EULAR revised recommendations for the management of fibromyalgia

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Abstract

Background: The original EULAR recommendations for the management of fibromyalgia assessed evidence up to and including 2005. The paucity of information at that time meant that most recommendations were "expert opinion". We now update the recommendations taking account of the many randomised controlled trials (RCT) conducted since that time.

Methods: A multidisciplinary group from 12 European countries assessed the available evidence and the focus was on systematic reviews and meta-analyses concerned with the pharmacological, non-pharmacological management or complementary and alternative medicine or therapies for fibromyalgia. A review using seven electronic databases was undertaken up to May 2015 and articles identified as eligible were assessed for quality. The key outcomes assessed were pain, fatigue, sleep and daily functioning. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used for making recommendations: strong for/weak for/ weak against/ strong against or allowing a recommendation "use only for research"

Results: A total of 2979 titles were identified. From these, 571 abstracts and then 275 full papers were selected for review, and 107 reviews (and/or meta-analyses) evaluated as eligible. A graduated approach, following four main stages is suggested underpinned by shared decision-making with patients. Initial management should involve patient education and be focussed on non-pharmacological therapies. The only "strong for" therapy-based recommendation in the guidelines was for exercise. In case of non-response, further therapy 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 dysfunction).

Conclusion: This update allows EULAR to base recommendations for the management of fibromyalgia on scientific evidence from high-quality reviews and meta-analyses. However, the size of effect for many treatments is relatively modest. We propose research priorities clarifying who will derive benefit from specific interventions, their effect in combination, and the organisation of health care systems to optimise outcome.

Introduction

Fibromyalgia is common with a prevalence of 2% in the general population (Queiroz, 2013; Wolfe et al, 1995). However, its diagnosis and management remain a challenge for patients and healthcare professionals. It often takes more than 2 years for a diagnosis to be made with an average of 3.7 consultations with different physicians (Choy et al, 2010). Referral to specialists and investigations results in high healthcare utilisation, for up to 10 years prior to diagnosis, when compared with persons who do not have fibromyalgia (Boonen et al, 2005). 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 emphasize that it is a heterogeneous and complex condition (Hauser et al, 2008; Fietta et al, 2007).

The original EULAR recommendations for the management of fibromyalgia assessed evidence up to and including 2005 (Carville et al, 2008) 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 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 is provided in supplementary text available on-line.

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 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; cost. We used the

Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for making recommendations (Guyatt et al, 2011). This is a 4-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 (Andrews et al, 2013).

Two sub-groups 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 availability, cost, sustained effects and 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).

Evaluation of pharmacological medicines

Information on the reviews informing these recommendations on pharmacological therapy is collated in Supplementary Table A and information from one review, for each medicine, selected based on recency and quality is provided in Table 1.

Amitriptyline: Five reviews included up to 13 trials and a maximum of 919 subjects. Hauser et al (2011) reported that patients receiving amitriptyline were more likely to achieve 30% pain reduction (RR 1.60, 95% CI (1.15,2.24)), equivalent to a "number needed to treat" (NNT) of 3.54 95% CI (2.74, 5.01). There was a moderate effect on sleep (SMD -0.56, 95% CI -0.78,-0.34)[1] and small effect on fatigue (-0.44; -0.71, -0.16). There was no difference in discontinuation rates compared to patients receiving placebo. Nishishinya et al (2008) in their high-quality review concluded that 25mg/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 7 studies and a maximum of 3344 patients. A recent Cochrane review (Üçeyler et al, 2013) reported patients receiving active treatment were more likely to have 30% pain reduction RR 1.37 95% CI (1.22, 1.53) with a "number needed to benefit" (NNTB) over placebo of 9 95% CI (7, 13). There was a very small effect on fatigue (-0.17; -0.25, -0.09) and small effect on sleep (-0.35; -0.43, -0.27) but no effect on disability (-0.01; -0.11, 0.09). A single, moderate quality, study of gabapentin in 150 subjects (e.g. in Moore, et al, 2014) showed a significant

[1] All effect sizes are expressed as SMD with 95% CI unless otherwise stated.

effect on 30% pain reduction (RR 1.65 95% CI 1.10, 2.48), a small effect on sleep (-0.71; -1.08, -0.24) and a large effect on disability (-0.94; -1.32, -0.56). *Anticonvulsant Evaluation*: *Pregabalin - Weak for (94% agreement); Gabapentin – Research only (100% agreement)*

Cyclobenzaprine: A single systematic review of 5 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, 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) (Tofferi et al, 2004). *Cyclobenzaprine Evaluation: Weak for (75% agreement)*

Growth hormone: A single systematic review of 2 studies involving 74 patients reported an effect size on pain of 1.36 (0.01, 1.34)(Perrot and Russell, 2014). The improvement in functional deficit was not statistically significant (1.24; −0.36, 2.84). There are concerns on safety (sleep apnoea, carpal tunnel syndrome). The drug is not approved for FM or related disorders in Europe. *Growth hormone Evaluation: Strong against (94% agreement)*

Monoamine Oxidase Inhibitors (MAOIs): Four reviews identified up to 3 studies and 241 patients. Hauser et al (2009b) reported a moderate effect on pain across the studies (-0.54; -1.02, - 0.07), but the single studies which 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. *MAOIs Evaluation: Weak against (81% agreement)*

NSAIDs: A single review (Choy et al, 2011) identified two small trials with no evidence of improved outcome compared to placebo (Choy et al, 2011). One low quality review was not considered *NSAIDs Evaluation*: *Weak against (100% agreement)*

Serotonin-Noradrenalin re-uptake inhibitors (SNRIs): Eight systematic reviews were identified which presented data separately for duloxetine. The largest review of 2249 subjects (Lunn et al, 2014) reported duloxetine, short term (up to 12 wks)and long-term (up to 28 wks), was more effective than placebo at reducing pain (RR > 30% pain RR 1.38, 95% CI 1.22, 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 60mg/day up to 12 weeks, was 6 95% CI (3, 12). A previous review reported small effects on sleep (-0.24; -0.37,-0.12) and disability (-0.33; -0.43,-0.24) but no effect on fatigue (Hauser et al, 2013). Seven systematic reviews were identified of milnacipran, a recent one of which evaluated 5 trials (Hauser et al, 2013). Patients taking milnacipran were more likely, at the end of treatment, to have 30% pain reduction (RR 1.38, 95% CI 1.25, 1.51) but there was only a small benefit on fatigue (-0.14; -0.19, -0.08), disability (-0.16; -0.23,-0.10) and no effect on sleep. *Duloxetine and Milnacipran Evaluation: Weak for (100% agreement)*

Selective Serotonin Reuptake Inhibitors (SSRIs): Seven systematic reviews included up to 11 trials and a maximum of 521 subjects. Given that reviews have not focussed on specific drugs or comparisons, drugs within this class were considered together. The most recent review, of medium quality included 7 trials and reported that patients receiving SSRIs were more likely to achieve 30% pain reduction (RR 1.59, 95% CI (1.01,2.52)), equivalent to a NNTB of 6.3 95% CI (4.1, 13.1). There was a moderate effect

on sleep (-0.56; -0.78,-0.34) and no effect on fatigue (-0.17; -0.46, 0.11)(Perrot and Russell, 2014). *SSRI Evaluation: Weak against (94% agreement)*

Sodium Oxybate: A single systematic review of 5 studies including 1535 patients reported small effects sizes on pain (0.44; 0.31, 0.58], sleep problems (0.47; 0.28, 0.66) and fatigue [0.48; 0.35, 0.60). EMA and FDA refused the approval for FM because of safety concerns (Perrot and Russell, 2014). The drug is only approved for narcolepsy. *Sodium Oxybate evaluation: Strong against (94% agreement)*

Tramadol, a weak opioid with mild SNRI activity, was considered by two reviews. Roskell et al (2011) 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, 2.48). *Tramadol Evaluation*: *Weak for (100% agreement)*

The literature search did not identify any reviews on corticosteroids, strong opioids, cannabinoids, and anti-psychotics. 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.

<u>Evaluation of non-pharmacological therapies; complementary and alternative medicines and therapies</u>

Information on the reviews informing these recommendations on non-pharmacological, complementary and alternative medicines and therapies is collated in Supplementary Table B and information from one review, for each individual therapy, selected based on recency and quality is provided in Table 2.

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 (Deare et al 2013). Electric acupuncture was also associated with improvements in pain (22%; 4%, 41%), stiffness (9%; 4%, 16%) and fatigue (11%; 2%, 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)*.

Biofeedback: Two reviews included up to seven trials and 307 participants. Glombiewski et al (2013) reviewed seven studies, comprising 321 participants. Treatment sessions varied from 6-22; 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, 1.36) although all trials were poor quality. There was no evidence of effectiveness in terms of fatigue, sleep, depression, or quality of life, and sub-group analysis suggested that any effect was limited to electromyographic (0.86; 0.11, 1.62) rather than electroencephalographic biofeedback (0.71; -0.37, 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 (De Souza Nascimento et al 2013). 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 were 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 (Ernst et al 2009). One study was an open pilot study, one quasi-randomised, and in the third no between-group differences were observed in terms of pain, tenderness and Fibromyalgia Impact Questionnaire. The studies were poor quality and lacked robust interpretable data. *Chiropractic evaluation: Strong against (93% agreement)*.

Cognitive behavioural therapies (CBTs): 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 (Bernardy et al 2013). CBTs were effective in reducing pain (-0.29; -0.49, -0.17), disability (-0.30; -0.51, -0.08) and negative mood (-0.33; -0.49, -0.17) at the end of treatment, compared to a variety of controls groups, and results were sustained long term. *Behavioural therapy evaluation: Weak for (100% agreement)*.

Exercise: 20 reviews included up to 34 trials and at least 2494 participants[2]. The largest, a Cochrane review, considered 47 different exercise interventions (Busch et al 2008). Aerobic exercise was associated with improvements in pain (0.65; -0.09, 1.39), physical function (0.66; 0.41, 0.92), well-being (0.49; 0.23, 0.75) and tender-points (0.23; -0.18, 0.65). Busch et al (2013) reviewed five trials with 219 participants and concluded that resistance training resulted in a significant improvement in pain, compared to control (-3.3cm on a 10cm scale; -6.35, -0.26) as well as function, tenderness and strength. There is some consistency with regards to aerobic and strengthening exercises, although insufficient evidence to suggest superiority of one over the other; land and aquatic exercise appear equally effective. (Bidonde et al 2014). *Exercise therapy evaluation: Strong for (100% agreement)*.

Hydrotherapy / spa therapy: Four reviews included up to 21 trials and 1306 participants. One high quality review included ten trials, 446 participants, and compared a median of 4hrs hydrotherapy (range 200-300mins) against various comparators (Langhorst et al 2009). There was a significant improvement in pain (-0.78; -1.42, -0.13) and health-related quality of life (-1.67; -2.91, -0.43) 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 regards to the evidence for hydrotherapy and balneotherapy, although little evidence to suggest superiority of one over the other (Naumann and Sadaghiani 2014). *Hydrotherapy evaluation: Weak for (93% agreement)*.

Hypnotherapy: One review included four trials, although the number of participants is unclear (Bernardy et al 2011). Although six trials of hypnotherapy and/or guided imagery were reviewed, only four examined hypnotherapy in isolation. Median treatment duration (where reported) was 360 minutes 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 is 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).*

[2] It 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.

Massage: Six reviews have been reported and one meta-analysis with nine trials and 404 patients (Li et al 2014) with sessions lasting 25-90 mins, and treatment duration ranging from 1-24 weeks (median five weeks). Comparator treatments, included 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, 0.93) and of the two ITT analyses, one favoured massage and one favoured control (both significant). A sub-group 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 7 trials, with 362 participants randomised to tai chi, yoga, qigong, or body awareness therapy (Langhorst et al 2013). Total treatment time ranged from 12-24hrs and was compared to 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, -0.27), fatigue (-0.66; -0.99, -0.34), and quality of life (-0.59; -0.93, -0.24) 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 6 trials, with 674 patients (Lauche et al 2013b) provided evidence that mindfulness-based stress reduction resulted in improvements in pain (-0.23; -0.46, -0.01) and quality of life (-0.35; -0.57, -0.12) immediately post-treatment, when compared to usual care, and when compared to active control interventions (-0.44; -0.73, -0.16, and -0.32; -0.59, -0.04, respectively). However, these effects were not robust against bias. *Mindfulness / mind-body therapy evaluation*: *Weak for (73% agreement)*.

Multi-component therapy: Two reviews including up to 27 trials and 2407 participants examined the additional benefit of combining therapies, compared to individual therapy. Häuser et al (2009a) conducted a review of management involving both educational or psychological therapies and exercise. In a meta-analysis of nine trials and 1119 patients, multi-component therapy was effective in reducing pain (-0.37; -0.62, -0.13), and fatigue and depression, immediately post-treatment, compared to waiting-list, relaxation, treatment as usual, and education. It also was associated with improvements in quality of life, self-efficacy and fitness. However, for most outcomes, effects were short-lived. *Multi-component therapy evaluation: Weak for (93% agreement)*.

S-Adenosyl methionine (SAMe): Two reviews each included one trial with, in combination, 74 participants. De Silva et al (2010) reported that, after the end of treatment, significant improvements were observed in pain, fatigue, disease activity, stiffness and mood compared to placebo. Sim and Adams (2002) reviewed a trial comparing SAMe with transcutaneous electrical nerve stimulation (TENS) but data on the main trial comparison is omitted. Side-effects are usually mild and infrequent. However, the number of patients and trials were 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, -0.87) and quality of life (-2.51; -3.28, -1.74) (Bernardy et al 2011). Two reviews of homeopathy, including four trials and 163 participants (Perry et al 2010; Boehm et al 2014). 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 (Ricci et al 2010); phytothermotherapy (Tenti et al 2013); music therapy, journaling/story-telling (Crawford et al 2014), and static magnet therapy (Eccles et al 2005), although each was insufficient to allow a recommendation. Marlow et al (2013) 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 firstly 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 ten 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. We also gave a “weak for” recommendation to multi-component therapies which, in comparison, to individual therapies improved a range of short-term outcomes. 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: 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 non-pharmacological therapy, we recommend individualized 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) , while multimodal rehabilitation ("weak for") programs should be considered for those with severe dysfunction. We did not recommend several pharmacological therapies including NSAIDs, MAOIs, 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 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. However all the recommendations are now firmly evidence-based. This evidence provides support for some additional non-pharmacological therapies. 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 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 which have been compared with respect to their recommendations (Ablin et al, 2013). 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, 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 recommend 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 secondly 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 i.e. “research gaps”. We discussed their relatively 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?
- Is combined pharmacological and non-pharmacological approaches to management more effective than single modality management?
- Are there characteristics of patients with fibromyalgia which predict response to specific therapies?
- How should fibromyalgia be managed when it occurs as a co-morbidity 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 randomised controlled trials. 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, 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.

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 which are predominantly based on expert opinion to ones which 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 focussing 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.

Acknowledgements and Contribution

The project was funded by EULAR. GJM, FA, PS-P, EC and GTJ were applicants on the grant. EF and LD undertook the literature search and together with FA identified eligible reviews. EF, LD, 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) participated in a two-day project meeting, and all authors made important intellectual contributions on the manuscript.

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