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Is combination pharmacotherapy effective for management of fibromyalgia in adults? - A Cochrane Review summary with commentary

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The aim of this commentary is to discuss in a rehabilitation perspective the published Cochrane Review "Combination pharmacotherapy for the treatment of fibromyalgia in adults"[1] by J Thorpe & B Shum[a], under the direct supervision of Cochrane Pain, Palliative and Supportive Care Group. This Cochrane Corner is produced in agreement with Journal of Musculoskeletal and Neuronal Interactions by Cochrane Rehabilitation.

Background

Fibromyalgia is a chronic painful condition which can present with various symptoms including generalized pain for more than three months, fatigue, nonrestorative sleep, and cognitive problems including anxiety and depression[2]. It negatively affects the quality of life, social functioning of the patient and puts financial burden on the society[2]. The pathophysiology includes alterations in different central and peripheral nervous system pathways, leading to an increased pain sensitivity and resulting symptoms[3]. The global prevalence of fibromyalgia has been estimated to be 2% of the general population[4]. However, exact estimates can vary between different regions. Correct diagnosis and adequate management are challenging; it may take more than two years for health care professionals to correctly diagnose fibromyalgia[5], and different management strategies have been recommended[2,3,5]. A multidisciplinary approach involving pharmacotherapy along with physical therapy and cognitive therapies are generally advised as the first-line treatment.6 The pharmacological options for fibromyalgia include non-steroidal anti-inflammatory drugs (NSAID), anticonvulsants, opioids and antidepressants[3,5,6].

Combination pharmacotherapy for the treatment of fibromyalgia in adults

(Joelle Thorpe, 2018)

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The views expressed in the summary with commentary are those of the Cochrane Corner authors and do not represent the Cochrane Library or Wiley.

What is the aim of this Cochrane review?

The aim of this Cochrane Review was to compare the effectiveness, safety and acceptability of combination pharmacological intervention compared to single drug or dummy pill or both for management of fibromyalgia pain in adults.

What was studied in the Cochrane review?

The population addressed in this review was adults (≥18 years) diagnosed with fibromyalgia. The authors included only double-blind, randomized controlled trials (RCT). The interventions studied were any combination of two or more drugs administered via any route. The intervention was compared to placebo and/or other comparators. Primary outcomes included patient-reported pain relief of 30% or greater, patient-reported pain relief of 50% or greater and patient-reported global impression of clinical change (much or very much improved). Secondary outcomes included any pain-related outcome indicating some improvement, any adverse event (both specific and serious) and withdrawals due to adverse events or lack of efficacy.

Search methodology and up-to-dateness of the Cochrane review?

The review authors searched for studies that had been published up to September 2017 on Cochrane Central Register of Controlled Trials, MEDLINE and MEDLINE in Process, Embase, ISCRTN Registry, Clinicaltrials.gov, WHO International Clinical Trials Registry Platform and reference lists of published reviews.

What are the main results of the Cochrane review?

The review included 16 RCTs, involving 1474 participants, mostly women. All studies had duration of 4 weeks or more. Narrative description of results was provided due to insufficient data that could be used for meta-analyses. Only 2 studies reported data for primary outcome measures defined in this review. In the Summary of findings tables, quality of evidence for the seven highlighted outcomes was graded as very low due to lack of data for analysis. Serious adverse effects were not reported in any study.

NSAIDs combined with benzodiazepines

Three studies (306 participants) combined an NSAID (ibuprofen or tenoxicam) with a benzodiazepine (alprazolam or bromazepam):

- Participants in the alprazolam and the ibuprofen alone groups had significantly fewer tender points than the combination and placebo groups at 4 weeks.
- Clinicians rated more participants in the ibuprofen and alprazolam alone groups (70% and 58%, respectively) as being much or very much improved by the end of the trial, compared to the combination and double-placebo groups (40% and 30%, respectively). However, this difference was not statistically significant.
- In one trial, combination treatment (alprazolam and ibuprofen) significantly decreased pain and tender point index, but not dolorimeter score or physician-rated global assessment.
- The most common minor side effects noted were headache, sedation, drowsiness, blurred vision, nasal congestion and gastrointestinal symptoms like nausea.

Amitriptyline combined with fluoxetine

Amitriptyline and fluoxetine alone and in combination were evaluated in two studies with 89 participants:

- There was very low quality evidence that that combination of amitriptyline and fluoxetine is better than monotherapy or placebo in improving self-reported visual analogue scale (VAS) scores of pain, sleep, and global well-being, and Fibromyalgia Impact Questionnaire (FIQ) scores.
- The most common minor side effects and reasons for withdrawal from the study included sedation, headache, dryness, gastrointestinal-related symptoms and worsening of fibromyalgia symptoms.

Amitriptyline combined with a drug from another class of medication

Two studies (92 participants) evaluated use of amitriptyline combined with a drug from another class of medication (oral naproxen or Intravenous lidocaine):

- There was very low quality evidence that oral amitriptyline alone or in combination with naproxen is better than placebo in improving VAS scores of global assessments, pain, sleep difficulty, fatigue, morning tiredness, and tender point scores. However, it was not clear if naproxen enhanced the efficacy of amitriptyline.
- When amitriptyline monotherapy was compared to combination therapy of amitriptyline and intravenous lidocaine in a 4-week trial, there was no significant difference between the groups in improving fatigue, number of tender points, VAS pain scores and morning stiffness.
- Adverse effects were reported only for the amitriptyline and naproxen combination study. These included dry mouth, dyspepsia and diarrhea.

Melatonin combined with an antidepressant

Two studies (163 participants) compared melatonin combined with an antidepressant (fluoxetine or amitriptyline) with fluoxetine or amitriptyline monotherapy:

- There was very low quality evidence that melatonin alone or in combination with fluoxetine can improve FIQ score and parameters like pain, fatigue, rest/sleep, stiffness, anxiety, and depression.
- There was very low quality evidence that melatonin alone

or in combination with amitriptyline when compared to amitriptyline monotherapy may result in improvement in the FIQ scores, reduced dose of analgesics, reduction in the number of tender points and a better quality of sleep.
- The side effects reported from melatonin alone or in combination with amitriptyline group included nausea, dizziness, weight gain, dry mouth, nightmares, crippling drowsiness, severe headache and increased pain.

Carisoprodol combined with paracetamol (acetaminophen) and caffeine

One study with 58 participants compared the combination of carisoprodol, paracetamol (acetaminophen), and caffeine to placebo, in a parallel-design, 8-week study:
- As compared to the combination therapy group, more participants in the placebo group took additional medication including analgesics, tricyclic antidepressants, anxiolytics, and sedatives.
- There were no statistically significant differences in VAS pain, sleep quality, and general feeling of sickness scores between treatment groups after eight weeks.
- Drowsiness was the only side effect reported in the study.

Tramadol combined with paracetamol (acetaminophen)

There was a single study with 315 participants which evaluated the combination of tramadol with paracetamol (acetaminophen) to placebo treatment in a 13-week, parallel-design trial:
- There was very low quality evidence that patient-reported pain relief of 30% or greater and patient-reported pain relief of 50% or greater was better in the combination group as compared to the placebo.
- There was very low quality evidence that the combination of tramadol and paracetamol (acetaminophen) is moderately effective in reducing pain and pain-related symptoms of fibromyalgia.
- The dropout rate was higher in the placebo group as compared to the combination group. (62% versus 48%).
- Adverse effects were more common in the combination group as compared to the placebo. These included nausea, dizziness, somnolence, and constipation.

Malic acid combined with magnesium

Only one study of 4-week duration with 24 participants compared the combination of malic acid and magnesium to placebo:
- Secondary outcome measures reported were VAS pain scores, tender point index, tender point average, Health Assessment Questionnaire scores, Center for Epidemiologic Studies Depression scale scores, and anxiety assessed by the Hassle scale scores. There was no significant difference between combination and placebo groups.
- Adverse events were reported in 13 patients, but none of the participant withdrew from study due to adverse events.

Monoamine oxidase inhibitor (MAOI) combined with 5-hydroxytryptophan (5-HTP)

Only one study (200 participants) of 12-month duration reported the results of MAOI alone, 5-HTP alone, amitriptyline alone and combination of MAOI and 5-5-HTP:
- There was a very low-quality evidence that combining MAO plus 5-HTP was more effective in reducing pain compared to each monotherapy and amitriptyline therapy in patients with fibromyalgia.
- The most common side effects reported included stiffness, nausea drowsiness and GI disturbance.

Pregabalin combined with duloxetine

A single study of 24-week duration with 39 participants studied effects of combination therapy of pregabalin and duloxetine compared with monotherapy for each drug and placebo:
- There was very low quality evidence that combination therapy of pregabalin and duloxetine is better than pregabalin alone (68% versus 42%) or duloxetine alone (68% versus 39%) or placebo (68% versus 18%) for improving patient-reported pain relief of 30% or greater.
- There was very low-quality evidence that combination therapy improved Short-form McGill Pain Questionnaire (SF-MPQ), FIQ, and SF-36 scores as compared to both monotherapy treatments and to placebo.

How did the authors conclude?

The authors concluded that currently there is insufficient evidence to support or refute the routine use of any specific drug combination for the treatment of fibromyalgia pain. Fibromyalgia is a chronic pain syndrome which persists for years and there is a need to have a long term follow-up beyond 12 months to determine the effectiveness of a combination drug therapy. There is also a need for better trials considering that a pragmatic approach might be helpful, while acknowledging that there are considerable differences between individuals in terms of drug response, and that these are not predictable[7]. In addition, clinicians must use caution while prescribing multimodal pharmacotherapy and monitor the patients for possible adverse effects. For example, combining different serotonin reuptake inhibitors like amitriptyline, desipramine, duloxetine and tramadol might result in a potentially life-threatening condition called “serotonin syndrome” (characterized by altered mental status, hyperactivity, and neuromuscular dysfunction)[1]. However, the authors concluded that no participants in the studies included in this review had any serious side effects and the side effect profile did not differ significantly between the combination therapy groups and monotherapy.

What are the implications of the Cochrane evidence for practice in rehabilitation?

Fibromyalgia is one of the chronic pain conditions which rehabilitation professionals see commonly in their clinical practice. Pharmacotherapy along with exercise prescription and counselling is an important part of the management strategy. Rehabilitation medicine physicians (physiatrists) routinely prescribe different drugs alone or in combination for symptomatic pain management. Based on this review, it is not clear whether combination pharmacotherapy is superior to monotherapy for treating fibromyalgia. Therefore, physiatrists should decide about using a combination or monotherapy by considering all factors such as side effect profile of the drug, patient preference, other co-morbidities, cost and their own clinical experience with drug management of fibromyalgia. Since the quality of currently available evidence is very low, there is also a need for better quality, adequately powered clinical trials with long term follow-up to determine if combination pharmacotherapy is better than monotherapy.

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