Combination therapy for pain management in inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis) (Review)


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# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Header</td>
<td>1</td>
</tr>
<tr>
<td>Abstract</td>
<td>1</td>
</tr>
<tr>
<td>Plain Language Summary</td>
<td>2</td>
</tr>
<tr>
<td>Background</td>
<td>3</td>
</tr>
<tr>
<td>Objectives</td>
<td>4</td>
</tr>
<tr>
<td>Methods</td>
<td>4</td>
</tr>
<tr>
<td>Results</td>
<td>7</td>
</tr>
<tr>
<td>Figure 1</td>
<td>8</td>
</tr>
<tr>
<td>Figure 2</td>
<td>10</td>
</tr>
<tr>
<td>Figure 3</td>
<td>11</td>
</tr>
<tr>
<td>Discussion</td>
<td>13</td>
</tr>
<tr>
<td>Authors’ Conclusions</td>
<td>14</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>15</td>
</tr>
<tr>
<td>References</td>
<td>15</td>
</tr>
<tr>
<td>Characteristics of Studies</td>
<td>20</td>
</tr>
<tr>
<td>Data and Analyses</td>
<td>62</td>
</tr>
<tr>
<td>What’s New</td>
<td>62</td>
</tr>
<tr>
<td>History</td>
<td>62</td>
</tr>
<tr>
<td>Contributions of Authors</td>
<td>62</td>
</tr>
<tr>
<td>Declarations of Interest</td>
<td>62</td>
</tr>
<tr>
<td>Sources of Support</td>
<td>62</td>
</tr>
<tr>
<td>Differences Between Protocol and Review</td>
<td>63</td>
</tr>
</tbody>
</table>
Combination therapy for pain management in inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis)

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ABSTRACT

Background

Despite optimal therapy with disease-modifying antirheumatic drugs, many people with inflammatory arthritis (IA) continue to have persistent pain that may require additional therapy.

Objectives

To assess the benefits and safety of combination pain therapy for people with IA (rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) and other spondyloarthritis (SpA)). We planned to assess differences in effects between patients on background disease-modifying antirheumatic drug (DMARD) therapy and patients on no background therapy in subgroup analyses.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library); MEDLINE; and EMBASE. We did not impose any date or language restrictions in the search. We also handsearched conference proceedings of the American College of Rheumatology and the European League against Rheumatism (2008-10).

Selection criteria

Randomised and controlled clinical trials (RCTs and CCTs) assessing combination therapy (at least two drugs from the following classes: analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, opioid-like drugs and neuromodulators (antidepressants, anticonvulsants and muscle relaxants)) compared with monotherapy, for adults with IA (RA, AS, PsA and other SpA). We specifically excluded studies that did not report pain or studies without a standardised pain scale as an outcome measure.
Data collection and analysis

Two review authors independently selected trials for inclusion, assessed risk of bias and extracted data.

Main results

Twenty-three trials (total of 912 patients) met the inclusion criteria (22 in RA; one in a mixed population of RA and osteoarthritis); all except one were published before 1990. Most study populations were not taking DMARDs (e.g. methotrexate, sulphasalazine, hydroxychloroquine and leflunomide) and all studies were performed prior to the introduction of biologic therapies (e.g. etanercept, infliximab and adalimumab). All trials were at high risk of bias, heterogeneity precluded meta-analysis, and we were only able to report a general description of results.

The majority (18 studies, 78%) found no differences between the combination and monotherapy treatments they studied, while five (22%) reported conflicting results, favouring either the combination or monotherapy arms.

From the 12 trials on NSAID + analgesic vs NSAID, nine reported no significant difference between the interventions, while three did: in two, the combination therapy achieved better pain control; and the third trial compared combination therapy with two different dosages of monotherapy (NSAID alone) and reported that a high dose phenylbutazone was superior to combination therapy (paracetamol + aspirin), which was superior to low dose phenylbutazone.

From the five studies on the combination of two NSAIDS vs one NSAID, four reported no significant differences between interventions, and one reported significantly better pain control with combination therapy.

The single trial comparing a combination of opioid + neuromodulator vs opioid reported better pain control with monotherapy.

The remaining trials (NSAID + neuromodulator vs NSAID (3 trials); opioid + NSAID vs NSAID (1 trial); and opioid + analgesic vs analgesic (1 trial)) found no significant difference between combination therapy and monotherapy.

Information regarding withdrawals due to inadequate analgesia and safety was incompletely reported, but in general there were no differences between combination therapy and monotherapy.

No data were available that addressed the value of combination pain therapy or monotherapy for people with IA who have optimal disease suppression. There were no studies that included patients with AS, PsA or SpA.

Authors’ conclusions

Based on 23 trials, all at high risk of bias, there is insufficient evidence to establish the value of combination therapy over monotherapy for people with IA. Importantly, there are no studies addressing the value of combination therapy for patients with IA who have persistent pain despite optimal disease suppression. Well designed trials are needed to address this question.

PLAIN LANGUAGE SUMMARY

Combining two or more drugs vs one drug for pain control in inflammatory arthritis

This summary of a Cochrane review presents what we know from research about the effect of a combination of two pain relieving drugs for pain control in inflammatory arthritis (IA).

We are uncertain if two pain relieving drugs such as paracetamol (also called acetaminophen) (e.g. Panadol® and Tylenol®) plus non-steroidal anti-inflammatory drugs (NSAIDs), or paracetamol plus aspirin compared with one drug improved pain, because only single studies of low quality evidence were available. For the same reason, we do not have precise information about side effects and complications.

What is IA, and what drugs are used to treat pain?

IA is a group of diseases that includes rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) and other spondyloarthritides (SpA). When you have IA, your immune system, which normally fights infection, attacks your joints. This makes your joints swollen, stiff and painful. In RA, the small joints of your hands and feet are usually affected first. In contrast, in AS, the joints of the spine are the most affected. PsA is characterised by inflammation of the skin, psoriasis, and joints and, depending on the disease type, can affect the small joints of the hands and feet or more the spine. There is no cure for IA at present, so the treatments aim to relieve pain and stiffness and improve your ability to move. Patients are started on disease-modifying antirheumatic drugs (DMARDs)
(e.g. methotrexate, sulphasalazine, hydroxychloroquine and leflunomide) as soon as possible in an attempt to control the inflammation and to prevent the progression of the disease. Many people continue to have pain despite optimal disease treatment and have the need for specific medication to control pain.

Several drugs can be used to treat pain in IA. Paracetamol/acetaminophen, is used to relieve pain but does not affect swelling; NSAIDs such as ibuprofen, diclofenac and COX-2s (e.g. celecoxib), are used to reduce pain and swelling; and opioids, such as codeine-containing Tylenol®, hydromorphone (Dilaudid), oxycodone (Percocet and Percodan), morphine and tramadol are powerful pain-relieving substances. Other drugs have some pain relieving properties and can therefore be used to mainly control pain. This is the case of the so-called neuromodulators, such as antidepressants (e.g. fluoxetine, paroxetine and amitriptyline), anticonvulsants (e.g. gabapentine and pregabaline) or muscle relaxants (e.g. diazepam). It is not clear if combining two of these drugs offers the best treatment and which drugs cause more side effects. It is known that, for instance, high doses of paracetamol/acetaminophen may cause stomach problems, such as ulcers, and NSAIDs may cause stomach, kidney or heart problems.

**Best estimate of what happens to people with IA who take combination therapy for pain**

There is insufficient evidence to establish the value of combination therapy over monotherapy for people with IA. We included 23 studies in this review, all at high risk of bias (i.e. high chance of giving invalid results). Twenty-two of the trials were in patients with RA and one in a mixed population (RA and osteoarthritis). There were no studies in patients with AS, PsA or SpA. Included studies were old (all but one were published before 1990) and patients were, in general, not on optimal disease-modifying antirheumatic drugs, as is standard current practice. Therefore, it is not possible to draw conclusions about the value of combination pain therapy over monotherapy for people with IA. Importantly, there are no studies addressing the value of combination therapy for patients with IA who have persistent pain despite optimal disease suppression. Well designed studies are needed to address this question.

**Description of the condition**

Inflammatory arthritis (IA) is the 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 estimated global prevalence of approximately 3% (Bergman 2006), comprising a prevalence of 1% for RA (Gabriel 2001) and 1.9% for SpA (including AS and PsA) (Braun 1998). They are progressive diseases, characterised by pain, joint destruction and decreased patient function (Bergman 2006). Furthermore, these diseases have a profound impact on the patient’s quality of life and on society in terms of medical costs and work disability (Bergman 2006).

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 (DMARDs) (e.g. methotrexate, sulphasalazine, hydroxychloroquine and leflunomide) (Smolen 2010a), and with the introduction of the efficacious biological disease-modifying antirheumatic drugs (bDMARDs) (e.g. etanercept, infliximab and adalimumab), remission of disease is considered the appropriate treatment target (Smolen 2010b). Nevertheless, despite these significant advances, many patients with IA continue to experience musculoskeletal pain (Kvien 2004). Evidence from randomised controlled trials (RCTs) indicates that bDMARDs improve most outcomes, except pain, an important patient-relevant outcome (Keystone 2004; Mease 2000; Van der Heijde 2005).

Addressing pain is an integral part of patient care, which has been recognised by the Joint Commission on Accreditation of Healthcare Organizations which has designated pain as the fifth vital sign, recommending it be monitored with the same vigilance as blood pressure, pulse, temperature and respiratory rate (Lanser 2001; Philips 2000). Pain is one of the most commonly reported complaints, especially among patients with rheumatic diseases (Kasis 1983) and studies have reported that patients with IA perceive pain to be their predominant impairment (Minnock 2003). Improvement in pain has been identified by patients with IA to be among their highest priorities (Da Silva 2010; Heiberg 2002), even amongst those who have achieved adequate disease control and are being treated with biologicals (Ten Klooster 2007). Chronic pain has a significantly negative impact on quality of life and this effect increases with the duration of pain (Skevington 1998).

**Description of the intervention**

The primary goal of treating patients with IA (such as RA) is to
maximise long-term, health-related quality of life through control of symptoms, prevention of structural damage, and normalisation of function and social participation (Smolen 2010b). Reducing pain is therefore, also one of the most important aims of therapy. Drug therapy to relieve pain may include analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, opioid-like drugs (e.g. tramadol) and neuromodulators (including antidepressants, anticonvulsants and muscle relaxants). In treating patients who have persistent pain, drugs from each of these classes can be prescribed as monotherapy, but may also be combined.

How the intervention might work

Combining drugs from different classes to treat persistent pain may achieve better pain control than monotherapy as a result of additive effects or synergistic mechanisms such that the final effect is more than the sum of the individual effects. On the other hand, combination therapy may also be associated with increased risks. Superiority of combination pain therapy could also be expected from what we know about pain management in neuropathic pain. A recent review of pharmacological treatment in neuropathic pain showed evidence in favour of better pain control with combination therapy over monotherapy, for example through the combination of an anticonvulsant with an opioid or with an antidepressant (Finnerup 2010).

Why it is important to do this review

Pain is a significant issue for people with IA, even in those who have optimally controlled disease. It is not known whether specific combinations of classes of drugs to treat pain are more effective than monotherapy to treat persistent pain in patients with IA or if adverse effects offset any benefits. The aim of this review was to summarise the existing data on the efficacy and safety of combination therapy for pain management in patients with IA. This will provide clinicians with information to guide their decisions on optimal pain management for patients with IA. The review was undertaken according to the previously published protocol (Ramiro 2010). Differences between the protocol and review are noted in the Differences between protocol and review section.

Objectives

To assess the benefits and safety of combination therapy for pain management in patients with IA.

Methods

Criteria for considering studies for this review

Types of studies

We included all published RCTs and quasi-randomised controlled clinical trials (CCTs) (i.e. where allocation was not truly randomised). We imposed no restrictions in length of follow-up or language of the paper. We only included trials that were published as full articles or were available as a full trial report. We excluded studies that did not contain pain as an outcome measure or that did not include an understandable pain scale.

Types of participants

We selected studies that included adults of at least 18 years of age with a clinical diagnosis of IA (RA, AS, PsA or SpA). Studies containing patients with other diagnoses were only eligible if the results from patients with IA were presented separately.

Types of interventions

We included studies that compared combination therapy for pain management with monotherapy. We considered the following drug classes.

- Analgesics
- NSAIDs
- Opioids
- Tramadol (i.e. opioid-like drugs)
- Neuromodulators (antidepressants, anticonvulsants and muscle relaxants)

Combination therapy was defined as the combination of at least two drugs of any of the drug classes presented. We included all the possible variations (dosage, intensity, mode of delivery, frequency of delivery, duration of delivery and timing of delivery).

Types of outcome measures

We chose the primary and secondary pain outcomes based upon those currently recommended by the Cochrane Pain, Palliative and Supportive Care Systematic Review Group editors and others, for systematic reviews on chronic pain (Moore 2010).

Main outcomes

1. Benefits: patient reported pain relief of 50% or greater.
2. Safety: number of withdrawals due to adverse events.
Minor outcomes
1. Pain:
   - patient-reported pain relief of 30% or greater;
   - patient-reported global impression of clinical change (PGIC) as “much” or “very much improved”;
   - proportion of patients achieving a pain score below 30/100mm on visual analogue scale; and
   - mean change in pain score on visual analogue scale or numerical rating scale.
2. Number of patients with adverse events.
3. Number of deaths.
4. Function - for example for RA, as measured by the Health Assessment Questionnaire (HAQ) or modified HAQ (Fries 1980; Pincus 1983), or by the Bath AS Functional Index (BASFI) (Calin 1994) for AS.
5. Quality of life - as measured by either generic instruments (such as the Short-Form-36 [SF-36]) (Ware 2001) or disease-specific tools, such as the RA Quality of Life instrument [RAQoL] (De Jong 1997) and AS Quality of Life Instrument (ASQoL) (Doward 2003).
6. Participant withdrawals due to inadequate analgesia.

If available in the included studies, we evaluated the outcomes for the following end-points. We also chose these time intervals based upon the recommendations of (Moore 2010).
- Short-term follow-up (< 2 weeks).
- Intermediate-term follow-up (2 to 6 weeks).
- Long-term follow-up (> 6 weeks).

We chose the short- and long-term outcomes for proportion reporting pain relief of 50% or greater, total number of withdrawals due to adverse effects, number of adverse events, function and quality of life as the most important ones to be presented in the summary of findings table.

Search methods for identification of studies

Electronic searches
We searched the following computerised bibliographical databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2010); MEDLINE (1950 to 4 May 2010); and EMBASE (EMBASE classic 1947 to 1979 and EMBASE 1980 to 4 May 2010). We imposed no language restrictions and used the highly sensitive Cochrane Collaboration search strategy, which aims to identify all RCTs (Lefebvre 2011). We used specific MeSH headings and additional keywords to identify all RCTs on combination therapy for pain management in IA. The complete search strategies for the database searches are provided in the Appendices (MEDLINE and CENTRAL search strategy Appendix 1, EMBASE search strategy Appendix 2). In order to retrieve additional references, we searched for systematic reviews in the Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE) (The Cochrane Library Issue 2, 2010).

Searching other resources
We screened references from included RCTs and other systematic reviews on combination therapy for pain management in IA in order to identify all possible studies for this systematic review. We also handsearched the conference proceedings for the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) for 2008 to 2010, to identify unpublished studies.

Data collection and analysis

Selection of studies
Two reviewers (SR, HR) independently assessed each title and abstract for suitability for inclusion in the review according to the predetermined selection criteria (see Criteria for considering studies for this review). In cases of doubt, we retrieved and read the full text article. We discussed disagreements between review authors about the eligibility of the articles in a consensus meeting and if there was non-consensus, a third review author made a decision (RL).

Data extraction and management
Two reviewers (SR and HR) independently extracted the data regarding study design, study duration, characteristics of study population, interventions, outcome measures and timing of outcome assessment, cointerventions, adverse effects, and loss to follow-up, by using a standardised data extraction form. We resolved differences in data extraction by referring back to the original articles and establishing consensus. We consulted a third review author (RL) to help resolve differences if needed.

For studies published in languages other than English, German, Portuguese, French, Spanish or Dutch, we obtained the help of a native speaker or translator with content and methodological expertise.

Assessment of risk of bias in included studies
Two reviewers (SR and HR) independently assessed the 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 (see Types of outcome measures); incomplete outcome data; selective outcome reporting; and other potential sources of bias, conforming to the methods recommended by the Cochrane Collaboration.
To determine the risk of bias of a study, we evaluated the presence of sufficient information and the likelihood of potential bias for each criterion. We rated each criterion as low risk of bias, high risk of bias, or unclear risk of bias (either lack of information or uncertainty over the potential for bias). In a consensus meeting, we discussed and resolved disagreements among the review authors. If consensus could not be reached, a third review author (RL) made the final decision.

Measures of treatment effect

In order to assess efficacy, we extracted, if available, from the published reports, raw data for outcomes of interest (means and standard deviations (SDs) for continuous outcomes, and number of events for dichotomous outcomes) as well as number of participants. If reported data needed to be converted or imputed, we recorded this in the notes section of the table Characteristics of included studies. The results of each trial were to be plotted as point estimates with 95% confidence intervals (CIs). We planned to present point estimates as risk ratios (RRs) for dichotomous outcomes, and mean differences (MDs) for continuous outcomes. A RR > 1.0 would indicate a beneficial effect of combination therapy (Deeks 2011). RRs are considered clinically relevant if RR < 0.66 or > 1.5, in favour of the intervention or control group, respectively. This resembles an absolute difference of 25%. For continuous data, results were to be analysed as MDs between the intervention and comparator group, with corresponding 95% CIs. The MD between treated group and control group is weighted by the inverse of the variance in the pooled treatment estimate. However, if different scales were used to measure the same conceptual outcome (e.g. functional status or pain), we planned to calculate standardised mean differences (SMDs) with corresponding 95% CIs instead. SMDs are calculated by dividing the MD by the SD, resulting in a unitless measure of treatment effect (Deeks 2011). SMDs ≥ 0.2 is considered a beneficial effect in favour of combination therapy for pain management. SMDs can be interpreted as described by Cohen 1988; i.e. a SMD of 0.2 is considered to indicate a small beneficial effect, 0.5 a medium effect, and 0.8 a large effect of combination therapy for pain management. SMD is considered to indicate a clinically relevant effect if SMD was > 0.5. Upon completion of the analysis, we planned to translate back any SMDs into a MD, on a scale of 0 to 10, which can be better appraised by clinicians.

Unit of analysis issues

In the event that we identified cross-over trials in which the reporting of continuous outcome data precluded paired analysis, we did not plan to include these data in a meta-analysis, in order to avoid unit-of-analysis error. Where carry-over effects were thought to exist, and where sufficient data existed, we only included data regarding the first period in the analysis (Higgins 2011b).

For studies containing more than two intervention groups, making multiple pair-wise comparisons between all possible pairs of intervention groups possible, if data were available we planned to include the same group of participants only once in the meta-analysis.

Dealing with missing data

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 randomised in the group as the denominator (worst case scenario). For continuous outcomes (e.g. mean change in pain score), we calculated the MD or SMD based on the number of patients analysed at that time point. If the number of patients analysed was not presented for each time point, we used the number of randomised patients in each group at baseline. Where possible, missing SDs were computed from other statistics such as standard errors (SEs), CIs or P values, according to the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011c). If we could not calculate SDs, we imputed them, for example from other studies in the meta-analysis (Higgins 2011b).

Assessment of heterogeneity

We first assessed the studies for clinical homogeneity with respect to the condition under study, intervention and control groups (drug classes being combined and compared), and the outcomes and timing of outcome assessment. For clinically homogeneous studies, we planned to test statistical heterogeneity using the I^2 statistic (Deeks 2011), using the following as a rough guide for interpretation: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% considerable heterogeneity. In cases of considerable heterogeneity (defined as I^2 ≥ 75%), we had planned to explore the data further, including subgroup analyses, in an attempt to explain the heterogeneity.

Assessment of reporting biases

An assessment of reporting biases was planned through the screening of the Clinical Trial Register at the International Clinical Trials Registry Platform of the World Health Organization (http://apps.who.int/trialsearch; De Angelis 2004) to determine whether the protocol of the RCT was published before recruitment of patients of the study was started. Furthermore, we planned a comparison between the fixed-effect estimate and the random-effects estimate, as well as a funnel plot, if data were available, in order to assess the possible presence of small sample bias and reporting bias, respectively.
Data synthesis
We planned to pool clinically homogeneous studies using the random-effects model.

Subgroup analysis and investigation of heterogeneity
We had planned the following subgroup analyses if data were available:
1. Effects of age, gender, and disease duration.
2. Difference in effects between the diagnoses (RA, AS, PsA, undifferentiated SpA).
3. Comparison of interventions belonging to the same drug classes (e.g. combination of NSAID + analgesic vs analgesic).
4. Difference in effects between patients on background DMARD therapy and patients on no background therapy.

Sensitivity analysis
We had planned sensitivity analyses for studies with regard to allocation concealment, blinding of outcome assessor, and loss to follow-up compared to studies with study limitations (low risk of bias versus high risk of bias or unclear risk of bias). However there were insufficient data for meta-analysis or sensitivity analysis.

Summary of findings table
The main results of the review were planned to be presented in a 'Summary of findings' table, which includes an overall grading of the evidence using the GRADE approach (GRADEpro) and a summary of the available data on the main outcomes (short- and long-term outcomes for proportion reporting pain relief of 50% or greater, total number of withdrawals due to adverse effects, number of adverse events, function and quality of life), as described in the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann 2011).

Grading of the evidence involves consideration of within-study risk of bias, directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias. However, other factors can affect the quality of evidence, for example it can be increased by a large magnitude of effect, plausible confounding, and dose-response gradients. Using this system, we planned to grade the quality of the body of evidence as 'high', 'moderate', 'low' or 'very low (Atkins 2004).

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies.
See: Characteristics of included studies; Characteristics of excluded studies

Results of the search
We found a total of 14,854 articles in the three databases and obtained an additional 160 meeting abstracts from conference proceedings (Figure 1). After de-duplication and title and abstract screening, we excluded 14,788 studies, leaving 66 articles for full paper review. The main reason for exclusion was wrong study type or wrong intervention. We read the 66 articles in detail and excluded 43 of them (see Excluded studies). We did not include any meeting abstracts, not even for detailed review. In the end, we included 23 articles (see Included studies).
Included studies

We included a total of 23 trials involving a total of 912 patients (range 12 to 134, mean 40 patients) with a study duration ranging from 2 days to 5 months. A full description of the included studies is provided in the table, Characteristics of included studies. Other than the trial by Seideman 1993, all trials were published before 1990. Twenty-two trials were reported in English and one trial was reported in German (Brooks 1975). In terms of study design there were five parallel RCTs (Brooks 1975; Coigley 1975; Puttini 1988; Sperryn 1973; Staunton 1980), one CCT (Beales 1972) and the remaining 17 studies were cross-over trials (Bedi 1969; Ekstrand 1981; Furst 1987; Grennan 1979; Haslock 1971; Hingorani 1973; Hobkirk 1977; Huskisson 1974; Kean 1981; Malcolm 1974; Mavrikakis 1977a; Mavrikakis 1977b; Mowat 1979; Saarialho-Kere 1988; Seideman 1988; Seideman 1993; Sharma 1978). Twenty-two trials included RA study populations, while one trial included a mixed population of patients with RA and osteoarthritis (Coigley 1975). For the latter trial, we have included only the results for the RA subset in this review. We did not find any trials for other types of IA.

All included studies recruited adult participants. Six studies (Furst 1987; Hobkirk 1977; Kean 1981; Seideman 1988; Seideman 1993; Sharma 1978) reported the mean age of the whole study population, which ranged from 44 to 56 years. Eight studies (Brooks 1975; Hobkirk 1977; Kean 1981; Mavrikakis 1977a; Mavrikakis 1977b; Saarialho-Kere 1988; Seideman 1988; Seideman 1993) 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 females in the study population was reported in nine studies (Furst 1987; Hobkirk 1977; Kean 1981; Mavrikakis 1977a; Mavrikakis 1977b; Puttini 1988; Saarialho-Kere 1988; Seideman 1993; Sharma 1978) and varied between 55% and 89%. Only six of the 23 studies provided information about concurrent DMARD therapy. One trial reported that no antirheumatic drugs were allowed (Brooks 1975), and the other five studies (Coigley 1975; Furst 1987; Saarialho-Kere 1988; Seideman 1988; Seideman 1993) reported allowance of stable doses of DMARDs,
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 biological DMARDs.

The interventions used in the trials were very heterogeneous: different drug classes, different drugs and different dosages. Several of the interventions studied are not in current practice, as for instance, benorylate or safapryn, which are a combination of aspirin and paracetamol (Beales 1972; Brooks 1975; Coigley 1975; Haslock 1971; Hingorani 1973; Malcolm 1974; Mavrikakis 1977a; Mavrikakis 1977b; Mowat 1979; Sperry 1973). The dosages were frequently suboptimal according to current recommendations (Dougdos 2011), in terms of their analgesic effect, for example, ibuprofen 1200 mg/day (Hingorani 1973) or indomethacin 100 mg/day (Hobkirk 1977). In several of the studies, the monotherapy drug was not part of the combination therapy, for example, one trial compared phenylbutazone to aspirin and paracetamol (Brooks 1975) while another trial compared naproxen to aspirin and paracetamol (Mowat 1979). 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 (Huskinson 1974) while another trial compared dextropropoxyphene 65 mg and amitriptyline 25 mg to dextropropoxyphene 130 mg (Saarialho-Kere 1988).

Categorising 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 (Beales 1972; Brooks 1975; Coigley 1975; Haslock 1971; Hingorani 1973; Malcolm 1974; Mavrikakis 1977a; Mavrikakis 1977b; Mowat 1979; Seideman 1988; Seideman 1993; Sperry 1973), followed by the combination of two NSAIDs vs one NSAID in five trials (Ekstrand 1981; Furst 1987; Grennan 1979; Kean 1981; Staunton 1980) and then a combination of NSAID + neuromodulator vs NSAID alone in 3 trials (Hobkirk 1977; Puttini 1988; Sharma 1978). Other combinations were only reported in one trial each: opioid + NSAID vs NSAID alone (Bedi 1969), opioid + analgesic vs analgesic alone (Huskinson 1974) and opioid + neuromodulator vs opioid alone (Saarialho-Kere 1988).

Of the 23 included trials, 12 primarily reported pain on a visual analogue scale (VAS) (Ekstrand 1981; Furst 1987; Grennan 1979; Hobkirk 1977; Mavrikakis 1977a; Mavrikakis 1977b; Mowat 1979; Puttini 1988; Saarialho-Kere 1988; Seideman 1993; Seideman 1988; Sharma 1978); 10 on a categorical scale (Beales 1972; Brooks 1975; Coigley 1975; Haslock 1971; Hingorani 1973; Huskinson 1974; Kean 1981; Malcolm 1974; Sperry 1973; Staunton 1980); and one described the outcome as an ordinal scale of improvement in pain (Bedi 1969).

Studies were heterogeneous with respect to which time points were presented and most studies failed to adequately report their results. For example, three studies reported both baseline and end of study pain outcomes (Haslock 1971; Puttini 1988; Saarialho-Kere 1988); seven only provided end of study pain outcomes (without baseline values) (Grennan 1979; Hobkirk 1977; Kean 1981; Mavrikakis 1977a; Mavrikakis 1977b; Seideman 1993; Sharma 1978); six trials reported baseline pain values and change scores only (Beales 1972; Coigley 1975; Furst 1987; Hingorani 1973; Mowat 1979; Sperry 1973); mean values for pain throughout the study were reported in two trials (Ekstrand 1981; Seideman 1988); a change score only was presented in three studies (Bedi 1969; Huskinson 1974; Malcolm 1974); and one trial reported baseline pain and mean pain over the course of the trial (Brooks 1975). One trial did not provide any numerical outcome data (Staunton 1980). Most trials did not report the time period that participants were asked to consider when assessing their pain. No study presented data for our primary efficacy endpoint (patient reported pain relief of 50% or greater) and no study reported any other dichotomous pain outcomes.

Physical function was only assessed in three trials (Furst 1987; Hingorani 1973; Seideman 1993) measured using functional capacity (Seideman 1993) or activities of daily living score (Furst 1987; Hingorani 1973) and none of the trials assessed quality of life.

**Excluded studies**

We excluded a total of 43 studies after detailed review. Reasons for exclusion are described in the Characteristics of excluded studies table. We excluded four studies due to including a mixed population without reporting results for patients with IA separately (Jaffe 1973; Lewis-Faning 1972; Mitchell 1984; Murphy 1978). We excluded nine trials as they reported a comparison of two monotherapies (Barnardo 1966; Lynch 2001; Maldykwowa 1983; Pavelka 1972; Perrot 2006; Raptopoulou 2008; Satisekhar 1973; Sidiropoulos 2008; Vergne-Salle 2009); one trial as it reported a comparison of two triple therapy interventions (Glowniak 1999); and one trial because it compared two different combination therapies (Maneksha 1973).

We excluded 15 trials due to absence of an outcome of interest. Eight trials did not include a pain assessment (Andrade-Padilla 1995; Dalmases 1966; Franke 1972; Jeremy 1970; Rudge 1982; Torgyn 1979; Van Hoek 1973; Willkens 1976); six trials did not include a global pain assessment (Bain 1970; Cardoe 1970; Chalmers 1978; Ridolfi 1982; Robinson 1975; Roth 1973); and in one trial the reported pain scale was not defined or understandable (Brooks 1977). Finally, we excluded 13 studies because of wrong study type (De Mattos 1968; Eberl 1968; Famaey 1971; Famaey 1972; France 1968; Hernandez-Pena 1973; Hersh 2007; Huss 1974; Lopez Prats 1968; Moll 1966; Triandaf 1970a; Triandaf 1970b; Wettreich 1966).

**Risk of bias in included studies**
We considered all included studies to be at high risk of bias. A description of the risk of bias of the included studies is presented in the Risk of Bias tables (Characteristics of included studies). A risk of bias graph and a risk of bias summary can be seen in Figure 2 and Figure 3, respectively.

**Figure 2. Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.**

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding (performance bias and detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other bias

Legend:
- Low risk of bias
- Unclear risk of bias
- High risk of bias
Figure 3. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.
We did not consider any trial to have an adequate sequence generation method. We classified one trial as having an inadequate sequence generation as patients were all allocated to the same treatment order in a cross-over trial (Furst 1987), and in all the other trials the adequacy of the sequence generation was unclear, due to lack of information reported in the paper.

We only considered one trial to have an adequate allocation concealment (Mowat 1979), one had an inadequate allocation concealment (Furst 1987) and all the others were unclear with respect to this item. We evaluated blinding as low risk of bias in two studies (Seideman 1988; Seideman 1993), as high risk of bias in three studies (due to lack of blinding of participants) (Beales 1972; Coigley 1975; Mowat 1979), and all the other trials were unclear. One trial presented complete outcome data (Seideman 1993), 13 studies had a high risk of bias on the incomplete outcome data item, mainly because of excluding withdrawals from the analyses (Beales 1972; Bedi 1969; Grennan 1979; Haslock 1971; Hingorani 1973; Hobkirk 1977; Malcolm 1974; Mavrikakis 1977a; Mavrikakis 1977b; Puttini 1988; Sharma 1978; Sperryn 1973; Staunton 1980), and the other trials were unclear on this item. We did not consider any study to have a low risk of bias in both selective reporting and other potential sources of bias; the majority of the trials were considered to have a high risk of bias, and some were unclear.

**Effects of interventions**

Due to multiple sources of heterogeneity, a meta-analysis could not be performed and we present a narrative summary of pertinent findings from the individual studies. The main reported findings for the individual trials are also summarised in the Notes sections in the Table, Characteristics of included studies.

**Efficacy**

The majority of studies (18/23, 78%) reported no differences in outcome between the combination and monotherapy treatments they studied, while five (22%) reported conflicting results, favouring either the combination or monotherapy arms.

**NSAID + ANALGESIC VS NSAID (12 studies)**

Nine studies (75%) reported no differences between the combination and monotherapy treatments with respect to pain (Beales 1972; Haslock 1971; Hingorani 1973; Malcolm 1974; Mavrikakis 1977a; Mavrikakis 1977b; Mowat 1979; Seideman 1988; Sperryn 1973). The other three trials reported a significant difference between the treatment groups (Brooks 1975; Coigley 1975; Seideman 1993). Two of these trials demonstrated better pain control with combination therapy: Seideman 1993 reported a lower pain score at two 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 (SD) 31.7 (9.6) vs 46.5 (14.6) respectively; P value < 0.05; Coigley 1975 described an overall mean improvement in pain (%) at two weeks of 73% in those who received paracetamol + aspirin (benorylate = 8 g) compared with 32% in those who received indomethacin 75 mg alone; P value < 0.05.

The third trial (Brooks 1975) comparing combination therapy with two 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 two weeks (adjusted for baseline pain score): 2.8 (0.2) on 300 mg phenylbutazone versus 3.1 (0.2) on paracetamol 3 g and aspirin 3.6 g and 3.3 (0.2) on phenylbutazone 50 mg; P value < 0.05).

**NSAID + NSAID VS NSAID (5 studies)**

Four studies (Furst 1987; Grennan 1979; Kean 1981; Staunton 1980) found no significant differences between the treatment arms. One study (Ekstrand 1981) reported a median pain score (0 to 100 VAS) over three 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 value < 0.05.

**NSAID + NEUROMODULATOR VS NSAID (3 studies)**

All trials (Hobkirk 1977; Puttini 1988; Sharma 1978) reported no significant differences between combination therapy and monotherapy.

**OPIOID + NSAID VS NSAID (1 study)**

Bedi 1969 found no significant difference between the treatment arms.

**OPIOID + ANALGESIC VS ANALGESIC (1 study)**

Huskisson 1974 found no significant difference between the treatment arms.

**OPIOID + NEUROMODULATOR VS OPIOID (1 study)**

Saarialho-Kere 1988 reported worse pain control with a combination of dextropropoxyphene 65 mg + amitriptyline 25 mg versus dextropropoxyphene 130 mg alone (mean (SD) pain score (0 to 100 VAS) at baseline and 4 hours 50 (6.6) and 44 (6.6) versus 46 (6.6).
(6.0) and 34 (4.8), respectively); P value < 0.05. However, participants in the monotherapy arm received double the dose of opioid compared to those in the combination therapy arm.

Due to lack of data, subgroup or sensitivity analyses could not be performed and a ‘Summary of Findings’ table could not be constructed.

**FUNCTION AND WITHDRAWALS DUE TO INADEQUATE ANALGESIA**

Of the three trials that reported function, none found a significant difference between combination and monotherapy. Withdrawals due to inadequate analgesia were incompletely assessed and/or reported in the included studies. Eight trials did not report this outcome (Huskinson 1974; Kean 1981; Malcolm 1974; Mavrikakis 1977a; Mavrikakis 1977b; Puttini 1988; Saarialho-Kere 1988; Seideman 1993), seven studies reported no withdrawals due to inadequate analgesia in at least one of the study arms (Beales 1972; Brooks 1975; Coigley 1975; Forst 1987; Grennan 1979; Haslock 1971; Mowat 1979; Sperryn 1973). A comparison of the withdrawals due to inadequate analgesia between the study groups (performed by the authors of the review) revealed no significant differences between the interventions, except for one comparison within one of the trials (Brooks 1975). One of this study’s monotherapy arms (phenylbutazone 50 mg) had a significantly higher number of withdrawals due to inadequate analgesia (2% under combination therapy of aspirin + paracetamol vs 33% under phenylbutazone 50 mg in monotherapy).

**SAFETY**

Withdrawals due to adverse events, our primary safety outcome, was incompletely reported in the included trials. Eight trials did not report this outcome at all, five trials reported that there were no withdrawals due to adverse events and the remaining ten trials reported a few withdrawals due to adverse events in at least one of the study arms (Beales 1972; Bedi 1969; Brooks 1975; Coigley 1975; Forst 1987; Grennan 1979; Haslock 1971; Mowat 1979; Sperryn 1973). For these ten 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 eighteen trials that either directly or indirectly reported on this outcome.

Of the ten trials that reported on the number of participants with adverse events (Bedi 1969; Coigley 1975; Haslock 1971; Hingorani 1973; Hobkirk 1977; Malcolm 1974; Mowat 1979; Seideman 1988; Sharma 1978; Sperryn 1973) all but one reported no differences between the combination and monotherapy arms. Seideman 1988 reported that 55% (11/20) of those who received combination therapy (indomethacin 50 mg + paracetamol 4 g) had at least one adverse event compared to 20% (4/20) of those who received indomethacin 150 mg alone, P value = 0.05.

**DISCUSSION**

**Summary of main results**

Overall, based on 23 trials, it is not possible to establish the efficacy and safety of combination therapy for pain management in people with IA. Pooling of data was not possible and the results have been presented descriptively. Five of the trials reported a significant difference in pain control between combination therapy and monotherapy: in three trials combination therapy was better, in one trial monotherapy was better and the fifth trial reported mixed results depending upon the dosage used in the monotherapy arm. Only three studies reported functional outcomes, and in neither case was there a difference between monotherapy and combination therapy. None of the included studies reported quality of life data. Statistically significant differences in safety between combination and monotherapy were not reported.

**Overall completeness and applicability of evidence**

We did not find any studies of combination pain therapy for AS, PsA and undifferentiated SpA.

For RA, there were 23 studies, all published between 1969 and 1993, preceding the significant advances that have occurred in therapeutics subsequently. Most study populations were not taking DMARDS, 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 likely that the results of these studies 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.

**Quality of the evidence**

The risk of bias of all included trials was high. Generation of an adequate randomisation sequence and concealment of treatment allocation were poorly performed and/or reported, and participants with missing data were often excluded from the analysis. Furthermore, the included trials were very small and significant results from small trials can easily be wrong (Peto 1976); while 17 of the 23 included studies were cross-over trials, which imply the possibility of carry-over and period-effects.
The interventions studied were heterogenous 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 visual analogue scales 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 four dichotomous pain outcomes we planned to include and that were recommended by the Cochrane Pain, Palliative and Supportive Care Systematic Review Group editors and others, for systematic reviews on chronic pain (Moore 2010). Group means for pain continuous measures are difficult to interpret in terms of their clinical relevance as the underlying distribution is often skewed (Moore 2010).

Potential biases in the review process
We believe that we identified all relevant studies. We devised a thorough search strategy and searched all major databases for relevant studies, and applied no language restrictions. Two review authors assessed the trials for inclusion in the review and risk of bias, with a third reviewer adjudicating if there was any discrepancy.

The biggest limitation of the review process was the heterogeneity between the trials and the lack of data in a form that could be extracted for meta-analysis.

Agreements and disagreements with other studies or reviews
We did not identify any other review on combination therapy for pain management in IA. However a systematic review of pharmacological treatment for neuropathic pain also considered the role of combination therapy in controlling pain (Finnerup 2010). They reported that the combination of an anticonvulsant or an antidepressant with an opioid achieved better pain control compared to monotherapy. These findings may be generalisable to patients with IA as similarly to persistent pain in patients with IA, neuropathic pain can be very disabling, severe and intractable (Saarto 2007), although this needs to be confirmed in high quality RCTs.

Implications for practice
Notwithstanding the dramatic advances that have occurred in the management of IA in the last decade, pain remains an important issue for patients. However, there is currently insufficient data to draw conclusions about the efficacy and safety of combination pain therapy in the management of patients with IA. Importantly, there are no studies addressing the value of combination pain therapy for patients with IA who have persisting pain despite optimal disease suppression.

Implications for research
More evidence regarding the efficacy and safety of combination therapy for pain management in IA is required. Well-designed RCTs in RA as well as other IAs including AS and PsA are needed to address this question. To be of relevance to current practice, included patients should have persistent pain despite optimal disease suppression with DMARD and/or biologic DMARDs. 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.

Future trials need to be rigorous in design and delivery, undertaken with high quality methodology that is described in enough detail to enable appraisal and interpretation of results. They need to have adequate power and be of sufficient duration (at least 12 weeks), report their methods of sequence generation and allocation concealment, and blind participants (especially important when the primary outcome of interest is pain), physicians and outcome assessors, and have an appropriate method for handling incomplete data.

Clinically-relevant pain outcomes should be collected, with special emphasis on including dichotomous pain outcomes as recommended by the Cochrane Pain, Palliative and Supportive Care Review Group editors and others (Moore 2010). Function and quality of life are important outcomes that should also be addressed in trials focusing on pain treatment. Lastly, a rigorous analysis of adverse events is indispensable to enable a comparison of the risk:benefit profile of combination analgesic therapy.

ACKNOWLEDGEMENTS
The authors thank Louise Falzon, Trials Search Coordinator of the Cochrane Musculoskeletal Group, for assisting with the design of the search strategy.

AUTHORS’ CONCLUSIONS

Combination therapy for pain management in inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis) (Review)
Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
REFERENCES

References to studies included in this review

Beales 1972 [published data only]

Bedi 1969 [published data only]

Brooks 1975 [published data only]

Coigley 1975 [published data only]

Ekstrand 1981 [published data only]

Furst 1987 [published data only]

Grennan 1979 [published data only]

Haslook 1971 [published data only]

Hingorani 1973 [published data only]

Hobbirk 1977 [published data only]

Huskisson 1974 [published data only]

Kean 1981 [published data only]

Malcolm 1974 [published data only]

Mavrikakis 1977a [published data only]

Mavrikakis 1977b [published data only]

Mowat 1979 [published data only]

Puttini 1988 [published data only]

Saarialho-Kere 1988 [published data only]

Seideman 1988 [published data only]

Seideman 1993 [published data only]

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References to studies excluded from this review

Andrade-Padilla 1995 [published data only]

Bain 1970 [published data only]

Barnardo 1966 [published data only]

Brooks 1977 [published data only]

Cardoe 1970 [published data only]

Chalmers 1978 [published data only]

Dalmases 1966 [published data only]

De Mattos 1968 [published data only]

Eberl 1968 [published data only]

Famaey 1971 [published data only]

Famaey 1972 [published data only]

France 1968 [published data only]
France O. Combination of ketophenylbutazone (Ketazon), oxyphenbutazone and proteolytic enzymes in rheumatic diseases [Associazione di Cetofenilbutazone (Ketazon) oxifenbutazone y enzimas proteolíticas en afecciones reumáticas]. Revista Medica de Chile 1968;96(8):531–4.

Franke 1972 [published data only]

Glowinski 1999 [published data only]

Hernandez Pena 1973 [published data only]

Hersh 2007 [published data only]

Huss 1974 [published data only]
Huss V. Combined drug therapy in highly acute attacks of pain in the course of rheumatic diseases [Kombinierte Combination therapy for pain management in inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis) (Review)]
Combination therapy for pain management in inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis) (Review)

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Combination therapy for pain management in inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis) (Review)

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**Higgins 2011a**

**Higgins 2011b**

**Higgins 2011c**

**Kasis 1983**

**Keystone 2004**

**Kvien 2004**

**Lanser 2001**

**Lefebvre 2011**

**Mease 2000**

**Minnock 2003**

**Moore 2010**

**Peto 1976**

**Phillips 2000**

**Pincus 1983**

**Ramiro 2010**

**Saarto 2007**

**Schünemann 2011**

**Skevington 1998**

**Smolen 2010a**
Smolen 2010b

Ten Klooster 2007

Van der Heijde 2005

Ware 2001

* Indicates the major publication for the study
### Characteristics of included studies {ordered by study ID}

**Beales 1972**

| Methods | Controlled clinical trial  
Study duration: 2 weeks  
Randomisation method: not specified, probably not randomised  
Blinding: single blinded study (only physicians blinded)  
Sample size calculation: not described |
|----------|--------------------------------------------------|
| Participants | 72 patients  
Inclusion criteria: definite or classical RA (as defined by the ARA criteria)  
Exclusion criteria: gold therapy in the year preceding the study or current therapy with corticosteroid or antimalarial drugs; history of renal, hepatic, or cardiac dysfunction or pregnancy; history of dyspepsia or intolerance to aspirin  
Mean age (years): combination therapy arm 51 ± 1; monotherapy arm 54 ± 2  
Gender (% female): combination therapy arm 66.7; monotherapy arm 44.4  
Disease duration (years): combination therapy arm 7.5 ± 1; monotherapy arm 9 ± 2  
Comedication not specified  
Withdrawals: 6 patients |
| Interventions | Group 1 (combination therapy): benorylate (aspirin + paracetamol) 8 g (n = 36)  
Group 2 (monotherapy): aspirin 4.8 g (n = 36) |
| Outcomes | 1) Diurnal pain score at 2 weeks (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 |
| Notes | Pain at 2 weeks - percentage improvement from baseline (negative scores mean the pain improved):  
Group 1 (combination therapy): baseline pain level 0: 0%; 1: 39% (n = 14), 2: 44% (n = 16), 3: 14% (n = 5); change from baseline: -41%  
Group 2 (monotherapy): baseline pain level 0: 3% (n =1), 1: 33% (n = 12), 2: 39% (n = 14), 3: 19% (n = 7); change from baseline: -48%  
No significant difference between the groups, as reported by the authors, P value > 0.05  
Withdrawals due to adverse events: (interpretation of the authors of the review from what is reported)  
Group 1 (combination therapy): 3% (n = 1)  
Group 2 (monotherapy): 3% (n = 1)  
Withdrawals due to inadequate analgesia: (interpretation of the authors of the review from what is reported)  
Group 1 (combination therapy): 0% (n = 0)  
Group 2 (monotherapy): 5.5% (n = 2)  
No deaths were reported (interpretation of the authors of the review from what is reported) |
No information on the number of patients with adverse events in the whole trial is reported in the paper.

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Not specified. The word randomised does not appear in the text</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>High risk</td>
<td>Single-blinded study: “They were asked not to discuss their treatment among themselves nor to let the examining physician know whether they were receiving the tablets or the suspension”. This could bias patient-reported outcome assessment</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Withdrawals are excluded from the analysis</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Pain measurement is only presented in % of change and not in absolute value or not individualised per category of the categorical variable, as it has been presented for baseline</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No specification whether attempts were made to limit cointerventions</td>
</tr>
</tbody>
</table>

**Bedi 1969**

**Methods**
- Cross-over trial
- Study duration: 2 weeks total (1 week in each arm, no washout)
- Randomisation method: not specified
- Blinding: participants and outcome assessor blinded
- Sample size calculation: not described

**Participants**
- 51 patients
- Inclusion criteria: patients with definite or classical RA with moderate to severe pain (not further defined)
- Exclusion criteria: not specified
- Mean age, gender, disease duration and comedication not specified
- Withdrawals: 5 patients
### Interventions

<table>
<thead>
<tr>
<th>Group 1 (combination therapy):</th>
<th>aspirin 500 mg + dextropropoxyhene napsilate 50 mg (completing the treatment: n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2 (monotherapy):</td>
<td>aspirin 500 mg (completing the treatment: n = 22)</td>
</tr>
<tr>
<td>Dosage of both arms:</td>
<td>1 tablet 3xday for the first 2 days and 6 tablets in divided dosage daily thereafter</td>
</tr>
<tr>
<td>Number of patients randomised to each group not presented, only the number of patients completing the treatment</td>
<td></td>
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</tbody>
</table>

### Outcomes

| Outcomes                      | 1) Improvement in pain (better, no change, worse) at the end of each treatment  
2) Number and type of adverse events (although not specified in the methods) |

### Notes

For the purpose of this review results were extracted from the first period for efficacy and from both periods for safety

**Improvement in pain (end of treatment, 1 week):**
- Group 1 (combination therapy): worse 2 (9%); no change 7 (32%); better 13 (59%)
- Group 2 (monotherapy): worse 4 (17%); no change 9 (39%); better 10 (44%)

No significant difference between the groups, all P values > 0.05 (calculated by authors of the review)

Withdrawals due to adverse events: (interpretation and calculation by the authors of the review from what is reported)
- Group 1 (combination therapy): 3 (6%)
- Group 2 (monotherapy): 0

Number of patients with adverse events:
- Group 1 (combination therapy): 17 (33%) - lightheadedness (n = 7); constipation (n = 6); tinnitus (n = 4); dizziness (n = 4); heartburn (n = 3); nausea (n = 3); vomiting (n = 2); allergic rash (n = 1)
- Group 2 (monotherapy): 19 (37%) - lightheadedness (n = 4); constipation (n = 3); tinnitus (n = 4); dizziness (n = 2); heartburn (n = 4); nausea (n = 6); vomiting (n = 2)

No withdrawals due to inadequate analgesia and no deaths were reported (interpretation of the authors of the review from what is reported)

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
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</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Only information in the text: “Double-blind study. The hospital pharmacist alone knew what drug each patient had received”. No information on how blinding was assured or on an analysis of the patients perception of which arm they were in</td>
</tr>
</tbody>
</table>
Bedi 1969  *(Continued)*

<table>
<thead>
<tr>
<th>Incomplete outcome data (attrition bias)</th>
<th>High risk</th>
<th>6 patients were excluded from the analyses of the trial, although they were reported to have been allocated to one of the treatment groups. Number of patients randomised into each group not clear (only number of patients finishing each arm is presented)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Outcome is not clearly defined. Emphasis is put on the significant difference found between the 2 drugs in the second period of the cross-over trial</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Outcome not clearly defined, outcome scale not reported. Baseline characteristics not presented, so similarity cannot be assured. Crossover design with possible carry-over effect. Statistical analysis not detailed. No specification whether attempts were made to limit cointerventions</td>
</tr>
</tbody>
</table>

Brooks 1975

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study duration:</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Randomisation method:</td>
<td>not specified</td>
</tr>
<tr>
<td>Blinding:</td>
<td>not specified</td>
</tr>
<tr>
<td>Sample size calculation:</td>
<td>not described</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>134 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>seropositive classical or definite RA (according to the ARA criteria)</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>hypersensitivity to aspirin or phenylbutazone; renal or hepatic diseases; symptoms of gastric or duodenal ulcer; changes in medication in the preceding months; current therapy with gold, corticosteroids, immunosuppressing agents, D-penicillamine or anticoagulants</td>
</tr>
<tr>
<td>Mean age (years):</td>
<td>combination therapy arm: 53.7 ± 1.35; monotherapy arm 1: 54.2 ± 1.48; monotherapy arm 2: 50.8 ± 1.57</td>
</tr>
<tr>
<td>Gender (% female):</td>
<td>not specified</td>
</tr>
<tr>
<td>Mean disease duration (years):</td>
<td>10.4</td>
</tr>
<tr>
<td>Comedication:</td>
<td>No antirheumatic drugs allowed</td>
</tr>
<tr>
<td>36 withdrawals</td>
<td></td>
</tr>
</tbody>
</table>

| Interventions                    | Group 1 (combination therapy): safapryn (paracetamol 3g + aspirin 3.6g) (n = 44) |
|----------------------------------| Group 2 (monotherapy 1): phenylbutazone 50 mg (n = 45) |
|                                  | Group 3 (monotherapy 2): phenylbutazone 300 mg (n = 45) |

| Outcomes                         | 1) Pain throughout 2 weeks (0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe); 2) Patient global score |
Notes

Pain (throughout 2 weeks):
Group 1 combination therapy: baseline 3.2 ± 0.1; throughout 2 weeks 3.0 ± 0.1 (adjusted for baseline pain score 3.1 ± 0.2)
Group 2 monotherapy 1: baseline 3.0 ± 0.1; throughout 2 weeks 3.3 ± 0.1 (adjusted for baseline pain score 3.3 ± 0.2)
Group 3 monotherapy 2: baseline 2.8 ± 0.1; throughout 2 weeks 2.7 ± 0.1 (adjusted for baseline pain score 2.8 ± 0.2)
Significant difference between the groups, as reported by the authors, but no P-value shown
Withdrawals due to adverse events:
Group 1 (combination therapy): 14% (n = 6)
Group 2 (monotherapy 1): 0% (n = 0)
Group 3 (monotherapy 2): 2% (n = 1)
Withdrawals due to inadequate analgesia:
Group 1 (combination therapy): 2% (n = 1)
Group 2 (monotherapy 1): 33% (n = 15)
Group 3 (monotherapy 2): 4% (n = 2)
No deaths were reported (interpretation of the authors of the review from what is reported). No information on the number of patients with adverse events

Risk of bias

Bias | Authors’ judgement | Support for judgement
--- | --- | ---
Random sequence generation (selection bias) | Unclear risk | Only information in the text: allocation by randomisation
Allocation concealment (selection bias) | Unclear risk | Not mentioned
Blinding (performance bias and detection bias)
All outcomes | Unclear risk | Not mentioned
Incomplete outcome data (attrition bias)
All outcomes | Unclear risk | Not clear how the withdrawals were addressed and it appears they were excluded from the analyses
Selective reporting (reporting bias) | Unclear risk | Number of patients with adverse events and type of adverse events not clear. Statistical comparison between the groups not very clear, not clear which groups are significantly different in terms of pain control
Other bias | High risk | Very high drop-out rate (less than 50% out of each group finished the trial)
### Coigley 1975

<table>
<thead>
<tr>
<th>Methods</th>
<th>Parallel RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study duration: 2 weeks</td>
<td></td>
</tr>
<tr>
<td>Randomisation method: not specified</td>
<td></td>
</tr>
<tr>
<td>Blinding: only outcome assessors blinded</td>
<td></td>
</tr>
<tr>
<td>Sample size calculation: not described</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>95 patients, 41 of which with RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: RA or osteoarthrosis (not further defined)</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: known pregnancy; age &lt; 20 years; presence of renal or hepatic disease, peptic ulceration, or painful neurological conditions; those who needed to continue taking analgesic/anti-inflammatory agents</td>
<td></td>
</tr>
<tr>
<td>Mean age (years): combination therapy arm: 62.3; monotherapy arm: 60.6</td>
<td></td>
</tr>
<tr>
<td>Gender (% female): combination therapy arm: 78; monotherapy arm: 78</td>
<td></td>
</tr>
<tr>
<td>Disease duration (years): combination therapy arm: 7; monotherapy arm: 5</td>
<td></td>
</tr>
<tr>
<td>Comedication: patients were permitted to continue maintenance doses of gold or corticosteroids</td>
<td></td>
</tr>
<tr>
<td>6 withdrawals</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Group 1 (combination therapy): benorylate (paracetamol + aspirin) 8 g (n = 46; patients with RA: n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2 (monotherapy): indomethacin 75 mg (n = 49; patients with RA: n = 26)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>2) Morning stiffness</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
<th>For the purpose of this review results were extracted from the subgroup of patients with RA for efficacy and from the whole population for safety (available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in pain (end of treatment, 2 weeks):</td>
<td></td>
</tr>
<tr>
<td>Group 1 (combination therapy): 73%</td>
<td></td>
</tr>
<tr>
<td>Group 2 (monotherapy): 32%</td>
<td></td>
</tr>
<tr>
<td>Significant difference between the groups (P &lt; 0.05)</td>
<td></td>
</tr>
<tr>
<td>Number of patients with adverse events:</td>
<td></td>
</tr>
<tr>
<td>Group 1 (combination therapy): 22% (n = 10): tinnitus and other salicylate-based symptoms, indigestion, diarrhoea (n not specified)</td>
<td></td>
</tr>
<tr>
<td>Group 2 (monotherapy): 25% (n = 12): headache, diplopia and other CNS effects, indigestion, intermittent infection (n not specified)</td>
<td></td>
</tr>
<tr>
<td>Withdrawals due to adverse events: (interpretation of the authors of the review from what is reported)</td>
<td></td>
</tr>
<tr>
<td>Group 1 (combination therapy): 9% (n = 4)</td>
<td></td>
</tr>
<tr>
<td>Group 2 (monotherapy): 8% (n = 4)</td>
<td></td>
</tr>
<tr>
<td>Withdrawals due to inadequate analgesia: (interpretation of the authors of the review from what is reported)</td>
<td></td>
</tr>
<tr>
<td>Group 1 (combination therapy): 2% (n = 1)</td>
<td></td>
</tr>
<tr>
<td>Group 2 (monotherapy): 8% (n = 4)</td>
<td></td>
</tr>
<tr>
<td>No deaths were reported (interpretation of the authors of the review from what is reported)</td>
<td></td>
</tr>
</tbody>
</table>

### Risk of bias

---

**Combination therapy for pain management in inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis) (Review)**

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Only information in the text: “They were assigned on a random basis”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>High risk</td>
<td>Single-blinded study and “The observer did not know which preparation was being administered”. Besides observer blinding, nothing is mentioned regarding participant blinding, which could bias patient-reported outcome assessment</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Not clear how the withdrawals were addressed and whether or not they were included in the analyses although it appears unlikely that they were included as a total N per outcome is not provided</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>2 outcomes are reported, but it is not clear if these are all the measured ones; the outcome assessment method is not clear either</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Not all the results are separately reported for patients with RA (e.g. Baseline value of pain), so the data need to be interpreted with caution</td>
</tr>
</tbody>
</table>

**Ekstrand 1981**

<table>
<thead>
<tr>
<th>Methods</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-over trial</td>
<td></td>
</tr>
<tr>
<td>Study duration: 2 weeks wash-out period + 6 weeks (3 weeks on each dose of acetylsalicylic acid, no washout)</td>
<td></td>
</tr>
<tr>
<td>Randomisation method: not specified</td>
<td></td>
</tr>
<tr>
<td>Blinding: reference to double-blinded, not specified</td>
<td></td>
</tr>
<tr>
<td>Sample size calculation: not described</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>12 patients</td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria: classical or definite RA according to the criteria of the ARA, disease activity stable during the previous 6 months</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: treatment with corticosteroids, antimalarials or gold during the previous 6 months</td>
<td></td>
</tr>
<tr>
<td>Mean age, gender, disease duration and comedication not specified</td>
<td></td>
</tr>
<tr>
<td>No withdrawals</td>
<td></td>
</tr>
</tbody>
</table>
### Interventions

<table>
<thead>
<tr>
<th>Group 1 (combination therapy 1): acetylsalicylic acid 2 g + indomethacin 50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2 (monotherapy 1) acetylsalicylic acid 2 g (+ placebo)</td>
</tr>
<tr>
<td>Group 3 (combination therapy 2): acetylsalicylic acid 4.5 g + indomethacin 50 mg</td>
</tr>
<tr>
<td>Group 4 (monotherapy 2): acetylsalicylic acid 4.5 g (+ placebo)</td>
</tr>
</tbody>
</table>

Indomethacin 50 mg was just given on the 13th and 20th day of each 3-week period.

### Outcomes

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 (0-100mm VAS)
5. Grip strength
6. Articular index
7. Size of PIP joints

### Notes

Results reflect the average of all cross-over periods (only available ones)

Pain (throughout the 3-week treatment): (median values presented, available ones)

- Group 1 (combination therapy 1): 43
- Group 2 (monotherapy 1): 53
- Group 3 (combination therapy 2): 40
- Group 4 (monotherapy 2): 42

Comparison of pain level on the day after indomethacin/placebo between monotherapy and combination therapy only significantly different in the low-dose group (P < 0.05) - data not shown in the paper.

No withdrawals due to inadequate analgesia, no withdrawals due to adverse events and no deaths were reported (interpretation of the authors of the review from what is reported)

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Only information in the text: “On the 13th and 20th day of each 3-week period, the patients were instructed to take a suppository containing either 50 mg of indomethacin or placebo in randomised order”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Only information in the text: “Each patient was given two dosages of acetylsalicylic acid double-blind.” No information on who exactly was blinded, how blinding was assured or on an analysis of the patients’ perception of which arm they were in</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Incomplete data not clear, N per outcome not specified</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>No measures of spread (SD) are presented with the means. Only the outcomes with significant differences are reported. Several outcomes reported in the methods are then not presented in the results. Outcomes are not clearly defined, regarding scales, units of measurement, etc. Separate results of each cross-over period are not presented.</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Baseline characteristics of the groups not presented. Time points of the outcomes not clear (pain reported to be assessed throughout the period and on the day after indomethacin/placebo, and then not clear in the results) Safety data not presented individually for each treatment arm.</td>
</tr>
</tbody>
</table>

**Furst 1987**

**Methods**
- Cross-over trial
- Study duration: 4 weeks run-in period (therapeutic salicylate concentrations were obtained) + washout until flare + 4 months (1 month in each arm, no washout) + washout until flare
- Randomisation method: no randomisation
- Blinding: reference to double-blinded, not specified
- Sample size calculation: not described

**Participants**
- 84 patients
- Inclusion criteria: active classic or definite RA according to the ARA criteria. Patients were considered to have active disease if at least 3 of the following were present: 1) > 6 painful or tender joints on motion; 2) >3 swollen joints; 3) > 45 min of morning stiffness; 4) ESR ≥ 28 mm/h
- Exclusion criteria: joint injection with corticosteroids within the last 4 weeks; onset or stop of antimalarial drugs, immunosuppressive drugs, or penicillamine in the past 3 months; active peptic ulcer disease; significant renal or cardiovascular disease; functional class IV by Steinbrocker's criteria; pregnancy; other NSAIDs use during the trial; known hypersensitivity to salicylates or naproxen; inability or unwillingness to comply with requirements of the study; discontinuation of gold therapy, defined as a stable dose of gold therapy within the past 3 months
- Mean age (years): 56 ± 13
- Gender (% female): 74
- Disease duration: not specified
- Comedication: stable gold therapy (≥ 20 weeks) was allowed
- 37 withdrawals (19 during the run-in period and 18 during the cross-over periods)

**Interventions**
- Group 1 (combination therapy 1): naproxen 1500 mg + choline magnesium trisalicylate (therapeutic salicylate concentrations)
- Group 2 (monotherapy 1): naproxen 1500 mg
| Group 3 (combination therapy 2): naproxen 750 mg + half dose choline magnesium trisalicylate  |
| Group 4 (monotherapy 2): choline magnesium trisalicylate (therapeutic salicylate concentrations) |

### Outcomes

1. Joint tenderness
2. Joint swelling
3. Duration of time to beginning amelioration of morning stiffness
4. Grip strength
5. Physicians' global assessment
6. Patient's global assessment
7. Patient's pain evaluation (0 to 100 mm VAS) - absolute (percentage) change from flare
8. Patient's subjective evaluation of ability to complete activities of daily living (0 to 180, maximum score 180): absolute (percentage) change from flare

### Notes

Results reflect the average of all cross-over periods (all the 4 treatment periods on each drug) (only available ones)

Pain - absolute (percentage) change from flare (negative scores mean the pain improved):

| Group 1 (combination therapy 1): -26 (-37%) |
| Group 2 (monotherapy 1): -24 (-35%) |
| Group 3 (combination therapy 2): -15 (-22%) |
| Group 4 (monotherapy 2): -15 (-22%) |

Mean at first flare only reported for the whole study population: 66
No significant difference between the groups (P = 0.94)

Activities of daily living - absolute (percentage) change from flare (negative scores mean the pain improved):

| Group 1 (combination therapy 1): -27 (237%) |
| Group 2 (monotherapy 1): -23 (-21%) |
| Group 3 (combination therapy 2): -18 (-17%) |
| Group 4 (monotherapy 2): -16 (-15%) |

No significant difference between the groups (P = 0.80)

Withdrawals due to adverse events: (interpretation of the authors of the review from what is reported)

| Group 1 (combination therapy): 11.2% (both groups of combination therapy) |
| Group 2 (monotherapy): 5.2% (both groups of monotherapy) |

Withdrawals due to inadequate analgesia: (interpretation of the authors of the review from what is reported)

| Group 1 (combination therapy): 5% (n = 3) |
| Group 2 (monotherapy): 6% (n = 4) |

Number of patients with adverse events not specified. No deaths were reported (interpretation of the authors of the review from what is reported)

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bias Type</td>
<td>Risk Level</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>No randomisation. “In this study, a cyclic permutation Latin-square design was used, and each treatment was always followed by the same treatment, a cyclic permutation of the numbers 4, 2, 1, 3), except when it followed the flare”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>No randomisation</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>Only information in the text: “Double-blind..”, “CMT, N and matching placebos were supplied and packaged in appropriately blinded individual dosage packets”. No information on who exactly was blinded, how blinding was assured or on an analysis of the patients’ perception of which arm they were in</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Description in the methods:“Because some patients did not complete all phases of the study, a general linear model was used for efficacy analysis. It allowed all patients to be included in the analysis, even those who did not complete all phases”. But then the numbers in terms of withdrawals and patients in each treatment arm do not match, not understandable what happened to all the patients and how they were (or not) included in the analyses</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Outcomes are presented as a difference between final value and mean at first flare, which emphasises the improvement obtained with the drug. Absolute end values should be presented in order to enable the calculation of the difference to the mean baseline score. No measures of spread are presented with the means (SD). Number of adverse events not clear; not clear to which patients they refer to. Separate results of each cross-over period are not presented</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Cross-over design with possible carry-over effect, although the authors advocate: “When testing for carry-over effects, 5 of 42 instances were significant, but given the number of comparisons, this was not surprising. We interpreted the results as showing that if any carry-over effect occurred, it</td>
</tr>
</tbody>
</table>

Furst 1987 (Continued)
**Furst 1987**  \( (Continued) \)

<table>
<thead>
<tr>
<th>was of limited significance * * *</th>
</tr>
</thead>
</table>

| Comparison of baseline characteristics very limited |

<table>
<thead>
<tr>
<th>Grennan 1979</th>
</tr>
</thead>
</table>

| Methods | Cross-over trial  
Study duration: 16 weeks (8 weeks for each trial part, and each of them with 2 weeks in each of the 4 arms, being placebo one of them, no washout)  
Randomisation method: not specified  
Blinding: reference to double-blinded, not specified  
Sample size calculation: not described |
| --- |

| Participants | 16 patients (Part I); 14 patients (Part II)  
Inclusion criteria: definite or classical RA (defined by the ARA criteria)  
Exclusion criteria: previous history of peptic ulceration, renal or hepatic disease; current therapy with gold, penicillamine or corticosteroids  
Mean age, gender, disease duration not specified  
Comedication: not specified  
Withdrawals not specified |
| --- |

| Interventions | Group 1 (combination therapy): aspirin + ibuprofen  
Group 2 (monotherapy 1): aspirin  
Group 3 (monotherapy 2): ibuprofen  
Part I of the trial: 2.4 g aspirin + 800 mg ibuprofen  
Part II of the trial: 3.6 g aspirin + 1600 mg ibuprofen |
| --- |

| Outcomes | 1) Articular index  
2) Duration of morning stiffness  
3) Pain score at 2 weeks (0 to 10 cm VAS)  
4) Patient global subjective score  
5) Global observer score  
6) Time to walk 50 feet  
7) Grip strength |
| --- |

| Notes | Results reflect the average of all cross-over periods (all the 4 treatment periods on each drug) (only available ones)  
Pain (at 2 weeks of treatment):  
Part I of the trial  
Group 1 (combination therapy): 5.6 ± 2.3  
Group 2 (monotherapy 1): 6.3 ± 2.7  
Group 3 (monotherapy 2): 6.6 ± 2.8  
Part II of the trial  
Group 1 (combination therapy): 4.7 ± 2.1  
Group 2 (monotherapy 1): 5.4 ± 2.6  
Group 3 (monotherapy 2): 5.3 ± 2.3  
No significant difference between the groups, as reported by the authors, but no P value shown  
Withdrawals due to adverse events and due to inadequate analgesia not clearly reported |
Continued

Numbers presented for patients not finishing one study arm and continuing to the next, but not exactly withdrawing from the study
Number of patients with adverse events not specified. No deaths were reported (interpretation of the authors of the review from what is reported)

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Only information in the text: “Pre-packed, randomised supplies of 300 mg tablets of soluble aspirin and dummy soluble aspirin tablets, 200 mg ibuprofen tablets and dummy ibuprofen tablets were supplied by Boots of Australia”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Only information in the text: “…double-blind”, “Pre-packed, randomised supplies of 300 mg tablets of soluble aspirin and dummy soluble aspirin tablets, 200 mg ibuprofen tablets and dummy ibuprofen tablets were supplied by Boots of Australia”. No information on who exactly was blinded, how blinding was assured or on an analysis of the patients’ perception of which arm they were in</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Not clear how the withdrawals were addressed and whether or not they were included in the analyses although it appears unlikely that they were included, as a total N per outcome is not provided</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>No baseline values are presented. Separate results of each cross-over period are not presented</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Baseline characteristics not presented. Number of randomised patients and patients finishing each trial arm not clear. Cross-over design with possible carry-over effect</td>
</tr>
</tbody>
</table>
Cross-over trial
Study duration: 8 weeks (4 weeks in each arm, no washout)
Randomisation method: predetermined random code
Blinding: reference to double-blinded, not specified
Sample size calculation: not described

33 patients
Inclusion criteria: definite or classical RA of at least one year's duration and an ESR ≥ 20 mm/h
Exclusion criteria: corticosteroids, gold or antimalarial therapy in the preceding 6 months
Mean age and disease duration not specified
Gender (% female): combination therapy arm: 76; monotherapy arm: 73
Comedication: “No physiotherapy was undertaken during the trial, and all other analgesic and anti-inflammatory drugs were withdrawn three weeks before the trial period, paracetamol being substituted until the therapy commenced”
1 withdrawal (severe dizziness not related to the trial drug)

Group 1 (combination therapy): benorylate (aspirin + paracetamol) 6g
Group 2 (monotherapy): phenylbutazone 160 mg

1) Grip strength
2) Patient own assessment of overall pain at 4 weeks (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain, 4 = unbearably severe pain)
3) Duration of morning stiffness
4) Adverse events

Results reflect the average of both cross-over periods (only available ones)

Pain:
Group 1 (combination therapy): baseline 2.6 ± 0.3; 4 weeks 2.4 ± 0.4
Group 2 (monotherapy): baseline 2.9 ± 0.4; 4 weeks 2.0 ± 1.0
Values read by the review authors from a graph
Withdrawals due to inadequate analgesia: (interpretation of the authors of the review from what is reported)
Group 1 (combination therapy): 9% (n = 3)
Group 2 (monotherapy): 0% (n = 0)
Number of patients with adverse events: (interpretation of the authors of the review from what is reported)
Group 1 (combination therapy): 18% (n = 6): brown-coated tongue (n = 1); hunger and losing weight (n = 1); irritation of the skin (n = 1); vomiting and diarrhoea (n = 1); diarrhoea and loss of energy (n = 1); nausea, anorexia and depression (n = 1)
Group 2 (monotherapy): 21% (n = 7): abdominal discomfort (n = 1); polyuria (n = 2); dizziness and faintness (n = 1); headache, lack of energy, itchy eyes (n = 1); indigestion (n = 1); rash and swollen neck glands (n = 1)
No withdrawals due to adverse events or deaths were reported (interpretation of the authors of the review from what is reported)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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Risk of bias
<table>
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<tr>
<th>Haslock 1971</th>
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<tr>
<td>Allocation concealment (selection bias)</td>
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</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
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<td>Incomplete outcome data (attrition bias)</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
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<th>Hingorani 1973</th>
<th></th>
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</thead>
</table>
| Methods | Cross-over trial  
Study duration: 8 weeks (1 week paracetamol + 3 weeks in one arm + 1 week paracetamol + 3 weeks in another arm)  
Randomisation method: not specified  
Blinding: reference to double-blinded, not specified  
Sample size calculation: not described |
| Participants | 27 patients  
Inclusion criteria: classical RA with hand involvement  
Exclusion criteria: known hepatic or renal disease; existing pregnancy; current therapy with gold, steroids (> 10 mg/day) or antimalarials  
Mean age not specified  
Gender (% female): combination therapy arm: 100; monotherapy arm: 82  
Median disease duration (years): combination therapy arm: 6; monotherapy arm: 7  
Comedication: not specified  
3 withdrawals |
| Interventions | Group 1 (combination therapy): benorylate (aspirin + paracetamol) 8 g  
Group 2 (monotherapy): ibuprofen 1200 mg |
Outcomes

1) Pain score (0 = none, 1 = mild, 2 = moderate, 3 = severe) at 3 weeks of treatment
2) Grip strength
3) Functional grip strength
4) Morning stiffness
5) Functional capacity

Notes

For the purpose of this review results were extracted from the first period for efficacy and from both periods for safety

Pain:
Group 1 (combination therapy): baseline 2.23 ± 0.23; improvement at 3 weeks of treatment -0.5 ± 0.2
Group 2 (monotherapy): baseline 2.00 ± 0.33; improvement at 3 weeks of treatment -0.8 ± 0.3
No significant difference between the groups, as reported by the authors, but no P value shown

Number of patients with adverse events: (interpretation of the authors of the review from what is reported)
Group 1 (combination therapy): 54% (n = 13): vomiting (n = 3); headache (n = 3); constipation (n = 2); nausea (n = 1); tinnitus (n = 4); other (n = 8)
Group 2 (monotherapy): 29% (n = 7): headache (n = 1); constipation (n = 2); nausea (n = 3); tinnitus (n = 1); other (n = 4)

Functional capacity (presented, but not clearly defined):
Group 1 (combination therapy): baseline mild 77% (n = 10); moderate 23% (n = 3); severe 0% (n = 0); improvement at 3 weeks of treatment +0.2 ± 0.1
Group 2 (monotherapy): baseline mild 82% (n = 9); moderate 18% (n = 2); severe 0% (n = 0); improvement at 3 weeks of treatment +0.2 ± 0.18
No significant difference between the groups, as reported by the authors, but no P value shown

No withdrawals due to adverse events, withdrawals due to inadequate analgesia or deaths were reported (interpretation of the authors of the review from what is reported)

Risk of bias

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<td>Only information in the text: “Double-blind study” and “Each treatment appeared identical in that while on benorylate they also received 6 placebo Tablets and while on ibuprofen, placebo emulsion.” No information on who exactly was blinded, how blinding was assured or on an analysis of the patients’ perception of which arm they</td>
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### Hingorani 1973 (Continued)

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<th>Bias Type</th>
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<th>Comments</th>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Withdrawals were excluded from the analyses: “Three patients failed to complete the study for various personal and domestic reasons. These patients were excluded from the study”</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Although the study reported baseline and end values for each group, no statistical comparison between groups was reported.</td>
</tr>
<tr>
<td>Other bias</td>
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<td>Outcomes are not clearly defined, regarding scales, units of measurement (e.g. functional capacity).</td>
</tr>
</tbody>
</table>

### Hobkirk 1977

**Methods**

- Cross-over trial
- Study duration: 2 days (1 night in each arm, no washout)
- Randomisation method: not specified
- Blinding: reference to double-blinded, not specified
- Sample size calculation: not described

**Participants**

- 18 patients
- Inclusion criteria: hospitalisation for treatment of active RA (not further specified)
- Exclusion criteria: current therapy with corticosteroids or >75 mg indomethacin daily, known hypersensitivity to either trial medication
- Mean age (years): 54.5 ± 17.4
- Gender (% female): 76
- Mean disease duration (years): 6.8 ± 8.9
- Comedication: not specified
- 1 withdrawal

**Interventions**

- Group 1 (combination therapy): indomethacin 100 mg + diazepam 10 mg
- Group 2 (monotherapy): indomethacin 100 mg

**Outcomes**

- 1) Morning stiffness
- 2) Pain (0 to 10 cm VAS)
- 3) Sleep
- 4) Adverse events

**Notes**

- Results reflect the average of both cross-over periods (only available ones)
- Pain (at 1 day of treatment): Group 1 (combination therapy): 0.83
  Group 2 (monotherapy): 1.28
- No significant difference between the groups, as reported by the authors, but no P value shown
- Withdrawals due to adverse events:
Group 1 (combination therapy): 6% (n = 1)
Group 2 (monotherapy): 0% (n = 0)

Number of patients with adverse events:

Group 1 (combination therapy): 17% (n = 3): headache (n = 2); dizziness (n = 1)
Group 2 (monotherapy): 17% (n = 3): headache (n = 2); nausea (n = 1)

No withdrawals due to inadequate analgesia or deaths were reported (interpretation of the authors of the review from what is reported)

<table>
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<td>(selection bias)</td>
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<td>and detection bias)</td>
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<td>All outcomes</td>
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<td>High risk</td>
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<tr>
<td>Other bias</td>
<td></td>
<td>High risk</td>
</tr>
</tbody>
</table>

**Huskisson 1974**

**Methods**

Cross-over trial
-
Study duration: 18 days: 1 day on one drug, the 2nd day on another drug, 3rd day washout; all 6 possible treatment pairs (see below in interventions + placebo) compared
-
Randomisation method: not specified
-
Blinding: reference to double-blinded, not specified
-
Sample size calculation: not described

**Participants**

Trial 1: 30 patients
-
Trial 2: 24 patients
-
Inclusion criteria: definite or classical RA (ARA criteria) with pain of sufficient severity
to require "on demand" analgesics at least once a day
Exclusion criteria: not specified
Mean age, gender, disease duration and comedication not specified
Trial 1: 7 withdrawals; Trial 2: 2 withdrawals

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Trial 1:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (combination therapy): paracetamol 650 mg + dextropropoxyphene 65 mg</td>
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<tr>
<td></td>
<td>Group 2 (monotherapy): paracetamol 1000 mg OR Pentazocine 50 mg</td>
</tr>
<tr>
<td></td>
<td>Number of patients randomised to each group not presented</td>
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<tr>
<td></td>
<td>Trial 2:</td>
</tr>
<tr>
<td></td>
<td>Group 1 (combination therapy): aspirin 1000 mg + codeine 16 mg OR paracetamol 650 mg + dextropropoxyphene 65 mg</td>
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<tr>
<td></td>
<td>Group 2 (monotherapy): aspirin 600 mg</td>
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</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>1) Pain relief score at 6 hours (0 - none, 1 - slight, 2 - moderate, 3 - complete)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2) Preference for treatment</td>
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<table>
<thead>
<tr>
<th>Notes</th>
<th>Results reflect the average of all cross-over periods (all the 3 treatment periods on each drug) (only available ones)</th>
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<tbody>
<tr>
<td></td>
<td>Pain relief score (at 6 hours):</td>
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<tr>
<td></td>
<td>Trial 1:</td>
</tr>
<tr>
<td></td>
<td>Group 1 (combination therapy): 1.18</td>
</tr>
<tr>
<td></td>
<td>Group 2 (monotherapy): 1.09 (paracetamol); 1.25 (pentazocine)</td>
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<tr>
<td></td>
<td>No significant difference between the groups (P &gt; 0.05)</td>
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<tr>
<td></td>
<td>Trial 2:</td>
</tr>
<tr>
<td></td>
<td>Group 1 (combination therapy): 0.95 (paracetamol + codeine); 0.91 (paracetamol + dextropropoxyphene)</td>
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<tr>
<td></td>
<td>Group 2 (monotherapy): 0.72</td>
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<td>No significant difference between the groups (P &gt; 0.05)</td>
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</table>

<table>
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<tr>
<th>Risk of bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Only information in the text: Trial 1 - “Treatment order was randomized and balanced so far as possible”; Trial 2 - “The order of treatment and the colours used were randomized…”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
</tbody>
</table>
| Blinding (performance bias and detection bias) All outcomes | Unclear risk                                                                                           | Only information in the text: Trial 1 - “The double-placebo method was used to ensure that the trial was double blind and each patient was therefore given 4 tablets in each dose”; Trial 2 - “The tablets were identical in shape and size but each was made in 4 colours, red, blue, green and yellow. Four
Huskinson 1974 (Continued)

| Incomplete outcome data (attrition bias) | Unclear risk | Colour codes were used to ensure that each treatment in a pair comparison appeared different. For a particular patient the same colour code was used throughout. “No information on who exactly was blinded (especially in Trial 2), how blinding was assured (especially in Trial 1) or on an analysis of the patients’ perception of which arm they were in.

| Selective reporting (reporting bias) | High risk | Not clear how the withdrawals were addressed and whether or not they were included in the analyses although it appears unlikely that they were included, as a total N per outcome is not provided.

| Other bias | High risk | Pain outcome measurement is not clear, not explained. No baseline values are presented. No measures of spread (SD) are presented. Separate results of each cross-over period are not presented.

Kean 1981

| Methods | Cross-over trial  
Study duration: 2 weeks (1 week in each arm, no washout)  
Randomisation method: not specified  
Blinding: reference to double-blinded, not specified  
Sample size calculation: not described |

| Participants | 24 patients  
Inclusion criteria: classical or definite RA (not further specified)  
Exclusion criteria: not specified  
Mean age (years): 44.6  
Gender (% female): 58  
Mean disease duration (years): 6.4  
Comedication: not specified  
Withdrawals not stated |

| Interventions | Group 1 (combination therapy): enteric coated aspirin 3.6g + azapropazone 1200 mg  
Group 2 (monotherapy 1): enteric-coated aspirin 3.6 g  
Group 3 (monotherapy 2): azapropazone 1200 mg |

| Outcomes | 1) Pain score at 1 week (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe)  
2) Patient global assessment |
Kean 1981

| 3) Severity of morning stiffness |
| 4) Grip strength |
| 5) Joint circumference |
| 6) Articular index |

**Notes**
- Results reflect the average of both cross-over periods (only available ones)
- Pain (at 1 week of treatment):
  - Group 1 (combination therapy): 2.08 ± 0.18
  - Group 2 (monotherapy 1): 2.08 ± 0.18
  - Group 3 (monotherapy 2): 1.92 ± 0.16
- No significant difference between the groups, as reported by the authors, but no P value shown
- No information on withdrawals due to adverse events, withdrawals due to inadequate analgesia or adverse events reported in the paper

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Only information in the text: “The study was a double-blind crossover with randomisation of treatment sequence order by the Latin squares method”</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Only information in the text: “The study was a double-blind crossover …” No information on who exactly was blinded, how blinding was assured or on an analysis of the patients’ perception of which arm they were in</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Number of patients randomised into each group and patients finishing the treatment not clear</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Separate results of each cross-over period are not reported. No baseline values are reported</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Cross-over design with possible carry-over effect. No specification whether attempts were made to limit cointerventions. No information on safety</td>
</tr>
</tbody>
</table>
Malcolm 1974

| Methods       | Cross-over trial  
|               | Study duration: 8 weeks (1 week paracetamol + 3 weeks trial drug + 1 week interval under paracetamol + 3 weeks other trial drug)  
|               | Randomisation method: not specified  
|               | Blinding: reference to double-blinded, not specified  
|               | Sample size calculation: not described  
| Participants  | 17 patients  
|               | Inclusion criteria: patients between the ages of 18 and 65 years with active RA of the hands (not further specified)  
|               | Exclusion criteria: peptic ulcer, impaired renal function, pregnancy, therapy with steroids or anticoagulants during the previous 6 months  
|               | Mean age, gender, disease duration and comedication not specified  
|               | 5 withdrawals  
| Interventions | Group 1 (combination therapy): benorylate (aspirin + paracetamol) 8 g  
|               | Group 2 (monotherapy): indomethacin 75 mg  
| Outcomes      | 1) Pain at 3 weeks (0 = none, 1 = mild, 2 = moderate, 3 = severe)  
|               | 2) Tenderness  
|               | 3) Grip strength  
|               | 4) Finger swelling  
|               | 5) Overall clinical assessment  
| Notes         | Results reflect the average of both cross-over periods (only available ones)  
|               | Improvement in pain, at 3 weeks of treatment (negative scores mean the pain improved)  
|               | Group 1 (combination therapy): -0.83  
|               | Group 2 (monotherapy): -0.33  
|               | No significant difference between the groups, as reported by the authors, but no P value shown  
|               | Withdrawals due to adverse events (interpretation of the authors of the review from what is reported):  
|               | Group 1 (combination therapy): 6% (n = 1)  
|               | Group 2 (monotherapy): 12% (n = 2)  
|               | Number of patients with adverse events: (interpretation of the authors of the review from what is reported)  
|               | Group 1 (combination therapy): 29% (n = 5) - not specified  
|               | Group 2 (monotherapy): 29% (n = 5) - not specified  
|               | No withdrawals due to inadequate analgesia or deaths were reported (interpretation of the authors of the review from what is reported)  

Risk of bias

<table>
<thead>
<tr>
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<tbody>
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<td>Only information in the text: “Patients entering the trial were consecutively numbered and the order in which they received</td>
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### Malcolm 1974 (Continued)

<table>
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<tr>
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<tbody>
<tr>
<td>Blinding (performance bias and detection bias)</td>
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<td>Only information in the text: “Double-blind…” and “In order to preserve the double-blind nature of the trial double placebos were used”. No information on who exactly was blinded, how blinding was assured or on an analysis of the patients’ perception of which arm they were in</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>5 withdrawals were excluded from the analyses</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Pain measurements are not reported. No baseline values are presented. No measures of spread (SD) are presented. Separate results of each cross-over period are not presented</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>No specification whether attempts were made to limit cointerventions</td>
</tr>
</tbody>
</table>

### Mavrikakis 1977a

| Methods | Cross-over trial  
Study duration: 3 weeks (1 week in each of the study arms, being placebo one of them, no washout)  
Randomisation method: not specified  
Blinding: reference to double-blinded, not specified  
Sample size calculation: not described |
|---|---|
| Participants | 18 patients  
Inclusion criteria: classical RA (not further specified), an articular index of joint tenderness exceeding 15 score units and a degree of clinical reversibility, as judged by one rheumatologist  
Exclusion criteria: current or previous therapy with corticosteroids, chrysotherapy or cytotoxic drugs; pregnancy  
Mean age (years): 46.3 (female) and 47.2 (males)  
Gender (% female): 67  
Disease duration (years): 6.1  
Comedication: not stated  
Withdrawals not stated |
| Interventions | Group 1 (combination therapy): benorylate (aspirin + paracetamol) 6 g  
Group 2 (monotherapy): ibuprofen 1600 mg |
### Outcomes

1. Pain at 1 week (scale not described but values ranged from 0 to 10)
2. Articular index
3. Duration of morning stiffness
4. Grip strength
5. PIP joint circumference
6. Patient's assessment of change in disease activity
7. Physician's assessment of change in disease activity

### Notes

Results reflect the average of both cross-over periods - only available ones

Pain (at 1 week of treatment):
- Group 1 (combination therapy): 1.77 ± 0.22
- Group 2 (monotherapy): 1.77 ± 0.19

No significant difference between the groups, p-value < 0.95
No information on withdrawals due to adverse events, withdrawals due to inadequate analgesia or adverse events reported in the paper.

### Risk of bias

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<tr>
<td>Blinding (performance bias and detection bias)</td>
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<td>Only information in the text: “The design of the study was that of a double-blind crossover nature”. No information on who exactly was blinded, how blinding was assured or on an analysis of the patients’ perception of which arm they were in</td>
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<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Number of patients randomised into each group and patients finishing the treatment not clear</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Separate results of each cross-over period are not reported. No baseline values are reported. Scale measurement of the outcomes not mentioned, e.g. pain scale</td>
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<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Cross-over design with possible carry-over effect. No information on safety</td>
</tr>
</tbody>
</table>
**Mavrikakis 1977b**

| **Methods** | **Cross-over trial**  
Study duration: 3 weeks (1 week in each of the study arms, being placebo one of them, no washout)  
Randomisation method: not specified  
Blinding: reference to double-blinded, not specified  
Sample size calculation: not described |
| **Participants** | **18 patients**  
Inclusion criteria: classical or definite RA (not further specified) and continued joint pain despite antirheumatic drug therapy  
Exclusion criteria: current or previous therapy with corticosteroids, chrysotherapy or cytotoxic drugs  
Mean age (years): 47.3 (female) and 51.5 (males)  
Gender (% female): 72  
Disease duration (years): 6.1  
Comedication: not stated  
Withdrawals not stated |
| **Interventions** | **Group 1 (combination therapy): benorylate (aspirin + paracetamol) 6 g**  
**Group 2 (monotherapy): sulindac 400 mg** |
| **Outcomes** | **1) Pain at 1 week (scale not described but values ranged from 0 to 10)**  
**2) Articular indices**  
**3) Duration and severity of morning stiffness**  
**4) Grip strength**  
**5) PIP joint circumference**  
**6) Patient’s assessment of change in disease activity** |
| **Notes** | **Results reflect the average of both cross-over periods (only available ones)**  
Pain (at 1 week of treatment):  
**Group 1 (combination therapy): 2.05 ± 0.22**  
**Group 2 (monotherapy): 1.88 ± 0.29**  
No significant difference between the groups, as reported by the authors, but no P value shown  
No information on withdrawals due to adverse events, withdrawals due to inadequate analgesia or adverse events reported in the paper |

**Risk of bias**

<table>
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<th><strong>Bias</strong></th>
<th><strong>Authors’ judgement</strong></th>
<th><strong>Support for judgement</strong></th>
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<td>Not specified. The word randomised does not appear in the text</td>
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<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Only information in the text: “The design of the study was that of a double-blind crossover type”. No information on who</td>
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</table>
Mavrikakis 1977b  (Continued)

<table>
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<tbody>
<tr>
<td></td>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Number of patients randomised into each group and patients finishing the treatment not clear</td>
</tr>
<tr>
<td></td>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Separate results of each cross-over period are not reported. No baseline values are reported. Scale measurement of the outcomes not mentioned, e.g. pain scale</td>
</tr>
<tr>
<td></td>
<td>Other bias</td>
<td>High risk</td>
<td>Cross-over design with possible carry-over effect. No information on safety</td>
</tr>
</tbody>
</table>

Mowat 1979

<table>
<thead>
<tr>
<th>Methods</th>
<th>Cross-over trial Study duration: 8 weeks (4 weeks in each arm, no washout) Randomisation method: not specified Blinding: single-blinded (only physicians blinded) Sample size calculation: not described</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>31 patients Inclusion criteria: definite or classical RA (not further specified) Exclusion criteria: aspirin-hypersensitivity, breast feeding or pregnancy and compromised hepatic or renal function Mean age (years): combination therapy arm: 59.6; monotherapy arm: 54.4 Gender (% female): combination therapy arm: 58.8; monotherapy arm: 50 Disease duration not specified Comedication: all other NSAIDs were withdrawn 4 withdrawals</td>
</tr>
<tr>
<td>Interventions</td>
<td>Group 1 (combination therapy): benorylate (aspirin + paracetamol), starting dose 4 g, maximum 8 g Group 2 (monotherapy): naproxen, starting dose 500 mg, maximum 1 g Patients were allowed to increase their dose of drug every 4th day up to the maximum daily dosage</td>
</tr>
<tr>
<td>Outcomes</td>
<td>1) Pain at 4 weeks (0 to 10cm VAS) 2) Morning stiffness 3) Joint pain on full range of active movement 4) Adverse events</td>
</tr>
</tbody>
</table>
| Notes                         | For the purpose of this review results were extracted from the first period for efficacy and from both periods for safety Pain (negative scores mean the pain improved): Group 1 (combination therapy): baseline 4.50 ± 1.48; improvement at 4 weeks of treat-
ment -0.29 ± 1.69
Group 2 (monotherapy): baseline 4.57 ± 2.44; improvement at 4 weeks of treatment -0.29 ± 2.38
No significant difference between the groups, as reported by the authors, but no P value shown
Withdrawals due to adverse events:
Group 1 (combination therapy): 7% (n = 2)
Group 2 (monotherapy): 3% (n = 1)
Withdrawals due to inadequate analgesia:
Group 1 (combination therapy): 3% (n = 1)
Group 2 (monotherapy): 0% (n = 0)
Number of patients with adverse events:
Group 1 (combination therapy): 55% (n = 17): nausea, constipation, indigestion, vomiting, hearing upset, headache, dry skin, rash (n per adverse event not specified)
Group 2 (monotherapy): 45% (n = 14): nausea, constipation, indigestion, vomiting, hearing upset, dry skin, rash (n per adverse event not specified)
No deaths were reported (interpretation of the authors of the review from what is reported)

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Only information in the text: “Patients were randomly divided into 2 groups”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>“The drugs were supplied in identical sealed boxes with a medicine measure”</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>High risk</td>
<td>Single-blinded study and “Patients were asked not to reveal details of the physical characteristics of the suspensions to the physician to keep the trial single-blind”. This could bias patient-reported outcome assessment</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Unclear how incomplete outcome data were handled</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Only the significant comparisons between 2 treatment groups are reported, putting emphasis on the time points in which there is a significant difference between the groups</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Cross-over design with possible carry-over effect. Baseline characteristics poorly compared (only age and sex)</td>
</tr>
</tbody>
</table>
### Methods
- **Parallel RCT**
- Study duration: 7 weeks (1 week washout period + 4 weeks study treatment + 2 weeks ibuprofen)
- Randomisation method: not specified
- Blinding: reference to double-blinded, not specified
- Sample size calculation: not described

### Participants
- **60 patients**
- Inclusion criteria: classical or definite active RA (according to the ARA criteria), satisfying at least 3 of the following criteria: Ritchie's index $>15$; ESR $>25$; duration of morning stiffness $\geq 30$ min; and subjective pain index $>50$ mm
- Exclusion criteria: Hamilton rating scale for depression score of 7 to 19
- Mean age (years): depressed patients $48.1 \pm 2.0$; not depressed patients $50.2 \pm 2.1$
- Gender (% female): 87
- Disease duration (years): depressed patients $10.1 \pm 1.9$; not depressed patients $8.1 \pm 1.3$
- Comedication: not specified
- 10 withdrawals

### Interventions
- **Group 1 (combination therapy):** dothiepin 75 mg + ibuprofen 1800 mg
- **Group 2 (monotherapy):** ibuprofen 1800 mg

### Outcomes
- 1) Hamilton rating scale for depression
- 2) Cassano-Castrogiovanni self-evaluation rating scale for depression
- 3) Ritchie's index
- 4) Lee index
- 5) Duration of morning stiffness
- 6) Grip strength
- 7) Pain (0-100mm VAS)
- 8) Daytime pain
- 9) Night-time pain
- 10) Physician's evaluation of the efficacy of treatment
- 11) Patient's evaluation of the efficacy of treatment

### Notes
- **Pain at 4 weeks of treatment:**
  - **Group 1 (combination therapy):**
    - not depressed patients: baseline $57.0 \pm 0.8$; 4 weeks of treatment $43.0 \pm 1.0$
    - depressed patients: baseline $58.0 \pm 0.5$; 4 weeks of treatment $43.0 \pm 0.5$
  - **Group 2 (monotherapy):**
    - not depressed patients: baseline $47.0 \pm 0.7$; 4 weeks of treatment $43.0 \pm 1.0$
    - depressed patients: baseline $59.0 \pm 0.8$; 4 weeks of treatment $51.7 \pm 0.8$
- No significant difference between the groups, as reported by the authors, but no P value shown
- No information on withdrawals due to adverse events, withdrawals due to inadequate analgesia or number of patients with adverse events reported in the paper. No deaths were reported (interpretation of the authors of the review from what is reported)

### Risk of bias
<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>

**Combination therapy for pain management in inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis) (Review)**

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Puttini 1988 (Continued)

<table>
<thead>
<tr>
<th>Risk of Bias</th>
<th>Unclear Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Only information in the text: “…were randomly added to the ibuprofen therapy in a double-blind design”</td>
<td></td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Not mentioned</td>
<td></td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Only information in the text: “…were randomly added to the ibuprofen therapy in a double-blind design”. No information on who exactly was blinded, how blinding was assured or on an analysis of the patients’ perception of which arm they were in.</td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>10 withdrawals excluded from the analyses. Not clear how other missing data were approached, since a total n per outcome is not given, and the number per randomised group not mentioned either</td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Not all outcomes are reported (e.g. grip strength, morning stiffness, although reported in the methods)</td>
<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>Baseline characteristics not presented. No specification whether attempts were made to limit cointerventions. No safety data provided</td>
<td></td>
</tr>
</tbody>
</table>

### Saarialho-Kere 1988

<table>
<thead>
<tr>
<th>Methods</th>
<th>Cross-over trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study duration: 12 days (3 days on paracetamol + 3 days in each of the study arms, no washout)</td>
<td></td>
</tr>
<tr>
<td>Randomisation method: not specified</td>
<td></td>
</tr>
<tr>
<td>Blinding: reference to double-blinded, not specified</td>
<td></td>
</tr>
<tr>
<td>Sample size calculation: not described</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>16 patients</td>
</tr>
<tr>
<td>Inclusion criteria: classical RA (according to the ARA criteria) and current daily therapy with anti-inflammatory analgesics</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: gastrointestinal, hepatic, renal or psychic disease; previous intolerance to the drugs tested</td>
<td></td>
</tr>
<tr>
<td>Mean age (years): not specified</td>
<td></td>
</tr>
<tr>
<td>Gender (% female): 88</td>
<td></td>
</tr>
<tr>
<td>Disease duration (years): 6.2 ± 2.0</td>
<td></td>
</tr>
<tr>
<td>Co-medication: stable doses of DMARDs (gold, penicillamine, chloroquine) were maintained and unchanged throughout the study Patients were allowed to take extra paracetamol on days 1 to 5 to alleviate pain and the amount of paracetamol was recorded</td>
<td></td>
</tr>
</tbody>
</table>
1 withdrawal

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Group 1 (combination therapy): dextropropoxyphene 65 mg + amitriptyline 25 mg</th>
<th>Group 2 (monotherapy 1): dextropropoxyphene 130 mg</th>
<th>Group 3 (monotherapy 2): indomethacin 50 mg</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>1) Pain at 4 hours after the treatment (0 to 100 mm VAS)</th>
<th>2) Duration of morning stiffness</th>
<th>3) Grip strength</th>
<th>4) Articular index</th>
<th>5) Several psychomotor skills</th>
</tr>
</thead>
</table>

Notes

<table>
<thead>
<tr>
<th>Notes</th>
<th>Results reflect the average of both cross-over periods (only available ones)</th>
<th>Pain (at 4h after the treatment):</th>
<th>Group 1 (combination therapy): baseline 50 ± 6.6; 4 hours 44 ± 6.6</th>
<th>Group 2 (monotherapy 1): baseline 46 ± 6.0; 4 hours 34 ± 4.8</th>
<th>Group 3 (monotherapy 2): baseline 49 ± 6.9; 4 hours 36 ± 5.6</th>
</tr>
</thead>
</table>

Significant difference between combination therapy and monotherapy 1, as reported by the authors, P value < 0.05

No information on withdrawals due to adverse events, withdrawals due to inadequate analgesia or adverse events reported in the paper

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Only information in the text: “The trial comprised four randomized double-blind crossover treatment periods started at two-week intervals”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Only information in the text: “The trial comprised four randomized double-blind crossover treatment periods started at two-week intervals”. No information on who exactly was blinded, how blinding was assured or on an analysis of the patients’ perception of which arm they were in</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not clear how missing data were approached, since a total n per outcome is not given</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Not all outcomes are reported (e.g. grip strength, morning stiffness, although reported in the methods). No baseline values are presented. Separate results of each</td>
</tr>
</tbody>
</table>
**Seideman 1988**

**Methods**
- Cross-over trial
- Study duration: 3 days wash-out period without NSAIDs + 7 days run-in period (assess tolerability of indomethacin) + 4 weeks (2 weeks in each arm, no washout)
- Randomisation method: not specified
- Blinding: participants and outcome assessor blinded
- Sample size calculation: not described

**Participants**
- 20 patients
- Inclusion criteria: classic or definite RA (as diagnosed by ARA criteria) with pain of sufficient degree to require NSAID medication
- Exclusion criteria: gastrointestinal, hepatic or renal disease, known intolerance to indomethacin
- Mean age (years): 47 ± 10
- Gender: not specified
- Disease duration (years): 10 ± 8
- Comedication: DMARDs that had been given for at least 6 months were kept and not changed throughout the study
- 3 withdrawals

**Interventions**
- Group 1 (combination therapy): indomethacin 50 mg + paracetamol 4 g (randomised: n = 10; completing the treatment: n = 8)
- Group 2 (monotherapy): indomethacin 150 mg (randomised: n = 10; completing the treatment: n = 9)

**Outcomes**
- 1) Pain (0 to 100 mm VAS); mean pain estimate during the 2nd and 4th weeks
- 2) Duration of morning stiffness
- 3) Grip strength
- 4) Number of joints painful to digital pressure
- 5) Joint circumference

**Notes**
- Results reflect the average of both cross-over periods (only available ones)
- Mean values for pain:
  - Group 1 (combination therapy): 29.9 ± 26.4
  - Group 2 (monotherapy): 29.2 ± 26.4
- Mean of the estimates made during the second and fourth treatment weeks
- No significant difference between the groups, P value = 0.94 (calculated by authors of the review)
- Number of patients with adverse events:
  - Group 1 (combination therapy): 55% (n = 11): headache, tiredness and vertigo (n = 3); anorexia, dyspepsia and vomiting (n = 1)
  - Group 2 (monotherapy): 20% (n = 4): headache, tiredness and vertigo (n = 6); anorexia,
dyspepsia and vomiting (n = 5)
No withdrawals due to inadequate analgesia, no withdrawals due to adverse events and no deaths were reported (interpretation of the authors of the review from what is reported)

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Only information in the text: “Half of the patients were subsequently randomized to…”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Low risk</td>
<td>“The study was performed in a double-blind crossover manner”. “Due to differences in appearance of the formulations, a double-dummy technique was used”</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>3 patients withdrawn from the study, apparently for reasons different to the exclusion criteria. From the included patients, it is unclear which are the missing data since results are not presented with numbers of patients having been assessed per outcome and per time point</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>No baseline values are presented. Separate results of each cross-over period are not presented</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Cross-over trial with possible carry-over effects</td>
</tr>
</tbody>
</table>

Seideman 1993

Methods
- Cross-over trial
- Study duration: 3 to 7 day “flare” period + 4 weeks (2 weeks in each arm, no washout)
- Randomisation method: not specified
- Blinding: participants and outcome assessor blinded
- Sample size calculation: not described

Participants
- 20 patients
- Inclusion criteria: classic or definite RA (as diagnosed by ARA criteria) with pain of sufficient degree to require NSAID medication
- Exclusion criteria: not specified
- Mean age (years): 52.4
- Gender (% female): 55
Disease duration (years): 4
Co-medication: DMARDs that had been given for at least 6 months were kept and not changed throughout the study. 12 patients on 2nd line drugs (penicillamine: 4; aurothiomalate: 4; chloroquine: 4)
No withdrawals

**Interventions**

- **Group 1 (combination therapy 1):** naproxen 500 mg + paracetamol 4 g
- **Group 2 (monotherapy 1):** naproxen 500 mg
- **Group 3 (combination therapy 2):** naproxen 1000 mg + paracetamol 4 g
- **Group 4 (monotherapy 2):** naproxen 1000 mg

**Outcomes**

1) Number of joints painful to digital pressure or passive movements
2) Duration of morning stiffness
3) Pain at 2 weeks (0 to 100 mm VAS)
4) Global assessment of disease activity
5) Activity of daily living assessment at 2 weeks

**Notes**

Results correspond to the average from all cross-over periods and baseline is the average pre-treatment value, so not individualised for each group (only available ones)

**Pain at 2 weeks:**
- Pretreatment (all the groups): 75 ± 16
- Group 1 (combination therapy 1): 45.7 ± 14.6
- Group 2 (monotherapy 1): 61.5 ± 15.9
- Significant difference between the groups (P < 0.001)
- Group 3 (combination therapy 2): 31.7 ± 9.6
- Group 4 (monotherapy 2): 46.5 ± 14.6
- Significant difference between the groups (P < 0.05)

**Function at 2 weeks:**
- Pretreatment (all the groups): 3.8 ± 0.7
- Group 1 (combination therapy 1): 4.6 ± 0.3
- Group 2 (monotherapy 1): 4.5 ± 0.3
- No significant difference between the groups, as reported by the authors, no P value shown
- Group 3 (combination therapy 2): 4.6 ± 0.3
- Group 4 (monotherapy 2): 4.6 ± 0.3
- No significant difference between the groups, as reported by the authors, no P value shown

No withdrawals due to inadequate analgesia, no withdrawals due to adverse events and no deaths were reported (interpretation of the authors of the review from what is reported)

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Only information in the text: “Each dose was given for 2-week periods in a randomized order”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
</tbody>
</table>
### Seideman 1993  
(Continued)

| Blinding (performance bias and detection bias) | Low risk | “The study was double-blind with identical naproxen tablets and placebo and identical paracetamol and placebo”. “Due to differences in appearance of the formulations, a double-dummy technique was used” |
| Incomplete outcome data (attrition bias) | Low risk | No missing outcome data |
| Selective reporting (reporting bias) | High risk | No baseline values are presented. Separate results of each cross-over period are not presented |
| Other bias | High risk | Cross-over design with possible carry-over effects. Safety data not presented |

### Sharma 1978

| Methods | Cross-over trial  
Study duration: 3 days (1 night in each arm, no washout)  
Randomisation method: not specified  
Blinding: reference to double-blinded, not specified  
Sample size calculation: not described |
| Participants | 18 patients  
Inclusion criteria: hospitalisation for the treatment of active RA, classical and definite (as defined by the ARA)  
Exclusion criteria: current therapy with corticosteroids, > 75 mg indomethacin or any additional dose of sulindac; known hypersensitivity to any of the trial medications  
Mean age (years): 47.6  
Gender (% female): 89  
Disease duration not specified  
Comedication: no other analgesic or hypnotic  
1 withdrawal |
| Interventions | Group 1 (combination therapy 1): sulindac 200 mg + diazepam 10 mg  
Group 2 (monotherapy): sulindac 200 mg  
Group 3 (combination therapy 2): indomethacin 100 mg + diazepam 10 mg |
| Outcomes | 1) Duration of morning stiffness  
2) Night pain at 1 day of treatment (0 to 10 cm VAS)  
3) Quality of sleep  
4) Adverse events |
| Notes | Results reflect the average of all cross-over periods (only available ones)  
Pain (at 1 day of treatment);  
Group 1 (combination therapy 1): 4.76  
Group 2 (monotherapy): 4.07 |
Group 3 (combination therapy 2): 3.39
No significant difference between groups 1 and 2, as reported by the authors, but no P value shown
No significant difference between groups 2 and 3, as reported by the authors, P value = 0.061
Number of patients with adverse events:
Group 1 (combination therapy 1): 22% (n = 4); headache (n = 1); drowsiness (n = 3)
Group 2 (monotherapy): 22% (n = 4); headache (n = 1); drowsiness (n = 2); depression (n = 1)
Group 3 (combination therapy 2): 33% (n = 6): drowsiness (n = 5); depression (n = 1)
1 patient withdrew due to adverse events, but it is not clear in which arm he/she was
No withdrawals due to inadequate analgesia and no deaths were reported (interpretation of the authors of the review from what is reported)

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
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</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Only information in the text: “…and the treatment order was randomized”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Only information in the text: “The double-blind nature of the trial was ensured by using appropriate dummy tablets or capsules”. No information on who exactly was blinded, how blinding was assured or on an analysis of the patients’ perception of which arm they were in</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>One withdrawal excluded from the analysis, after being included in the study. Number of patients randomised into each group not clear</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Separate results of each cross-over period are not reported. No baseline values are reported. No measures of spread are presented with the means (SD)</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Cross-over design with possible carry-over effect. Number of patients randomised for each treatment order is not clear</td>
</tr>
</tbody>
</table>
Methods

Parallel RCT
Study duration: 13 weeks (1 week of placebo + 12 weeks in one of the study arms)
Randomisation method: predetermined random code
Blinding: reference to double-blinded, not specified
Sample size calculation: not described

Participants

41 patients
Inclusion criteria: classical or definite RA (not further specified)
Exclusion criteria: therapy with steroids, gold or antimalarial drugs within the previous year; definite history of aspirin intolerance
Mean age (years): combination therapy arm: 59; monotherapy arm: 56
Gender (% female): combination therapy arm: 81; monotherapy arm: 76
Disease duration not specified
Comedication: no other analgesics or anti-inflammatory drugs were permitted and physiotherapy was withheld for the duration of the trial
8 withdrawals

Interventions

Group 1 (combination therapy): benorylate (aspirin + paracetamol) 6 g (n = 20)
Group 2 (monotherapy): aspirin 4 g (n = 21)

Outcomes

1) Pain severity (1 = mild, 2 = moderate, 3 = severe) at 12 weeks of treatment
2) Number of inflamed joints
3) Morning stiffness
4) Articular index
5) Grip strength
6) Functional status

Notes

Improvement in pain, at 12 weeks of treatment:
Group 1 (combination therapy): baseline pain level 0: 0%; 1: 0%; 2: 30% (n = 6); 3: 45% (n = 9); at 12 weeks: better 50% (n = 10); unchanged 20% (n = 4); worse 10% (n = 2)
Group 2 (monotherapy): baseline pain level 0: 0%; 1: 0%; 2: 43% (n = 9); 3: 38% (n = 8); at 12 weeks: better 48% (n = 10); unchanged 24% (n = 5); worse 10% (n = 2)
No significant difference between the groups, P value > 0.05
Withdrawals due to adverse events:
Group 1 (combination therapy): 10% (n = 2)
Group 2 (monotherapy): 10% (n = 2)
Withdrawals due to inadequate analgesia:
Group 1 (combination therapy): 0% (n = 0)
Group 2 (monotherapy): 10% (n = 2)
Number of patients with adverse events:
Group 1 (combination therapy): 45% (n = 9): indigestion; nausea; flatulence; constipation; drowsiness; tinnitus; itchy legs; nocturia (n per adverse event not specified)
Group 2 (monotherapy): 71% (n = 15): indigestion; nausea; flatulence; constipation; drowsiness; macular rash; sweating; nocturia (n per adverse event not specified)
No deaths were reported (interpretation of the authors of the review from what is reported)
### Sperryn 1973

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Only information in the text: “...patients were treated according to a predetermined random code”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>Only information in the title: “Double-blind comparison...” No information on who exactly was blinded, how blinding was assured or on an analysis of the patients’ perception of which arm they were in</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Withdrawals were excluded from the analyses, even after having been assigned to a treatment group</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Not all outcomes are presented, e.g. functional status. No measures of spread are presented with some of the means (SD). Some outcomes (e.g. pain, morning stiffness, grip strength) presented in a different way than what was described in methods, and also differently compared to the baseline value presentation</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Scale measurement of the outcomes not always clear and varying between the presentation of baseline results and of the change results</td>
</tr>
</tbody>
</table>

### Staunton 1980

<table>
<thead>
<tr>
<th>Methods</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Study duration: 6 weeks (2 weeks on indomethacin 75 mg + 4 weeks in one of the study arms)</td>
<td></td>
</tr>
<tr>
<td>Randomisation method: not specified</td>
<td></td>
</tr>
<tr>
<td>Blinding: reference to double-blinded, not specified</td>
<td></td>
</tr>
<tr>
<td>Sample size calculation: not described</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>18 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: classical or definite RA (according to the ARA criteria). Only those patients aged 30 to 70 years were included and the diagnosis must have been established at least 6 months prior to entry. Clear evidence of active disease had to be apparent when the patients were off all anti-inflammatory and analgesic drugs</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: pregnancy and lactation; ARA functional class I; therapy with systemic or intra-articular steroid therapy or ACTH within 6 weeks prior to entry, immunosup-</td>
<td></td>
</tr>
</tbody>
</table>
pressive therapy during the previous year, penicillamine within 6 months prior to entry, anticoagulants, oral hypoglycaemic agents, barbiturates and phenothiazines (cryotherapy was permitted, as long as the dosage regime had not altered within 6 months prior to entry); presence of any other rheumatic or collagen disorder or evidence of concomitant disease that might affect joints
Mean age (years): combination therapy arm: 56.5 ± 10.5; monotherapy arm: 50.3 ± 12.4
Gender (% female): combination therapy arm: 56; monotherapy arm: 100
Mean disease duration (years): combination therapy arm: 12; monotherapy arm: 6.9
Comedication: patients were requested to stop taking any current anti-inflammatory or analgesic drugs for a withdrawal period of 2 to 7 days and during the study these drugs were not allowed (except for the trial drugs)
2 withdrawals (while on indomethacin only, so not during the 4 weeks under study drugs)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Group 1 (combination therapy): diflunisal 500 mg + indomethacin 75 mg (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 2 (monotherapy): indomethacin 75 mg (n = 9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>1) Ritchie articular index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2) Grip strength</td>
</tr>
<tr>
<td></td>
<td>3) Morning stiffness</td>
</tr>
<tr>
<td></td>
<td>4) Pain during the day and during the night (1 = none; to 4 = very severe pain)</td>
</tr>
<tr>
<td></td>
<td>5) Physician’s global evaluation</td>
</tr>
<tr>
<td></td>
<td>6) Patient’s global evaluation</td>
</tr>
</tbody>
</table>

| Notes | Pain: No significant difference between the groups, as reported by the authors; neither the results, nor the P value for the comparison is shown. No withdrawals due to adverse events, withdrawals due to inadequate analgesia or deaths were reported (interpretation of the authors of the review from what is reported). No information on the number of adverse events is reported in the paper |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Only information in the text: “A double-blind randomized trial...”, “Patients were given an allocation number and then received indomethacin 25 mg capsules three times daily for two weeks. They were then allocated to one of two treatment groups according to their allocation number...”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>Only information in the text: “A double-blind randomized trial...”. No information on who exactly was blinded, how blinding was assured or on an analysis of the patients’</td>
</tr>
</tbody>
</table>
Incomplete outcome data (attrition bias)  
All outcomes |
---|---|---
High risk | Not clear which are incomplete outcome data. Data not presented. Number of patients finishing each arm not presented. 2 withdrawals, that withdrew during the run-in period, but not even clear if they were included in the analyses.

Selective reporting (reporting bias) |
---|---|---
High risk | Not all outcomes are presented, e.g. grip strength. No measures of spread are presented with some of the means (SD). No figures for pain assessment are presented. No baseline value for all the outcomes reported.

Other bias |
---|---|---
High risk | Differences in baseline characteristics

### Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrade-Padilla 1995</td>
<td>Outcome - no pain assessment</td>
</tr>
<tr>
<td>Bain 1970</td>
<td>Outcome - wrong assessment (no global pain assessment)</td>
</tr>
<tr>
<td>Barnardo 1966</td>
<td>Intervention - monotherapy</td>
</tr>
<tr>
<td>Brooks 1977</td>
<td>Outcome - no understandable pain scale</td>
</tr>
<tr>
<td>Cardoe 1970</td>
<td>Outcome - wrong assessment (no global pain assessment)</td>
</tr>
<tr>
<td>Chalmers 1978</td>
<td>Outcome - wrong assessment (no global pain assessment)</td>
</tr>
<tr>
<td>Dalmas 1966</td>
<td>Outcome - no pain assessment</td>
</tr>
<tr>
<td>De Mattos 1968</td>
<td>Study type - observational study</td>
</tr>
<tr>
<td>Eberl 1968</td>
<td>Study type - observational study</td>
</tr>
<tr>
<td>Famaey 1971</td>
<td>Study type - observational study</td>
</tr>
</tbody>
</table>

ARA - American Rheumatism Association; ESR - erythrocyte sedimentation rate; VAS - visual analogue scale; PIP - proximal interphalangeal
<table>
<thead>
<tr>
<th>Study/Reference</th>
<th>Study type/Outcome/Intervention</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Famaey 1972</td>
<td>Study type - observational study</td>
<td></td>
</tr>
<tr>
<td>France 1968</td>
<td>Study type - observational study</td>
<td></td>
</tr>
<tr>
<td>Franke 1972</td>
<td>Outcome - no pain assessment</td>
<td></td>
</tr>
<tr>
<td>Glowinski 1999</td>
<td>Intervention - triple therapy</td>
<td></td>
</tr>
<tr>
<td>Hernandez Pena 1973</td>
<td>Study type - observational study</td>
<td></td>
</tr>
<tr>
<td>Hersh 2007</td>
<td>Study type - observational study</td>
<td></td>
</tr>
<tr>
<td>Huss 1974</td>
<td>Study type - observational study</td>
<td></td>
</tr>
<tr>
<td>Jaffé 1973</td>
<td>Population - mixed population without separate results on IA</td>
<td></td>
</tr>
<tr>
<td>Jeremy 1970</td>
<td>Outcome - no pain assessment</td>
<td></td>
</tr>
<tr>
<td>Lewis-Faning 1972</td>
<td>Population - mixed population without separate results on IA</td>
<td></td>
</tr>
<tr>
<td>Lopez Prats 1968</td>
<td>Study type - observational study</td>
<td></td>
</tr>
<tr>
<td>Lynch 2001</td>
<td>Intervention - monotherapy</td>
<td></td>
</tr>
<tr>
<td>Maldykowa 1983</td>
<td>Intervention - monotherapy</td>
<td></td>
</tr>
<tr>
<td>Maneksha 1973</td>
<td>Comparator - wrong comparator</td>
<td></td>
</tr>
<tr>
<td>Mitchell 1984</td>
<td>Population - mixed population without separate results on IA</td>
<td></td>
</tr>
<tr>
<td>Moll 1966</td>
<td>Study type - observational study</td>
<td></td>
</tr>
<tr>
<td>Murphy 1978</td>
<td>Population - mixed population without separate results on IA</td>
<td></td>
</tr>
<tr>
<td>Pavelka 1972</td>
<td>Intervention - monotherapy</td>
<td></td>
</tr>
<tr>
<td>Perrot 2006</td>
<td>Intervention - monotherapy</td>
<td></td>
</tr>
<tr>
<td>Raptopoulou 2008</td>
<td>Intervention - monotherapy</td>
<td></td>
</tr>
<tr>
<td>Ridolfo 1982</td>
<td>Outcome - wrong assessment (no global pain assessment)</td>
<td></td>
</tr>
<tr>
<td>Robinson 1975</td>
<td>Outcome - wrong assessment (no global pain assessment)</td>
<td></td>
</tr>
<tr>
<td>Roth 1975</td>
<td>Outcome - wrong assessment (no global pain assessment)</td>
<td></td>
</tr>
</tbody>
</table>
(Continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rudge 1982</td>
<td>Outcome - no pain assessment</td>
</tr>
<tr>
<td>Sasisekhar 1973</td>
<td>Intervention - monotherapy</td>
</tr>
<tr>
<td>Sidiropoulos 2008</td>
<td>Intervention - monotherapy</td>
</tr>
<tr>
<td>Torgyan 1979</td>
<td>Outcome - no pain assessment</td>
</tr>
<tr>
<td>Triandaf 1970a</td>
<td>Study type - observational study</td>
</tr>
<tr>
<td>Triandaf 1970b</td>
<td>Study type - observational study</td>
</tr>
<tr>
<td>Van Hoek 1973</td>
<td>Outcome - no pain assessment</td>
</tr>
<tr>
<td>Vergne-Salle 2009</td>
<td>Intervention - monotherapy</td>
</tr>
<tr>
<td>Wettreich 1966</td>
<td>Study type - observational study</td>
</tr>
<tr>
<td>Willkens 1976</td>
<td>Outcome - no pain assessment</td>
</tr>
</tbody>
</table>
DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 30 October 2010.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 November 2010</td>
<td>Amended</td>
<td>CMSG ID A059</td>
</tr>
</tbody>
</table>

HISTORY

Protocol first published: Issue 12, 2010

Review first published: Issue 10, 2011

CONTRIBUTIONS OF AUTHORS

SR wrote the first draft of the review.

HR, AVT, RL, DvdH, RB and DA contributed to the final version of the review by providing comments and suggestions on draft versions of the review.

All authors approved the final version of the manuscript.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of Medicine, Division of Rheumatology, Maastricht University Medical Centre, Netherlands.
  In kind support
- Division of Rheumatology, Department of Internal Medicine 3, Medical University Vienna, Austria.
  In kind support
- Department of Clinical Epidemiology, Cabrini Hospital; Department of Epidemiology and Preventive Medicine, Monash University, Australia.
  In kind support
Differences Between Protocol and Review

The primary outcome was changed to “Patient reported pain relief of 50% or greater” instead of “Patient reported pain relief of 30% or greater” on the recommendation of the CMSG. The latter was considered to be a secondary outcome. The change was made because 50% improvement in pain is more commonly assessed in IA (e.g. ACR50 improvement in RA).

Clinical heterogeneity of the included studies precluded pooling of the data, statistical heterogeneity assessment and subsequent sensitivity and subgroup analyses, as well as the summary of findings table presentation. Results of the included studies could only be described.