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J Rheumatol 2012;90;47-55
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ABSTRACT. Objective. To assess the efficacy and safety of combination pain therapy for people with inflammatory arthritis (IA).

Methods. Systematic review of randomized controlled trials using Cochrane Collaboration methodolo-
gy. Combination therapy was defined as at least 2 drugs from the following classes: analgesics, non-
steroidal antiinflammatory drugs (NSAID), opioids, opioid-like drugs, and neuromodulators (antide-
pressants, anticonvulsants, and muscle relaxants). The main efficacy and safety outcomes were pain and
withdrawals due to adverse events, respectively.

Results. Twenty-three trials (total of 912 patients) met inclusion criteria [22 in rheumatoid arthritis (RA)
and 1 in a mixed population of RA and osteoarthritis]. All except 1 were published before 1990. All tri-
ials were at high risk of bias, and heterogeneity precluded metaanalysis. Statistically significant differ-
ences between treatment groups were reported in only 5/23 (22%) trials: in 3 trials combination ther-
apy was better (2 trials with NSAID + analgesic versus NSAID only and 1 trial with 2 NSAID versus 1
NSAID), in 1 trial combination therapy was worse (opioid + neuromodulator versus opioid only), and
in the fifth trial (NSAID + analgesic versus NSAID alone) reported results were mixed depending on
the dosage used in the monotherapy arm. In general, there were no differences in safety and withdrawals
due to inadequate analgesia between combination and monotherapy.

Conclusion. Based on 23 trials, all at high risk of bias, there is insufficient evidence to establish the
value of combination therapy over monotherapy for pain management in IA. Well-designed trials are
needed to address this question. (J Rheumatol Suppl 2012; Sept;90:47–55; doi:10.3899/jrheum.120342)

Key Indexing Terms:

 Pain/Drug Therapy
 Analgesics
 Inflammatory Arthritis
 Spinal Arthritis
 Rheumatoid Arthritis
 Psoriatic Arthritis

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Based on a Cochrane Review published in the Cochrane Database of Systematic Reviews 2011, Issue 10, doi:10.1002/14651858.CD008922 (see www.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and the CDSR should be consulted for the most recent version of the review.

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Inflammatory arthritis (IA) is a term given to a group of chronic inflammatory rheumatic diseases that primarily include rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and undifferentiated spondyloarthritis (SpA). Together, they have an estimated prevalence of about 3%, comprising a prevalence of 1% for RA2 and 1.9% for SpA (including AS and PsA)3. The IA are progressive diseases, characterized by pain, joint destruction, and decreased function, and they have a profound effect on the patient’s quality of life and on society in terms of medical costs and work disability1.

The management of IA has dramatically changed over the last decade. The current approach focuses on early detection and management at an early stage of the disease with disease-modifying antirheumatic drugs (DMARD)4; moreover, with the introduction of the efficacious biological disease-modifying antirheumatic drugs (bDMARD), remission of disease is considered to be the appropriate treatment target5. Nevertheless, despite these significant advances, many patients with IA continue to experience musculoskeletal pain6,7. Studies have reported that patients with IA perceive pain to be their predominant impairment8, and improvement in pain to be among their highest priorities9, even among those who have achieved adequate disease control and are being treated with biologics10.
In treating patients who have persistent pain, drugs with analgesic effect can be prescribed as monotherapy or in combinations. Nevertheless, it is not known whether specific combinations of classes of drugs with analgesic potential are more effective than monotherapy to treat persistent pain in patients with IA, or if adverse effects offset any benefits. The aim of our review was to summarize the existing data on the efficacy and safety of combination therapy for pain management in patients with IA and is a shortened version of a Cochrane review.12

Our review is part of the 3e (Evidence, Expertise, Exchange) Initiative13,14,15 on Pain Management by Pharmacotherapy in Inflammatory Arthritis16. The objective of this report was to systematically review the literature concerning one of the 10 selected questions as an evidence base for generating the recommendations. The question was: “Is there any evidence that drugs with different modes of action in various combinations have added value?”

MATERIALS AND METHODS
Our systematic review used the methodology proposed by the Cochrane Collaboration17.

Rephrasing the research question. The clinical question, as formulated by the group of clinicians, was first rephrased in epidemiological terms to “What is the efficacy and safety of combination therapy for pain management in IA,” then restructured according to the PICO format18 (Patients, Interventions, Comparisons, and Outcomes), and the eligible study types were defined. Participants were defined as adults at least 18 years old with a clinical diagnosis of IA (RA, AS, PsA, or SpA). Studies containing patients with other diagnoses were eligible only if the results from patients with IA were presented separately.

The intervention was defined as a combination of at least 2 of the following drug classes: analgesics, nonsteroidal antiinflammatory drugs (NSAID), opioids, opioid-like drugs, and neuromodulators (antidepressants, anticonvulsants, muscle relaxants). The comparator was defined as any drug, from the previously mentioned drug classes, in monotherapy. All the possible variations for combination therapy or monotherapy were included (dosage intensity, mode of delivery, frequency of delivery, timing of delivery). The outcomes were divided into efficacy and safety.

For efficacy, the primary outcome was patient-reported pain relief ≥ 50%. For safety, the primary outcome was the number of withdrawals due to adverse events. Secondary outcomes were patient-reported pain relief ≥ 30%; patient-reported global impression of clinical change as “much” or “very much improved”; proportion of patients achieving a pain score below 30/100 mm on visual analog scale (VAS); mean change in pain score on VAS or numeric rating scale; physical function (on the Health Assessment Questionnaire for RA19,20 or Bath Ankylosing Spondylitis Functional Index for AS21), quality of life (on generic instruments such as the Medical Outcome Study Short-Form 3622 or disease-specific tools, such as the Rheumatoid Arthritis Quality of Life instrument23 and Ankylosing Spondylitis Quality of Life Instrument24), patient withdrawals due to inadequate analgesia, number of patients with adverse events, and number of deaths. These primary and secondary pain outcomes were chosen based upon those currently recommended by the Cochrane Pain, Palliative and Supportive Care Systematic Review Group editors and others, for systematic reviews (SLR) on chronic pain25.

The types of studies considered for inclusion were randomized controlled trials (RCT) and quasi-randomized controlled trials (CCT; i.e., where allocation was not truly at random). There were no restrictions in length of followup or language of the report. Only trials that were published as full articles or were available as a full trial report were included. Studies that did not contain pain as an outcome measure or that did not include an understandable pain scale were excluded.

Search strategy. The following computerized bibliographical databases were searched: Medline (1950 to 4 May 2010), Embase (Embase classic 1947 to 1979 and Embase 1980 to 4 May 2010), The Cochrane Central Register of Controlled Trials (Central) (The Cochrane Library, Issue 2, 2010) without language restrictions, using the highly sensitive Cochrane Collaboration search strategy, which aims to identify all RCT26. Specific MeSH headings and additional keywords were used to identify all RCT on combination therapy for pain management in IA. Details on complete search strategies for the database searches are provided in Appendix 1 available from www.3epain.com.

In order to retrieve additional references, an additional search for systematic reviews was carried out in the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects (The Cochrane Library, Issue 2, 2010). References from included RCT and other systematic reviews on combination therapy for pain management in IA were screened in order to identify all possible studies for this systematic review. Finally, the conference proceedings for the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) for 2008-2010 were also hand-searched to identify unpublished studies.

Selection of studies, data extraction, and assessment of risk of bias. Two reviewers (SR, HR) independently assessed each title and abstract for suitability for inclusion in the review, according to the predetermined selection criteria, followed by full-text article review where necessary. For included trials, they independently extracted data regarding study design, study duration, characteristics of study population, interventions, outcome measures and timing of outcome assessment, co-interventions, adverse effects, and loss to followup using a standardized data extraction form. Data from crossover trials were extracted regarding the first period, whenever available.

In order to assess efficacy, raw data for outcomes of interest (means and standard deviations for continuous outcomes and number of events for dichotomous outcomes), as well as number of participants, were extracted if available from the published reports.

The 2 reviewers independently assessed risk of bias of each included study with regard to the following items: random sequence generation, allocation concealment, blinding of participants, care provider and outcome assessor for each outcome measure, incomplete outcome data, selective outcome reporting, and other potential sources of bias, conforming to the methods recommended by the Cochrane Collaboration27. Each criterion was rated as “Yes” (low risk of bias), “No” (high risk of bias), or “Unclear” (either lack of information or uncertainty over the potential for bias). For all these steps, disagreements among the reviewers were discussed and resolved in a consensus meeting or involving a third reviewer (RL), if necessary.

Data analysis. In cases where individuals were missing from the reported results, we assumed the missing values to have a poor outcome. For dichotomous outcomes (e.g., number of withdrawals due to adverse events), the withdrawal rate was calculated using the number of patients randomized in the group as the denominator (worst-case scenario).

The results of each study were planned to be plotted as point estimates with 95% confidence intervals. Point estimates were planned to be measured as relative risk for dichotomous outcomes, and mean difference and standard deviation for continuous outcomes. For data with a sufficient level of clinical and statistical homogeneity, we planned to pool the results using a fixed-effects model, and in the case of clinical homogeneity but statistical heterogeneity, using a random-effects model. Subgroup and sensitivity analyses were planned to assess the effects of several variables on the efficacy of combination therapy and to explore the robustness of the conclusions, respectively.

RESULTS
Results of the search. The electronic database search yielded a total of 14,854 articles, and an additional 160 meeting abstracts were obtained from the conference proceedings. After de-duplication and title and abstract screening, 14,788
studies were excluded and all meeting abstracts were excluded, leaving 66 articles for full-text review. The main reason for exclusion was wrong study type or wrong intervention. After further review, 23 of the 66 articles met inclusion criteria\(^2\)\(^8\), 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50. The search process is illustrated in Figure 1, and the reasons for exclusion are described in Appendix 2, available online from www.3epain.com.

**Included studies.** The 23 included trials\(^2\)\(^8\), 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50 involved 912 patients (mean 40 participants per trial, range 12 to 134), and study duration ranged from 2 days to 5 months (Table 1). A full description of the studies is provided in Appendix 3, available online from www.3epain.com. Other than the trial by Seideman, et al published in 1993\(^47\), all trials were published before 1990. Twenty-two trials were reported in English and one in German\(^30\). There were 5 parallel RCT\(^30\),\(^31\),\(^44\),\(^49\),\(^50\), one CCT\(^28\), and 17 crossover trials\(^29\),\(^30\),\(^31\),\(^32\),\(^33\),\(^34\),\(^35\),\(^36\),\(^37\),\(^38\),\(^39\),\(^40\),\(^41\),\(^42\),\(^43\),\(^45\),\(^46\),\(^47\),\(^48\). Twenty-two trials included participants with RA, while one trial included a mixed population of RA and osteoarthritis\(^31\). For the latter trial, only the results for the RA subset have been included in this review. No trials were found for other types of IA.

Six studies\(^33\),\(^37\),\(^39\),\(^46\),\(^47\),\(^48\) reported the mean age of the whole study population, which ranged from 44 to 56 years. Eight studies\(^30\),\(^37\),\(^39\),\(^41\),\(^42\),\(^45\),\(^46\),\(^47\),\(^48\) reported the mean duration of disease for the whole population, which ranged from 4 to 10 years. The degree of disease activity of participants was not reported. The proportion of women in the study population, reported in 9 studies\(^33\),\(^37\),\(^39\),\(^41\),\(^42\),\(^44\),\(^45\),\(^47\),\(^48\), varied between 55% and 89%. Only 6 of the 23 studies provided information about concurrent DMARD therapy. One trial reported that no antirheumatic drugs were allowed\(^30\), and the other 5 studies\(^31\),\(^33\),\(^45\),\(^46\),\(^47\) reported allowance of stable doses of DMARD, such as gold, penicillamine, chloroquine, or steroids. No information was given about the proportion of patients taking DMARD therapy. None of the participants in the included studies was receiving bDMARD.

The interventions used in the trials were very heterogeneous: different drug classes, drugs, and dosages. Several of the interventions studied are not used in current practice, as for instance, benorylate or safapryn, which are a combination of aspirin and paracetamol\(^28\),\(^30\),\(^31\),\(^32\),\(^35\),\(^36\),\(^40\),\(^41\),\(^42\),\(^43\),\(^49\). The dosages were frequently suboptimal according to current recommendations\(^51\), in terms of their analgesic effect, for example, ibuprofen 1200 mg/day\(^36\) or indomethacin 100 mg/day\(^37\).

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**Figure 1.** Literature search from which 66 articles were selected for detailed review. Twenty-three articles met the inclusion criteria.
Table 1. Summary of clinical trials of combination therapy for pain management in inflammatory arthritis.

<table>
<thead>
<tr>
<th>Study, Author, Year</th>
<th>Sample Size, Design, Study Duration</th>
<th>Combination Therapy</th>
<th>Comparison Group, Monotherapy</th>
<th>Outcome Timing</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beales 1972&lt;sup&gt;28&lt;/sup&gt;</td>
<td>72, CCT, 2 wks</td>
<td>Benorylate (aspirin + paracetamol) 8 g</td>
<td>Aspirin 4.8 g</td>
<td>2 weeks</td>
<td>1. Diurnal pain score (0 = nil; 1 = mild; 2 = moderate; 3 = severe); 2. Severity of disease; 3. Functional grading; 4. Grip strength; 5. Finger stiffness; 6. Total ring size; 7. Articular index</td>
</tr>
<tr>
<td>Bedi 1969&lt;sup&gt;29&lt;/sup&gt;</td>
<td>51, crossover trial, 2 wks</td>
<td>Aspirin 500 mg + dextropropoxyphene napsilate 50 mg</td>
<td>Aspirin 500 mg</td>
<td>1 week</td>
<td>1. Improvement in pain (better, no change, worse); 2. Number and type of adverse events (although not specified in the methods)</td>
</tr>
<tr>
<td>Brooks 1975&lt;sup&gt;30&lt;/sup&gt;</td>
<td>134, parallel RCT, 2 wks</td>
<td>Salsalazine (paracetamol 3 g + aspirin 3.6 g)</td>
<td>1. Phenylbutazone 50 mg 2. Phenylbutazone 300 mg</td>
<td>Throughout 2 wks 2 wks</td>
<td>1. Pain (0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe); 2. Patient global score</td>
</tr>
<tr>
<td>Coigley 1975&lt;sup&gt;31&lt;/sup&gt;</td>
<td>95, parallel RCT, 2 wks</td>
<td>Benorylate (paracetamol + aspirin) 8 g</td>
<td>Indomethacin 75 mg</td>
<td>2 wks 2 wks</td>
<td>1. Improvement in pain (clinical assessment of pain lower by one or more categories, within the following: mild, moderate, severe) at the end of treatment; 2. Morning stiffness</td>
</tr>
<tr>
<td>Ekstrand 1981&lt;sup&gt;32&lt;/sup&gt;</td>
<td>12, crossover trial, 8 wks</td>
<td>1. Acetylsalicylic acid 2 g + indomethacin 50 mg; 2. Acetylsalicylic acid 4.5 g + indomethacin 50 mg</td>
<td>1. Acetylsalicylic acid 2 g 2. Acetylsalicylic acid 4.5 g</td>
<td>Throughout 3 wks</td>
<td>1. Overall global assessment; 2. Preference for one of the suppositories given; 3. Duration of morning stiffness; 4. Pain throughout the period and on the day after indomethacin/placebo (0-100 mm VAS); 5. Grip strength; 6. Articular index; 7. Size of PIP joints</td>
</tr>
<tr>
<td>Grennan 1979&lt;sup&gt;34&lt;/sup&gt;</td>
<td>16 + 14 (2 small trials), crossover trial, 16 wks</td>
<td>Aspirin + ibuprofen</td>
<td>Part I of the trial: 2.4 aspirin + 800 mg ibuprofen Part II of the trial: 3.6 g aspirin + 1600 mg ibuprofen</td>
<td>2 wks</td>
<td>1. Articular index; 2. Duration of morning stiffness; 3. Pain score (0-10 cm VAS); 4. Patient global subjective score; 5. Global observer score; 6. Time to walk 50 feet; 7. Grip strength</td>
</tr>
<tr>
<td>Haslock 1971&lt;sup&gt;35&lt;/sup&gt;</td>
<td>33, crossover trial, 8 wks</td>
<td>Benorylate (aspirin + paracetamol) 6 g</td>
<td>Phenylbutazone 160 mg</td>
<td>Throughout 4 wks</td>
<td>1. Grip strength; 2. Patient own assessment of overall pain (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain, 4 = unbearable severe pain); 3. Duration of morning stiffness; 4. Adverse events</td>
</tr>
<tr>
<td>Hingorani 1973&lt;sup&gt;36&lt;/sup&gt;</td>
<td>27, crossover trial, 8 wks</td>
<td>Benorylate (aspirin + paracetamol) 8 g</td>
<td>Ibuprofen 1200 mg</td>
<td>3 wks</td>
<td>1. Pain score (0 = none, 1 = mild, 2 = moderate, 3 = severe); 2. Grip strength; 3. Functional grip strength; 4. Morning stiffness; 5. Functional capacity</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Intervention 1</td>
<td>Dose</td>
<td>Intervention 2</td>
<td>Dose</td>
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<tr>
<td>Hobkirk 1977</td>
<td>18, crossover trial, 2 days</td>
<td>Indomethacin 100 mg + diazepam 10 mg</td>
<td>1 day</td>
<td>1. Morning stiffness; 2. Pain (0-10 cm VAS); 3. Sleep; 4. Adverse events</td>
<td></td>
</tr>
<tr>
<td>Huskisson 1974</td>
<td>30 + 24 (2 small trials), crossover trial, 18 days</td>
<td>Trial 1: paracetamol 650 mg + dextropropoxyphene 65 mg</td>
<td>6 h</td>
<td>1. Pain relief score (0 - none, 1 - slight, 2 - moderate, 3 - complete); 2. Preference for treatment</td>
<td></td>
</tr>
<tr>
<td>Kean 1981</td>
<td>24, crossover trial, 2 wks</td>
<td>Enteric coated aspirin 3.6 g + azapropazone 1200 mg</td>
<td>1 week</td>
<td>1. Enteric coated aspirin 3.6 g; 2. Azapropazone 1200 mg</td>
<td></td>
</tr>
<tr>
<td>Mowat 1979</td>
<td>31, crossover trial, 8 wks</td>
<td>Benorylate (aspirin + paracetamol) 4 g (up to 8 g)</td>
<td>4 wks</td>
<td>1. Pain (0-10 cm VAS); 2. Morning stiffness; 3. Joint pain on full range of active movement; 4. Adverse events</td>
<td></td>
</tr>
<tr>
<td>Saarialho-Kere 1982</td>
<td>16, crossover trial, 12 days</td>
<td>Dextropropoxyphene 65 mg + amitriptyline 25 mg</td>
<td>4 h</td>
<td>1. Dextropropoxyphene 130 mg; 2. Indomethacin 50 mg; 3. Indomethacin 150 mg; Average of 2nd week</td>
<td></td>
</tr>
<tr>
<td>Seideman 1986</td>
<td>20, crossover trial, 5 wks</td>
<td>Indomethacin 50 mg + paracetamol 4 g</td>
<td>1. Pain (0-100 mm VAS); 2. Duration of morning stiffness; 3. Grip strength; 4. Number of joints painful to digital pressure; 5. Joint circumference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seideman 1993</td>
<td>20, crossover trial, 5 wks</td>
<td>1. Naproxen 500 mg + paracetamol 4 g; 2. naproxen 1000 mg + 4 g</td>
<td>2 wks</td>
<td>1. Number of joints painful to digital pressure or passive movements; 2. Duration of morning stiffness; 3. Pain (0-100 mm VAS); 4. Global assessment of disease activity; 5. Activity of daily living assessment</td>
<td></td>
</tr>
<tr>
<td>Sharma 1978</td>
<td>18, crossover trial, 3 days</td>
<td>Sulindac 200 mg + diazepam 100 mg; 2. Indomethacin 100 mg + diazepam 10 mg</td>
<td>1 day</td>
<td>1. Duration of morning stiffness; 2. Night pain (0-10 cm VAS); 3. Quality of sleep; 4. Adverse events</td>
<td></td>
</tr>
<tr>
<td>Sperry 1973</td>
<td>41, parallel RCT, 13 wks</td>
<td>Benorylate (aspirin + paracetamol) 6 g</td>
<td>12 wks</td>
<td>1. Pain severity (1 = mild, 2 = moderate, 3 = severe); 2. Number of inflamed joints; 3. Morning stiffness; 4. Articular index; 5. Grip strength; 6. Functional status</td>
<td></td>
</tr>
<tr>
<td>Staaunton 1980</td>
<td>18, parallel RCT, 6 wks</td>
<td>Diflunisal 500 mg + indomethacin 75 mg</td>
<td>4 wks</td>
<td>1. Ritchie articular index; 2. Grip strength; 3. Morning stiffness; 4. Pain during the day and during the night (1 = none; to 4 = very severe pain); 5. Physician's global evaluation; 6. Patient's global evaluation</td>
<td></td>
</tr>
</tbody>
</table>
In several of the studies, the monotherapy drug was not part of the combination therapy; for example, 1 trial compared phenylbutazone to aspirin and paracetamol\textsuperscript{30}, while another trial compared naproxen to aspirin and paracetamol\textsuperscript{43}. In other trials, despite the monotherapy drug being part of the combination therapy, their dosages differed: for example, one trial compared paracetamol 650 mg and dextropropoxyphene 65 mg to paracetamol 1000 mg\textsuperscript{38} while another trial compared dextropropoxyphene 65 mg and amitriptyline 25 mg to dextropropoxyphene 130 mg\textsuperscript{45}.

Categorizing the interventions of the trials according to the drug classes being combined, the most prevalent combination was NSAID + analgesic compared to a NSAID in 12 trials\textsuperscript{28,30,31,35,36,40,41,42,43,46,47,49}, followed by the combination of 2 NSAID versus 1 NSAID in 5 trials\textsuperscript{32,33,34,39,50} and then a combination of NSAID + neuromodulator versus NSAID alone in 3 trials\textsuperscript{37,44,48}. Other combinations were reported in only 1 trial each: opioid + NSAID versus NSAID alone\textsuperscript{29}, opioid + analgesic versus analgesic alone\textsuperscript{38}, and opioid + neuromodulator versus opioid alone\textsuperscript{45}.

Studies were heterogeneous with respect to how outcomes were measured and which timepoints were presented (see Table 1), and most studies failed to adequately report their results. Most trials did not report the time period that participants were asked to consider when assessing their pain. No study presented data for any dichotomous pain outcomes (e.g., patient-reported pain relief ≥ 50%). Physical function was assessed in only 3 trials\textsuperscript{33,36,47}, and none of the trials assessed quality of life.

Risk of bias in included studies. All included studies were considered to be at high risk of bias (Figure 2). (Further details are provided in Appendix 3 and 4, available online from 3epain.com.) The main issues we identified were: inadequate (1 trial) or unclear (22 trials) sequence generation method; inadequate (1 trial) or unclear (21 trials) allocation concealment; unclear (18 trials) or high risk of bias (3 trials) with respect to blinding; and unclear (9 trials) or high risk of bias (13 trials) with respect to completeness of outcome data reported.

Effects of interventions. Due to multiple sources of heterogeneity, a metaanalysis could not be performed, and we present a summary of pertinent findings from the individual studies (see also Notes in tables presenting characteristics of included studies, Appendix 3, available online from www.3epain.com).

Efficacy of combination therapy compared with monotherapy. The majority of studies (18/23, 78\%) reported no differences in outcome between the combination and monotherapy treatments they studied, while 5 (22\%) reported conflicting results, favoring either the combination or monotherapy arms.

NSAID + analgesic versus NSAID (12 studies). Nine studies (75\%) reported no differences between the combination and monotherapy treatments with respect to pain\textsuperscript{28,35,36,40,41,42,43,46,49}. The other 3 trials reported a significant difference between the treatment groups\textsuperscript{30,31,47}. Two of these trials demonstrated better pain control with combination therapy: Seideman 1993\textsuperscript{47} reported a lower pain score at 2 weeks in participants who received naproxen 1000 mg + paracetamol 4 g per day compared to those who received naproxen 1000 mg alone [mean pain score (0 to 100 VAS) 31.7 (SD 9.6) vs 46.5 (SD 14.6), respectively; p < 0.05]; Coigley 1975\textsuperscript{31} described an overall mean improvement in pain at 2 weeks of 73\% in those who received paracetamol + aspirin (benorylate = 8 g) compared with 32\% in those who received indomethacin 75 mg alone (p < 0.05). The third trial, Brooks, et al\textsuperscript{1975}30, comparing combination therapy with 2 different dosages of monotherapy, found conflicting results depending on the dose of the monotherapy. This study compared paracetamol 3 g and aspirin 3.6 g per day to either 50 mg or 300 mg phenylbutazone, and reported that high-dose phenylbutazone was superior to combination therapy, which was superior to low-dose phenylbutazone [pain score over 2 weeks (adjusted for baseline pain score): 2.8 (SD 0.2) on 300 mg phenylbutazone vs 3.1 (SD 0.2) on paracetamol 3 g and aspirin 3.6 g, and 3.3 (SD 0.2) on phenylbutazone 50 mg (p < 0.05)].

NSAID + NSAID versus NSAID (5 studies). Four studies\textsuperscript{33,34,39,50} found no significant differences between the...
treatment arms. One study, Ekstrand, et al 198132, reported a median pain score (0 to 100 VAS) over 3 weeks of 43 for those who received acetylsalicylic acid 2 g + indomethacin 50 mg compared with a score of 53 for those who received acetylsalicylic acid 2 g alone (no baseline values were reported; p < 0.05). NSAID + neuromodulator versus NSAID (3 studies). All trials37,44,48 reported no significant differences between combination therapy and monotherapy. Opioid + NSAID versus NSAID (1 study). Bedi 196929 found no significant difference between the treatment arms. Opioid + analgesic versus analgesic (1 study). Huskisson 197438 found no significant difference between the treatment arms. Opioid + neuromodulator versus opioid (1 study). Saarialho-Kere, et al 198845 reported worse pain control with a combination of dextropropoxyphene 65 mg + amitriptyline 25 mg versus dextropropoxyphene 130 mg alone [mean pain score (0 to 100 VAS) at baseline 50 (SD 6.6) and at 4 hours 44 (SD 6.6) vs 46 (SD 6.0) and 34 (SD 4.8), respectively; p < 0.05]. However, participants in the monotherapy arm received double the dose of opioid compared to those in the combination therapy arm.

Function and withdrawals due to inadequate analgesia. Of the 3 trials that reported function33,46,47, none found a significant difference between combination and monotherapy. Withdrawals due to inadequate analgesia were not reported in one of the trials, and in the remaining 2 trials, participants in the monotherapy arm received double the dose of opioid compared to those in the combination therapy arm.

Safety. Withdrawals due to adverse events, our primary safety outcome, were incompletely reported in the trials. Eight trials did not report this outcome at all, 5 trials reported that there were no withdrawals due to adverse events, and the remaining 10 trials reported a few withdrawals due to adverse events in at least 1 of the study arms28,29,30,31,33,34,37,40,43,49. For these 10 trials, there was no significant difference in the proportion of withdrawals due to adverse events between monotherapy and combination therapy arms (analysis performed by the authors of the review). No deaths were reported in the 18 trials that either directly or indirectly reported on this outcome.

DISCUSSION

Based on 23 trials, all at high risk of bias, there is insufficient evidence to establish the value of combination therapy over monotherapy for pain management in RA. No studies of combination pain therapy were found for AS, PsA, or SpA. For the RA trials, pooling of data was not possible. Eighteen trials found that there were no differences in pain control between combination and monotherapies, while conflicting results were found for the 5 trials that reported a significant difference in pain control between groups [combination therapy superior (n = 3), monotherapy superior (n = 1), and mixed results depending upon dosage used in the monotherapy arm (n = 1)]. Statistically significant differences in safety between combination and monotherapy were not reported.

All 23 RA studies were published between 1969 and 1993, preceding the significant advances that have occurred in therapeutics subsequently. Most study populations were not taking DMARD, and none were exposed to biologic therapy, suggesting that the majority had active disease, and the primary pain source was likely to be of inflammatory origin. It is therefore likely that the results of these trials cannot be transposed to current clinical practice without consideration. In addition, several of the trials included drugs, such as benorylate (a combination of aspirin and paracetamol) and anti-inflammatory doses of aspirin, that are no longer in common usage.

The risk of bias of all trials was high. Generation of an adequate randomization sequence and concealment of treatment allocation were poorly performed and/or reported, and participants with missing data were often excluded from the analysis. Further, the included trials were very small, and statistically significant results from small trials can easily be wrong52; while 17 of the 23 included studies were crossover trials, which implies the possibility of carryover and period effects. The interventions studied were heterogeneous in terms of drug combinations, treatment duration, drug class, drugs, and dosages. The comparator was also a source of heterogeneity and in several studies the monotherapy drug was not part of the combination therapy, precluding meaningful comparison for the purpose of our review.

The outcomes measured, how and when they were measured, and how the results were reported also varied widely between trials. For example, some trials measured pain while others measured improvement in pain; some used VAS for pain while others used a categorical scale; and some trials did
not report baseline and/or end values and/or change scores. None of the included trials reported any of the 4 dichotomous pain outcomes we had planned to assess as recommended by the Cochrane Pain, Palliative and Supportive Care Systematic Review Group editors and others for systematic reviews on chronic pain\(^5\). Group means for continuous measures of pain are difficult to interpret in terms of their clinical relevance as the underlying distribution is often skewed\(^25\).

We did not identify any other review on combination therapy for pain management in IA. Our results differ from a systematic review of pharmacological treatment for neuropathic pain, which considered the role of combination therapy, although the combination therapies studied differed\(^53\). This review reported that the combination of an anticonvulsant or an antidepressant with an opioid achieved better pain control compared to monotherapy. Whether these findings would be generalizable to patients with IA requires further study.

In summary, there are currently insufficient data to draw conclusions about the efficacy and safety of combination pain therapy in the management of patients with IA who have persistent pain despite optimal disease suppression. More evidence from well-designed RCT is needed to determine the efficacy and safety of combination therapy for pain management in IA.

To be of relevance to current practice, patients in new trials should have persistent pain despite optimal disease suppression. Trials should seek to compare the risk:benefit profile of different combination analgesic strategies, different drug classes being combined, different routes of administration, and different intervals.

ACKNOWLEDGMENT
Thanks to Louise Falzon, Trials Search Coordinator of the Cochrane Musculoskeletal Group, for assisting with the design of the search strategy.

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