ²⁶ | 3 (241) AMSTAR=9 | Pirlindole 150 mg/day, moclobemide 150–300 mg/day; 4–12 weeks | Low | MAOIs are known to cause potentially fatal hypertensive crises, serotonin syndrome and psychosis when they interact with foods containing tyramine and medications (many of which are commonly used in the treatment of FM), including SSRIs, tricyclic antidepressants and tramadol. The clinical trials had restrictions on concomitant medications. |
| NSAIDs ²¹ | 2 (242) AMSTAR=7 | Ibuprofen 600 mg four times a day, tenoxicam 20 mg/day; 6–8 weeks | Low | The adverse event profile, although not considered in this review, is well established for this class of drugs. |
| SNRIs—duloxetine ³¹ | 6 (2249) AMSTAR=10 | 20–120 mg/day; 12–28 weeks | Moderate | Dropout rates due to side effects across studies higher than with placebo. No difference in serious adverse events. |
| SNRIs—milnacipran ³⁰ | 5 (4118) AMSTAR=10 | 100 or 200 mg/day; 12–27 weeks | High | Dropout rates due to side effects across studies were double compared with placebo, but there was no difference in serious adverse events. |
| SSRIs ³⁶ | 7 (322) AMSTAR=8 | 20–40 mg/day citalopram, 20–80 mg/day fluoxetine, 20–60 mg/day paroxetine; 6–16 weeks | Moderate to high | Acceptability and tolerability were similar to placebo NNH 40, 95% CI 19 to 66. Although several studies excluded patients with depression/anxiety, Häuser <i>et al</i> ²⁶ showed a small effect of SSRIs in improving depressed mood (SMD -0.37, 95% CI -0.66 to -0.07). |
| Sodium oxybate ¹⁶ | 5 (1535) AMSTAR=5 | 4.5–6 g/day; 8–14 weeks | NE | There is the potential for abuse and central nervous system effects associated with abuse such as seizure, respiratory depression and decreased levels of consciousness. |
| Tramadol ²² | 1 (313) AMSTAR=3 | 37.5 mg tramadol/325 mg paracetamol 4×/day; 3 months | High | No significant difference in discontinuation due to adverse events (RR 1.62, 95% CI 0.94 to 2.80). A high-quality review (AMSTAR score 7) identified a single study, which, among persons who tolerated and benefitted from tramadol, demonstrated a lower discontinuation rate in a double-blind phase compared with placebo. ²¹ |

*According to the method of quality evaluation used in the review.

AMSTAR, Assessing the Methodological Quality of Systematic Reviews; FM, fibromyalgia; IGF, insulin growth factor; ITT, intention-to-treat; MAOIs, monoamine oxidase inhibitors; NE, not evaluated; NNH, number needed to harm; NSAIDs, non-steroidal anti-inflammatory drugs; RR, risk ratio; SMD, standardised mean difference; SNRI, serotonin-noradrenalin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Tramadol, a weak opioid with mild serotonin-noradrenalin reuptake inhibitor (SNRI) activity was considered by two reviews. Roskell *et al*²² identified a single study of tramadol with paracetamol. Those in the active arm were more likely to have 30% improvement in pain (RR 1.77, 95% CI 1.26 to 2.48). *Tramadol evaluation: weak for (100% agreement)*.

The literature search did not identify any reviews on corticosteroids, strong opioids, cannabinoids and antipsychotics. The committee made a ‘strong against’ evaluation (100% agreement) regarding the use of strong opioids and corticosteroids in patients with fibromyalgia on the basis of lack of evidence of efficacy and high risk of side effects/addiction reported in individual trials.

Evaluation of non-pharmacological therapies; complementary and alternative medicines and therapies

Acupuncture

Eight reviews included up to 16 trials and 1081 participants. One high-quality review included nine trials, with 395 patients, and demonstrated that acupuncture, added to standard therapy, resulted in a 30% (21%, 39%) improvement in pain.⁷⁰ Electric acupuncture was also associated with improvements in pain (22%; 4% to 41%) and fatigue (11%; 2% to 20%). Some adverse events were reported, but these were commonly mild and transient. There is little understanding of the active component of acupuncture, and the evidence supporting the use of real versus sham acupuncture was less consistent. *Acupuncture evaluation: weak for (93% agreement)*.

Table 2 Overview of results from selected systematic reviews of non-pharmacological; complementary and alternative medicine and therapy trials

| Treatment (review reference) | No. of trials (no. of participants*) Review quality | Dosages; durations of treatment | Overall trial quality† | Safety and comments |
|---|--|---|------------------------|---|
| Acupuncture ⁷⁰ | 9 (395) AMSTAR=11 | Treatment sessions ranged from 3 to 13 weeks (median=4), with needle retention ranging from 20 to 30 min. Only one study provided journal references for the acupuncture point selection, and the description of the type of needle stimulation/manipulation was clear in only three studies. | Moderate | One in six people who had acupuncture, and one in three controls, reported adverse events. Such events were minor and lasted less than one day. No serious adverse events were reported in any trials. |
| Biofeedback ⁹² | 7 (321) AMSTAR=8 | EMG biofeedback. Individual sessions varied between 45 and 180 min, and the number of sessions varied between 6 and 16. EEG biofeedback. 20–22 sessions of (where reported) 30 min duration. | Poor | Only two‡ trials reported adverse event data. 4% of patients in one trial receiving EMG biofeedback reported stress. And 74% of patients in another, receiving EEG biofeedback reported a variety of side effects, including: headache, fatigue and sleep problems. |
| Capsaicin ⁹⁴ | 2 (153) AMSTAR=5 | Topical application of <i>Capsicum annum L.</i> cream, either 0.025% capsaicin for 4 weeks or 0.075% for 12 weeks. | Not reported | Patients reported moderate, transient, burning or stinging. |
| Chiropractic ⁸⁹ | 3 (102) AMSTAR=4 | Little detail is given for any trials, but treatment elements included massage, stretching, spinal manipulation, education and resistance training. | Low | Around 50% of patients experience mild-to-moderate transient adverse effects after spinal manipulation.§ |
| CBT ⁵⁷ | 23 (2031) AMSTAR=11 | Median duration of therapy=10 weeks, with a median number of 10 sessions, and median total hours=18 hours. All but two studies delivered therapy face to face. Median follow-up (where this was performed 17/23 studies)=6 months. | Low | The assessment of safety in most studies was insufficient. Two studies reported dropout due to worsening of comorbid mental disorders. However, CBT is generally considered safe. |
| Exercise ⁴¹ | 34 (2276) AMSTAR=9 | Exercise programmes lasting 2.5–24 weeks. Aerobic exercise for ≥20 min, once a day (or twice for ≥10 min), 2–3 days a week. Strength training with ≥8 repetitions per exercise, 2–3 times a week. | Moderate | Although patients may initially notice a deterioration in symptoms, exercise is generally considered safe, especially when practised under supervision. |
| Hydrotherapy/spa therapy ⁷⁶ | 10 (446) AMSTAR=9 | Wide variation in precise treatment strategy between trials. Most consisted of water or mud baths at body temperature 36–37°C, or slightly above (40–45°C), with a median treatment time of 240 min (range 200–300), over several weeks. | Low | Three studies reported no side effects of treatment; one reported slight flashes in 10% of the patients. The remaining trials did not explicitly mention safety. |
| Hypnotherapy ⁹¹ | 4 (152) AMSTAR=11 | Some variation between trials ranging (where reported) from 300 to 420 min, delivered over 10–26 weeks. | Good | Adverse events were not reported in any of the trials. |
| Massage ⁶³ | 9 (404) AMSTAR=7 | Massage therapy time lasted 25–90 min, with between 1 and 20 massage sessions in total. | Low to moderate | No adverse events were reported in any of the trials. |
| Meditative movement ⁸⁰ | 7 (362) AMSTAR=9 | Wide variation in treatments between trials, and included yoga, tai chi, qigong or body awareness therapy. Median (range) duration of treatment=16 (6–24) hours, over 4–12 weeks. | Moderate | Although no serious adverse events were reported, six participants (3.1%) withdrew from the trials because of adverse events (increase of pain; muscle inflammation; chlorine hypersensitivity). The review authors concluded that the acceptance and safety of all types of meditative movement therapies were high. |
| Mindfulness/mind–body therapy ⁸⁴ | 6 (674) AMSTAR=9 | Some variation between trials. Single 2–3.5 hours session per week, for 8–10 weeks. Four out of six programmes also included daily home practice (30–45 min) plus a single all-day retreat. | Low | Safety was assessed and reported in none of the trials. |
| Multicomponent therapy ⁶⁰ | 9 (1119) AMSTAR=9 | Enormous variation in treatment strategies between trials. Most included different combinations of exercise (land and/or water based); education; relaxation; and/or some other specific therapeutic component (eg, Tai Chi; or massage). | Moderate | No adverse events were reported in any of the trials. |
| SAME ⁹³ | 1 (44) AMSTAR=6 | 400 mg tablet, twice a day, for 6 weeks. | Moderate | Mild adverse effects such as stomach upset and dizziness were reported. |
| Other: guided imagery ⁹¹ | 1 (48) AMSTAR=9 | Audiotape-led, individual, guided imagery: 30 min daily for 6 weeks recommended. Median of 44 exercises (range 37–136). | Good | Adverse events were not reported. |
| Other: homeopathy ⁹⁸ | 4 (163) AMSTAR=7 | Variation between trials. Two studied individualised homeopathic treatment, consisting of an initial consultation (and treatment), plus follow-up interviews every 4–8 weeks. Two studied <i>Arnica montana</i> , <i>Bryonia alba</i> or <i>Rhus toxicodendron</i> (potency 6c) daily for between 1 and 3 months. | Low to moderate | No information was provided on safety. |

*Total number of persons randomised.

†According to the method of quality evaluation used in the review.

‡Elsewhere in the review, it reports that three studies reported on adverse events. However, in the table where these data are presented, it is only clear for two. However, in a third trial, there were no dropouts due to side effects.

§These data were not contained in this review. The initial recommendation for chiropractic was weak against. However, after discussion, this was downgraded to strong against due to potential safety concerns.

CBT, cognitive behavioural therapy; EMG, electromyographic; SAME, S-adenosyl methionine.

Biofeedback

Two reviews included up to seven trials and 307 participants. Glombiewski *et al*⁹² reviewed seven studies, comprising 321 participants. Treatment sessions varied from 6 to 22; with control therapy comprising sham biofeedback, attention control, medication and treatment as usual. Biofeedback was effective in reducing pain intensity (Hedges' $g=0.79$; 0.22 to 1.36), although all trials were poor quality. There was no evidence of effectiveness in terms of fatigue or sleep and subgroup analysis suggested that any effect was limited to electromyographic (0.86; 0.11 to 1.62) rather than electroencephalographic biofeedback (0.71; -0.37 to 1.8). *Biofeedback evaluation: weak against (100% agreement)*.

Capsaicin

Two reviews included two trials and 153 participants. The most recent review, a narrative review of two trials, considered data on 153 patients.⁹⁴ Both showed some evidence of positive effect in terms of pain relief, although results were not consistent for other outcomes. Capsaicin gel is generally considered safe, although many users report a mild burning sensation when applied to the skin. However, the number of patients and trials was small and was therefore limited in the extent to which they can provide evidence for toxicity. *Capsaicin evaluation: weak against (86% agreement)*.

Chiropractic

Three reviews included up to 13 trials and 102 participants. The most recent review summarised three studies.⁸⁹ One study was an open pilot study, one quasi-randomised and in the third no between-group differences were observed in terms of pain. The studies were poor quality and lacked robust interpretable data. *Chiropractic evaluation: strong against (93% agreement)*.

Cognitive behavioural therapies

Five reviews included up to 30 trials and at least 2031 participants. One high-quality review included 23 trials, comprising >2000 patients, although the quality of individual trials was reported as generally poor.⁵⁸ Cognitive behavioural therapies (CBTs) were effective in reducing pain (-0.29; -0.49 to -0.17) and disability (-0.30; -0.51 to -0.08) at the end of treatment compared with a variety of controls groups, and results were sustained long term. *Behavioural therapy evaluation: weak for (100% agreement)*.

Exercise

Twenty reviews included up to 34 trials and at least 2494 participants.ⁱⁱ The largest, a Cochrane review, considered 47 different exercise interventions.⁴¹ Aerobic exercise was associated with improvements in pain (0.65; -0.09 to 1.39) and physical function (0.66; 0.41 to 0.92). Busch *et al*⁴² reviewed five trials with 219 participants and concluded that resistance training resulted in a significant improvement in pain (-3.3 cm on a 10 cm scale; -6.35 to -0.26) as well as function compared with control. There is some consistency with regard to aerobic and strengthening exercises, although insufficient evidence to suggest superiority of one over the other; land and aquatic exercise appear equally effective.⁵⁶ *Exercise therapy evaluation: strong for (100% agreement)*.

ⁱⁱIt is unclear from some of the reviews how many participants were included. The number of participants represents the minimum about which we can be confident.

Hydrotherapy/spa therapy

Four reviews included up to 21 trials and 1306 participants. One high-quality review included 10 trials, 446 participants and compared a median of 4-hour hydrotherapy (range 200–300 min) against various comparators.⁷⁶ There was a significant improvement in pain (-0.78; -1.42 to -0.13) at the end of therapy, maintained in the longer term (median 14 weeks), although the review authors noted that no trials conducted an ITT analysis. There was consistency with regard to the evidence for hydrotherapy and balneotherapy, although little evidence to suggest superiority of one over the other.⁷⁷ *Hydrotherapy evaluation: weak for (93% agreement)*.

Hypnotherapy

One review included four trials, although the number of participants is unclear.⁹¹ Although six trials of hypnotherapy and/or guided imagery were reviewed, only four examined hypnotherapy in isolation. Median treatment duration (where reported) was 360 min and hypnotherapy was compared with a variety of control therapies: cognitive intervention, active control (physical therapy/massage/relaxation/autogenic training) and treatment as usual. A meta-analysis is presented on all six trials, and isolated data for hypnotherapy are not presented. Two of the four hypnotherapy trials report some significant benefit in terms of pain, the other two demonstrate null, non-significant results. *Hypnotherapy evaluation: weak against (86% agreement)*.

Massage

Six reviews have been reported and one meta-analysis with nine trials and 404 patients⁶³ with sessions lasting 25–90 min, and treatment duration ranging from 1 to 24 weeks (median 5 weeks). Comparator treatments included transcutaneous electrical nerve stimulation (TENS), standard care, guided relaxation and acupuncture. Methodological problems were noted with all of the studies, only four were at low risk of bias in terms of random allocation and only two were analysed as ITT. Overall, massage was not associated with a significant improvement in pain (0.37; -0.19 to 0.93), and of the two ITT analyses, one favoured massage and one favoured control (both significant). A subgroup analysis revealed some evidence of a positive effect with massage of ≥ 5 weeks duration, although this was based solely on lower-quality trials. *Massage evaluation: weak against (86% agreement)*.

Meditative movement

Six reviews, including up to eight trials and 559 participants, focused on qigong, yoga, tai chi or a combination of these therapies. However, there was insufficient evidence to make individual recommendations. One review included seven trials, with 362 participants randomised to tai chi, yoga, qigong or body awareness therapy.⁸⁰ Total treatment time ranged from 12 to 24 hours and was compared with a variety of controls, including treatment as usual and active control groups (aerobics, wellness education and stretching). At the end of therapy, improvements were seen in sleep (-0.61; -0.95 to -0.27) and fatigue (-0.66; -0.99 to -0.34) some of which were maintained in the longer term. *Meditative movement evaluation: weak for (71% agreement)*.

Mindfulness/mind-body therapy

Six reviews included up to 13 trials and 1209 participants. One recent review, a meta-analysis of six trials, with 674 patients⁸⁴ provided evidence that mindfulness-based stress reduction

resulted in improvements in pain (−0.23; −0.46 to −0.01) immediately post treatment compared with usual care and compared with active control interventions (−0.44; −0.73 to −0.16). However, these effects were not robust against bias. *Mindfulness/mind–body therapy evaluation: weak for (73% agreement).*

Multicomponent therapy

Two reviews including up to 27 trials and 2407 participants examined the additional benefit of combining therapies compared with individual therapy. Häuser *et al*⁶⁰ conducted a review of management involving both educational or psychological therapies and exercise. In a meta-analysis of nine trials and 1119 patients, multicomponent therapy was effective in reducing pain (−0.37; −0.62 to −0.13), and fatigue, immediately post treatment, compared with waiting list, relaxation, treatment as usual and education. However, effects were short-lived. *Multicomponent therapy evaluation: weak for (93% agreement).*

S-Adenosyl methionine

Two reviews each included one trial with, in combination, 74 participants. De Silva *et al*⁹³ reported that, after the end of treatment, significant improvements were observed in pain and fatigue compared with placebo. Sim and Adams⁵² reviewed a trial comparing S-adenosyl methionine (SAMe) with TENS but data on the main trial comparison are omitted. Side effects are usually mild and infrequent. However, the number of patients and trials was small and therefore cannot provide a robust assessment of toxicity and safety. *SAMe evaluation: weak against (93% agreement).*

Other complementary and alternative therapies

Three reviews of guided imagery included up to six trials and 357 participants. The highest quality, including only one trial, provided some evidence that guided imagery may be effective in reducing pain (−1.52; −2.17 to −0.87).⁹⁰ Two reviews of homeopathy included four trials and 163 participants.^{97 98} Both contained a review including only four randomised trials, each of which showed some benefit of homeopathy, on some outcomes. However, none of the individual trials were without serious flaws. *Other complementary and alternative therapies (guided imagery, homeopathy): strong against (93% agreement).*

Reviews were identified that examined electrothermal and phototherapeutic therapy;⁹⁹ phytothermotherapy;¹⁰⁰ music therapy, journaling/storytelling¹⁰³ and static magnet therapy,¹⁰¹ although each was insufficient to allow a recommendation. Marlow *et al*¹⁰² examined the effectiveness of transcranial magnetic and/or direct current stimulation. Eight trials included 244 participants, although not all were analysed by ITT, and appropriate group comparisons were not presented for all studies. Overall, there was little evidence to support either therapy, and several studies reported an unacceptably high rate of adverse events and/or discontinuation due to headache.

EULAR revised recommendations

In terms of overall principles, we recommend, based on unanimous expert opinion, that optimal management requires prompt diagnosis and providing the patient with information (including written material) about the condition. There should be a comprehensive assessment of pain, function and the psychosocial context. Management should take the form of a graduated approach with the aim of improving health-related quality of life. It should focus first on non-pharmacological modalities. This is based on availability, cost, safety issues and patient preference.

We have used the evaluation of individual therapies (above) to make 10 specific recommendations, all based on evidence from systematic reviews and all but one from meta-analysis. The recommendations are given in table 3, and a flow chart of how these therapies may be used in management is shown in figure 2.

We were unanimous in providing a ‘strong for’ recommendation for the use of exercise, particularly given its effect on pain, physical function and well-being, availability, relatively low cost and lack of safety concerns. The available evidence did not allow us to distinguish between the benefits of aerobic or strengthening. We gave ‘weak for’ recommendations in relation to meditative movement therapies (which improved sleep, fatigue and quality of life) or mindfulness-based stress reduction (which improved pain and quality of life); the physical therapies acupuncture or hydrotherapy for which there was evidence that they improved pain/fatigue and pain/quality of life, respectively. The effects seen in pragmatic trials of such therapies will include specific and non-specific effects, and it is not possible to disentangle these. There were some non-pharmacological therapies we did not recommend because of lack of effectiveness and/or low study quality: biofeedback, capsaicin, hypnotherapy, massage, SAMe and other complementary and alternative therapies. We provided a ‘strong against’ evaluation for chiropractic based on safety concerns.

In case of lack of effect of the above therapeutic approaches, we recommend individualised treatment according to patient need. Psychological therapies (‘weak for’) should be considered for those with mood disorder or unhelpful coping strategies: CBT was effective at producing modest, long-term reductions in pain, disability and improving mood. Pharmacological therapies (all ‘weak for’) should be considered for those with severe pain (duloxetine, pregabalin, tramadol) or sleep disturbance (amitriptyline, cyclobenzaprine, pregabalin). Multimodal rehabilitation (‘weak for’) programmes should be considered for those with severe disability—in comparison to individual therapies, those that were multimodal improved a range of short-term outcomes. We did not recommend several pharmacological therapies including NSAIDs, MAOIs and SSRIs because of lack of efficacy and specifically gave a ‘strong against’ evaluation to growth hormone, sodium oxybate, strong opioids and corticosteroids based on lack of efficacy and high risk of side effects.

DISCUSSION

The previous EULAR recommendations provided an important milestone in the management of fibromyalgia. There were nine recommendations, but only three were supported by strong evidence from the scientific literature; most were based on expert opinion. Since that time, there have been a considerable number of trials published addressing issues in the management of fibromyalgia. The availability of systematic reviews and meta-analysis of randomised controlled trials (RCTs) for all the most common approaches to management allowed us to concentrate on these.

Comparison with 2007 EULAR recommendations

Despite the very large increase in the amount of trial data and summarised in meta-analyses, there are no major changes to the approach of managing patients with fibromyalgia, although we provide new evidence in support for some additional non-pharmacological therapies. In addition, all the recommendations are now firmly evidence based. We now recommend that non-pharmacological therapy should be first-line therapy and then if there is a lack of effect that there should be individualised

Table 3 Recommendations

| Recommendation | Level of evidence | Grade | Strength of recommendation | Agreement (%)* |
|---|-------------------|-------|----------------------------|----------------|
| <i>Overarching principles</i> | | | | |
| Optimal management requires prompt diagnosis. Full understanding of fibromyalgia requires comprehensive assessment of pain, function and psychosocial context. It should be recognised as a complex and heterogeneous condition where there is abnormal pain processing and other secondary features. In general, the management of FM should take the form of a graduated approach. | IV | D | | 100 |
| Management of fibromyalgia should aim at improving health-related quality of life balancing benefit and risk of treatment that often requires a multidisciplinary approach with a combination of non-pharmacological and pharmacological treatment modalities tailored according to pain intensity, function, associated features (such as depression), fatigue, sleep disturbance and patient preferences and comorbidities; by shared decision-making with the patient. Initial management should focus on non-pharmacological therapies. | IV | D | | 100 |
| <i>Specific recommendations</i> | | | | |
| Non-pharmacological management | | | | |
| Aerobic and strengthening exercise | Ia | A | Strong for | 100 |
| Cognitive behavioural therapies | Ia | A | Weak for | 100 |
| Multicomponent therapies | Ia | A | Weak for | 93 |
| Defined physical therapies: acupuncture or hydrotherapy | Ia | A | Weak for | 93 |
| Meditative movement therapies (qigong, yoga, tai chi) and mindfulness-based stress reduction | Ia | A | Weak for | 71–73 |
| Pharmacological management | | | | |
| Amitriptyline (at low dose) | Ia | A | Weak for | 100 |
| Duloxetine or milnacipran | Ia | A | Weak for | 100 |
| Tramadol | Ib | A | Weak for | 100 |
| Pregabalin | Ia | A | Weak for | 94 |
| Cyclobenzaprine | Ia | A | Weak for | 75 |

*Percentage of working group scoring at least 7 on 0–10 numerical rating scale assessing agreement.

therapy according to patient need, which may include pharmacological therapy.

Comparison with other recommendation

There are three recent guidelines on the management of FM from Canada, Israel and Germany that have been compared with respect to their recommendations.¹⁰⁵ These guidelines and our EULAR recommendations are in agreement on the principles of approach to management, the need for tailored therapy to the individual and the first-line role of non-pharmacological therapies. There are differences between our guidelines and previous guidelines, which can partly be explained by us using more recently available evidence. There are differences in the strength of recommendations relating to pharmacological therapies: anticonvulsants and SNRIs were strongly recommended by the Canadian and Israeli guidelines while the German and these EULAR guidelines provide a weak recommendation. There are also differences in relation to individual non-pharmacological therapies across guidelines in terms of whether they were assessed. For example, meditative movement is strongly recommended by the German guidelines, but recommended only for a minority of patients in Israel, while these EULAR guidelines provide a 'weak for' recommendation.

The committee recommended that an update is conducted after 5 years in order to determine whether for those therapies with relatively little current evidence further trials have been conducted and, second, whether any new therapies have emerged for the management of fibromyalgia.

Research priorities

In the course of discussion, we identified important questions in terms of guiding management where there was either

insufficient (or often no) evidence base to guide decisions, that is, 'research gaps'. We discussed their relative priority taking into account their potential to guide management, the likelihood that such studies could be conducted and were likely to be funded. We identified five such priority questions:

- ▶ Which type of exercise is most effective: strength and/or aerobic training?
- ▶ Are combined pharmacological and non-pharmacological approaches to management more effective than single-modality management?
- ▶ Are there characteristics of patients with fibromyalgia that predict response to specific therapies?
- ▶ How should fibromyalgia be managed when it occurs as a comorbidity to inflammatory arthritis?
- ▶ What aspects of a healthcare system optimise outcome for patients (who is best for the management of FM patients)?

Some of these questions are best answered by RCTs. Given, however, the expense of such studies and that they can take almost 10 years from identifying the questions to be answered to results being obtained, alternatives including registers and observational studies should be considered. These can be complemented by qualitative studies to determine the needs of patients.

Dissemination

These recommendations will be disseminated by the international working group through national rheumatology societies. This will include scientific meetings, newsletters and continuing education programmes. We will produce a summary of the recommendations suitable for dissemination through EULAR-affiliated patient groups and through national patient societies. We will investigate assessing agreement with the recommendations in the target population.

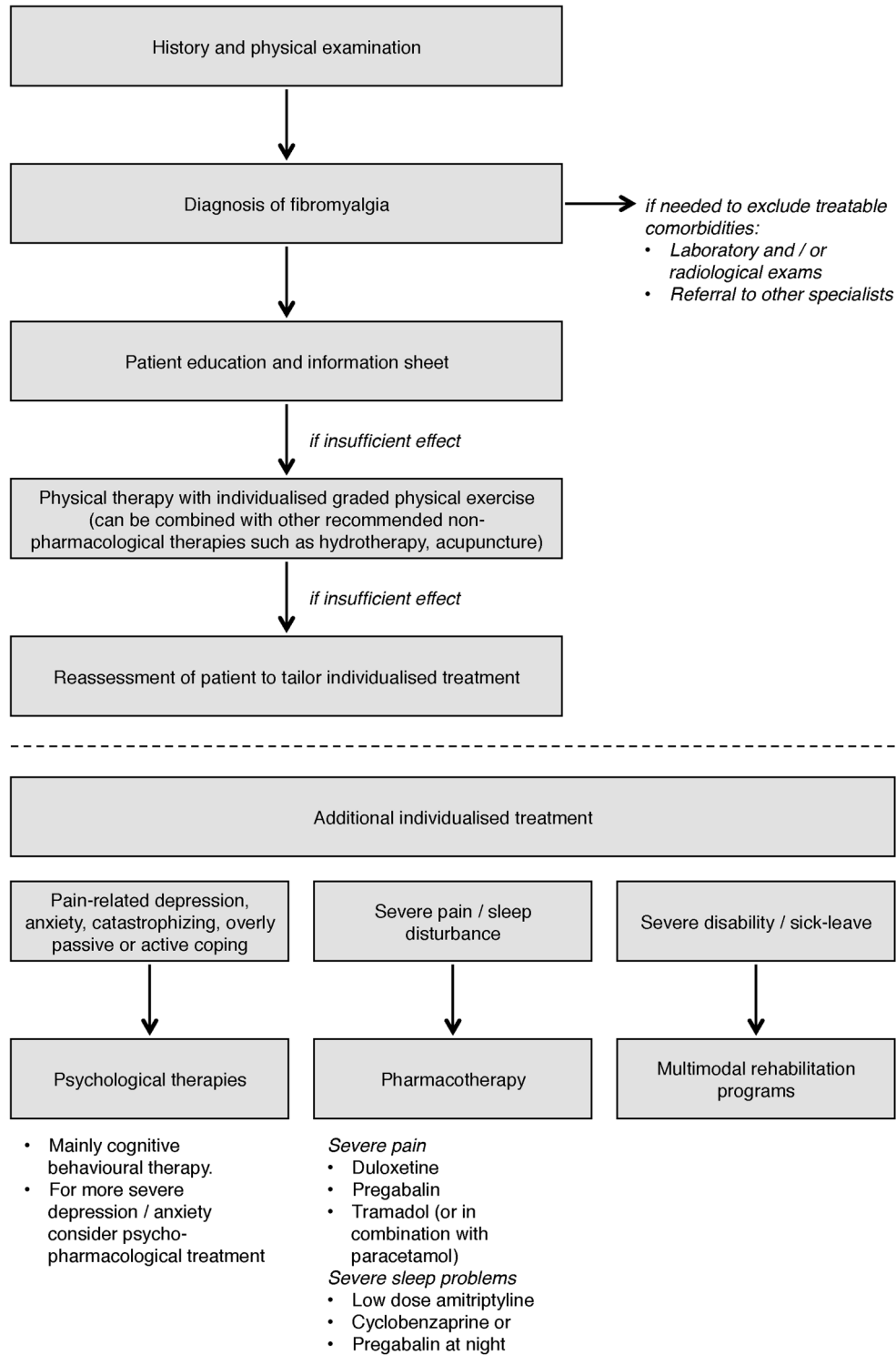


Figure 2 Management recommendations as flow chart.

SUMMARY

In summary, these revised EULAR recommendations newly incorporate a decade of evidence in relation to the pharmacological and non-pharmacological management of fibromyalgia. They allow EULAR to move from recommendations that are predominantly based on expert opinion to ones that are firmly based on scientific evidence from high-quality reviews and meta-analyses. Despite this evidence, however, the size of effect for many treatments is relatively modest. We propose focusing on the research

priorities we outline to address issues clarifying to whom certain interventions may best be delivered, their effect in combination, matching patients to therapies and the organisation of health-care systems to optimise outcome.

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Contributors GJM, FA, PS-P, EC and GTJ were applicants on the grant. EF and LED undertook the literature search and together with FA identified eligible reviews. EF, LED, FA and CK evaluated the quality of each of the eligible reviews. GTJ led the evaluation of non-pharmacological therapies and FA and CK led the evaluation of pharmacological therapies. GJM drafted the manuscript with input from GTJ, WH, EC, CK and EK. All authors (with the exception of FA and EF) participated in a 2-day project meeting, and all authors made important intellectual contributions to the manuscript.

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