Combination Therapy for Pain Management in Inflammatory Arthritis: A Cochrane Systematic Review

SOFIA RAMIRO, HELGA RADNER, DÉSIRÉE M. van der HEIJDE, RACHELLE BUCHBINDER, DANIEL ALETAHA, and ROBERT B. LANDEWÉ

ABSTRACT. *Objective.* To assess the efficacy and safety of combination pain therapy for people with inflammatory arthritis (IA).

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

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

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

Key Indexing Terms:
PAIN/DRUG THERAPY   ANALGESICS   RHEUMATOID ARTHRITIS
ANKYLOSING SPONDYLITIS   PSORIATIC ARTHRITIS

From the Department of Clinical Immunology and Rheumatology, Academic Medical Center, Amsterdam, The Netherlands; Department of Rheumatology, Hospital Garcia de Orta, Almada, Portugal; Division of Rheumatology, Department of Internal Medicine 3, Medical University of Vienna, Vienna, Austria; Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands; Monash Department of Clinical Epidemiology, Cabrini Hospital, and Department of Epidemiology and Preventive Medicine, Monash University, Malvern, Australia; and Department of Rheumatology, Atrium Medical Center, Heerlen, The Netherlands.

S. Ramiro, MD, Clinical Research Fellow, Department of Clinical Immunology and Rheumatology, Academic Medical Center; Rheumatology Fellow, Department of Rheumatology, Hospital Garcia de Orta; H. Radner, MD, Rheumatology Fellow, Division of Rheumatology, Department of Internal Medicine 3, Medical University of Vienna; D.M. van der Heijde, MD, PhD, Professor of Rheumatology, Department of Rheumatology, Leiden University Medical Center; R. Buchbinder, MBBS (Hons), MSc, PhD, FRACP, Rheumatologist, Director, Monash Department of Clinical Epidemiology, Cabrini Hospital, Professor, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University; D. Aletaha, MD, PhD, Professor of Rheumatology, Division of Rheumatology, Department of Internal Medicine 3, Medical University of Vienna; R.B. Landewé, MD, PhD, Professor of Rheumatology, Department of Clinical Immunology and Rheumatology, Academic Medical Center; Consultant Rheumatologist, Department of Rheumatology, Atrium Medical Center.

Address correspondence to Dr. S. Ramiro, Department of Rheumatology, Hospital Garcia de Orta, Av. Prof. Torrado da Silva, 2801-951 Almada, Portugal. E-mail: sofiaramiro@gmail.com

Inflammatory arthritis (IA) is a term given to a group of chronic inflammatory rheumatic diseases that primarily include rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and undifferentiated spondyloarthritis (SpA). Together, they have an estimated prevalence of about 3%[1], comprising a prevalence of 1% for RA[2] and 1.9% for SpA (including AS and PsA)[3]. The IA are progressive diseases, characterized by pain, joint destruction, and decreased function, and they have a profound effect on the patient's quality of life and on society in terms of medical costs and work disability[1].

The management of IA has dramatically changed over the last decade. The current approach focuses on early detection and management at an early stage of the disease with disease-modifying antirheumatic drugs (DMARD)[4]; moreover, with the introduction of the efficacious biological disease-modifying antirheumatic drugs (bDMARD), remission of disease is considered to be the appropriate treatment target[5]. Nevertheless, despite these significant advances, many patients with IA continue to experience musculoskeletal pain[6,7]. Studies have reported that patients with IA perceive pain to be their predominant impairment[8], and improvement in pain to be among their highest priorities[9,10], even among those who have achieved adequate disease control and are being treated with biologics[11].

In treating patients who have persistent pain, drugs with analgesic effect can be prescribed as monotherapy or in combinations. Nevertheless, it is not known whether specific combinations of classes of drugs with analgesic potential are more effective than monotherapy to treat persistent pain in patients with IA, or if adverse effects offset any benefits. The aim of our review was to summarize the existing data on the efficacy and safety of combination therapy for pain management in patients with IA and is a shortened version of a Cochrane review[12].

Our review is part of the 3e (Evidence, Expertise, Exchange) Initiative[13,14,15] on Pain Management by Pharmacotherapy in Inflammatory Arthritis[16]. The objective of this report was to systematically review the literature concerning one of the 10 selected questions as an evidence base for generating the recommendations. The question was: "Is there any evidence that drugs with different modes of action in various combinations have added value?".

MATERIALS AND METHODS
Our systematic review used the methodology proposed by the Cochrane Collaboration[17].

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

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

For efficacy, the primary outcome was patient-reported pain relief $\geq 50\%$. For safety, the primary outcome was the number of withdrawals due to adverse events. Secondary outcomes were patient-reported pain relief $\geq 30\%$; patient-reported global impression of clinical change as "much" or "very much improved"; proportion of patients achieving a pain score below 30/100 mm on visual analog scale (VAS); mean change in pain score on VAS or numeric rating scale; physical function (on the Health Assessment Questionnaire for RA[19,20] or Bath Ankylosing Spondylitis Functional Index for AS[21]), quality of life (on generic instruments such as the Medical Outcome Study Short-Form 36[22] or disease-specific tools, such as the Rheumatoid Arthritis Quality of Life instrument[23] and Ankylosing Spondylitis Quality of Life Instrument[24]), participant withdrawals due to inadequate analgesia, number of patients with adverse events, and number of deaths. These primary and secondary pain outcomes were chosen based upon those currently recommended by the Cochrane Pain, Palliative and Supportive Care Systematic Review Group editors and others, for systematic reviews (SLR) on chronic pain[25].

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

Search strategy. The following computerized bibliographical databases were searched: Medline (1950 to 4 May 2010), Embase (Embase classic 1947 to 1979 and Embase 1980 to 4 May 2010), The Cochrane Central Register of Controlled Trials (Central) (The Cochrane Library, Issue 2, 2010) without language restrictions, using the highly sensitive Cochrane Collaboration search strategy, which aims to identify all RCT[26]. Specific MeSH headings and additional keywords were used to identify all RCT on combination therapy for pain management in IA. Details on complete search strategies for the database searches are provided in Appendix 1 available from www.3epain.com.

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

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

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

The 2 reviewers independently assessed risk of bias of each included study with regard to the following items: random sequence generation, allocation concealment, blinding of participants, care provider and outcome assessor for each outcome measure, incomplete outcome data, selective outcome reporting, and other potential sources of bias, conforming to the methods recommended by the Cochrane Collaboration[27]. Each criterion was rated as "Yes" (low risk of bias), "No" (high risk of bias), or "Unclear" (either lack of information or uncertainty over the potential for bias). For all these steps, disagreements among the reviewers were discussed and resolved in a consensus meeting or involving a third reviewer (RL), if necessary.

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

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

RESULTS
Results of the search. The electronic database search yielded a total of 14,854 articles, and an additional 160 meeting abstracts were obtained from the conference proceedings. After de-duplication and title and abstract screening, 14,788

studies were excluded and all meeting abstracts were excluded, leaving 66 articles for full-text review. The main reason for exclusion was wrong study type or wrong intervention. After further review, 23 of the 66 articles met inclusion criteria[28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50]. The search process is illustrated in Figure 1, and the reasons for exclusion are described in Appendix 2, available online from www.3epain.com.

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

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

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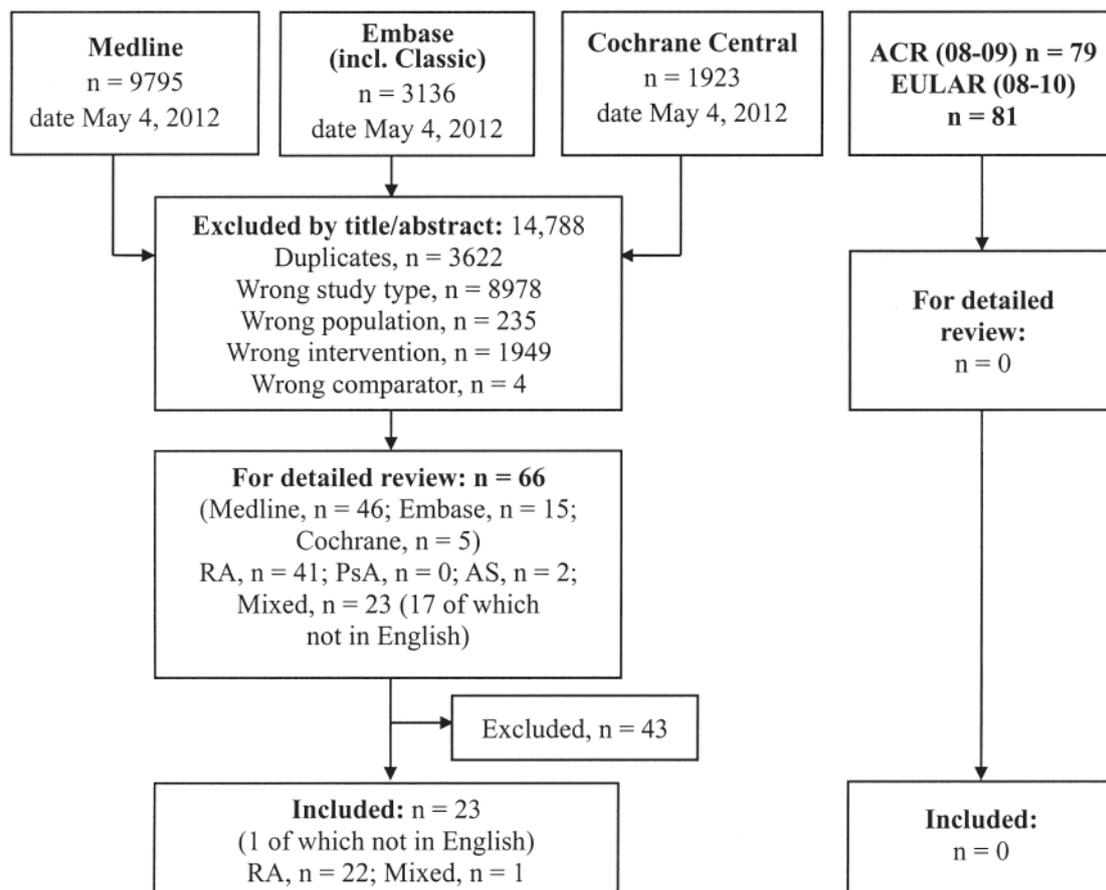

Figure 1. Literature search from which 66 articles were selected for detailed review. Twenty-three articles met the inclusion criteria.

Table 1. Summary of clinical trials of combination therapy for pain management in inflammatory arthritis.

Study, Author, Year	Sample Size, Design, Study Duration	Combination Therapy	Comparison Group, Monotherapy	Outcome Timing	Outcome Measures
Beales 1972[28]	72, CCT, 2 wks	Benorylate (aspirin + paracetamol) 8 g	Aspirin 4.8 g	2 weeks	1. Diurnal pain score (0 = nil; 1 = mild; 2 = moderate; 3 = severe); 2. Severity of disease; 3. Functional grading; 4. Grip strength; 5. Finger stiffness; 6. Total ring size; 7. Articular index
Bedi 1969[29]	51, crossover trial, 2 wks	Aspirin 500 mg + dextropropoxyphene napsilate 50 mg	Aspirin 500 mg	1 week	1. Improvement in pain (better, no change, worse); 2. Number and type of adverse events (although not specified in the methods)
Brooks 1975[30] Coigley 1975[31]	134, parallel RCT, 2 wks; 95, parallel RCT, 2 wks	Safapryn (paracetamol 3 g + aspirin 3.6 g) Benorylate (paracetamol + aspirin) 8 g	1. Phenylbutazone 50 mg 2. Phenylbutazone 300 mg Indomethacin 75 mg	Throughout 2 wks 2 wks	1. Pain (0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe); 2. Patient global score 1. Improvement in pain (clinical assessment of pain lower by one or more categories, within the following: mild, moderate, severe) at the end of treatment; 2. Morning stiffness
Ekstrand 1981[32]	12, crossover trial, 8 wks	1. Acetylsalicylic acid 2 g + indomethacin 50 mg; 2. Acetylsalicylic acid 4.5 g + indomethacin 50 mg	1. Acetylsalicylic acid 2 g 2. Acetylsalicylic acid 4.5g	Throughout 3 wks	1. Overall global assessment; 2. Preference for one of the suppositories given; 3. Duration of morning stiffness; 4. Pain throughout the period and on the day after indomethacin/placebo (0-100 mm VAS); 5. Grip strength; 6. Articular index; 7. Size of PIP joints
Furst 1987[33]	84, crossover trial, 20 wks	1. Naproxen 1500 mg + choline magnesium trisalicylate (therapeutic concentration) 2. Naproxen 750 mg + half dose choline magnesium trisalicylate	1. Naproxen 1500 mg 2. Choline magnesium trisalicylate (therapeutic concentration)	4 wks	1. Joint tenderness; 2. Joint swelling; 3. Duration of time to beginning amelioration of morning stiffness; 4. Grip strength; 5. Physician's global assessment; 6. Patient's global assessment; 7. Patient's pain evaluation (0-100 mm VAS) – absolute (percentage) change from flare; 8. Patient's subjective evaluation of ability to complete activities of daily living;
Grennan 1979[34]	16 + 14 (2 small trials), crossover trial, 16 wks	Aspirin + ibuprofen Part I of the trial: 2.4 aspirin + 800 mg ibuprofen Part II of the trial: 3.6 g aspirin + 1600 mg ibuprofen	1. Aspirin 2. Ibuprofen	2 wks	1. Articular index; 2.Duration of morning stiffness; 3. Pain score (0-10 cm VAS); 4. Patient global subjective score; 5. Global observer score; 6. Time to walk 50 feet; 7.Grip strength
Haslock 1971[35]	33, crossover trial, 8 wks	Benorylate (aspirin + paracetamol) 6 g	Phenylbutazone 160 mg	4 wks	1. Grip strength; 2. Patient own assessment of overall pain (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain, 4 = unbearably severe pain); 3. Duration of morning stiffness; 4. Adverse events
Hingorani 1973[36]	27, crossover trial, 8 wks	Benorylate (aspirin + paracetamol) 8 g	Ibuprofen 1200 mg	3 wks	1. Pain score (0 = none, 1 = mild, 2 = moderate, 3 = severe); 2. Grip strength; 3. Functional grip strength; 4. Morning stiffness; 5. Functional capacity

Study	Design	Combination	Comparator	Timepoint	Outcomes
Hobkirk 1977[37]	18, crossover trial, 2 days	Indomethacin 100 mg + diazepam 10 mg	Indomethacin 100 mg	1 day	1. Morning stiffness; 2. Pain (0-10 cm VAS); 3. Sleep; 4. Adverse events
Huskisson 1974[38]	30 + 24 (2 small trials), crossover trial, 18 days	Trial 1: paracetamol 650 mg + dextropropoxyphene 65 mg; Trial 2: 1. aspirin 1000 mg + codeine 16 mg ; 2. paracetamol 650 mg + dextropropoxyphene 65 mg	Trial 1: 1. paracetamol 1000 mg; 2 pentazocine 50 mg; Trial 2: aspirin 600 mg	6 h	1. Pain relief score (0 - none, 1 - slight, 2 - moderate, 3 - complete); 2. Preference for treatment
Kean 1981[39]	24, crossover trial, 2 wks	Enteric coated aspirin 3.6g + azapropazone 1200 mg	1. Enteric coated aspiring 3.6 g 2. Azapropazone 1200 mg	1 week	1. Pain score (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe); 2. Patient global assessment; 3. Severity of morning stiffness; 4. Grip strength; 5. Joint circumference; 6. Articular index
Malcolm 1974[40]	17, crossover trial, 8 wks	Benorylate (aspirin + paracetamol) 8 g	Indomethacin 75 mg	3 wks	1. Pain (0 = none, 1 = mild, 2 = moderate, 3 = severe); 2. Tenderness; 3. Grip strength; 4. Finger swelling; 5. Overall clinical assessment
Mavrikakis 1977[41]	18, crossover trial, 3 wks	Benorylate (aspirin + paracetamol) 6 g	Ibuprofen 1600 mg	1 week	1. Pain (VAS scale?. ; 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
Mavrikakis 1977b[42]	18, crossover trial, 3 wks	Benorylate (aspirin + paracetamol) 6 g	Sulindac 400 mg	1 week	1. Pain (VAS scale?); 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
Mowat 1979[43]	31, crossover trial, 8 wks	Benorylate (aspirin + paracetamol) 4 g (up to 8 g)	Naproxen 500 mg (up to 1 g)	4 wks	1. Pain (0-10cm VAS); 2. Morning stiffness; 3. Joint pain on full range of active movement; 4. Adverse events
Puttini 1988[44]	60, parallel RCT, 7 wks	Dothiepin 75 mg + ibuprofen 1800 mg	Ibuprofen 1800 mg	4 wks	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 (0-100 mm 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
Saarialho-Kere[45]	16, crossover trial, 12 days	Dextropropoxyphene 65 mg + amitriptyline 25 mg	1. Dextropropoxyphene 130 mg 2. Indomethacin 50 mg	4 h	1. Pain (0-100 mm VAS); 2. Duration of morning stiffness; 3. Grip strength; 4. Articular index; 5. Several psychomotor skills
Seideman 1988[46]	20, crossover trial, 5 wks	Indomethacin 50 mg + paracetamol 4 g	Indomethacin 150 mg	Average of 2nd week	1. Pain (0-100 mm VAS. ; 2. Duration of morning stiffness; 3. Grip strength; 4. Number of joints painful to digital pressure; 5. Joint circumference
Seideman 1993[47]	20, crossover trial, 5 wks	1.Naproxen 500 mg + paracetamol 4 g; 2. naproxen 1000 mg + 4 g	1. Naproxen 500 mg 2. Naproxen 1000 mg	2 wks	1. Number of joints painful to digital pressure or passive movements; 2. Duration of morning stiffness; 3. Pain (0-100 mm VAS); 4. Global assessment of disease activity; 5. Activity of daily living assessment
Sharma 1978[48]	18, crossover trial, 3 days	1. Sulindac 200 mg + diazepam 100 mg ; 2. Indomethacin 100 mg + diazepam 10 mg	Sulindac 200 mg	1 day	1. Duration of morning stiffness; 2. Night pain (0-10 cm VAS); 3. Quality of sleep; 4. Adverse events
Sperryn 1973[49]	41, parallel RCT, 13 wks	Benorylate (aspirin + paracetamol) 6 g	Aspirin 4g	12 wks	1. Pain severity (1 = mild, 2 = moderate, 3 = severe); 2. Number of inflamed joints; 3. Morning stiffness; 4. Articular index; 5. Grip strength; 6. Functional status
Staunton 1980[50]	18, parallel RCT, 6 wks	Diflunisal 500 mg + indomethacin 75 mg	Indomethacin 75 mg	4 wks	1. Ritchie articular index; 2. Grip strength; 3. Morning stiffness; 4. Pain during the day and during the night (1 = none; to 4 = very severe pain); 5. Physician's global evaluation; 6. Patient's global evaluation

In several of the studies, the monotherapy drug was not part of the combination therapy; for example, 1 trial compared phenylbutazone to aspirin and paracetamol[30], while another trial compared naproxen to aspirin and paracetamol[43]. In other trials, despite the monotherapy drug being part of the combination therapy, their dosages differed: for example, one trial compared paracetamol 650 mg and dextropropoxyphene 65 mg to paracetamol 1000 mg[38] while another trial compared dextropropoxyphene 65 mg and amitriptyline 25 mg to dextropropoxyphene 130 mg[45].

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

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

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

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

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

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

NSAID + NSAID versus NSAID (5 studies). Four studies[33,34,39,50] found no significant differences between the
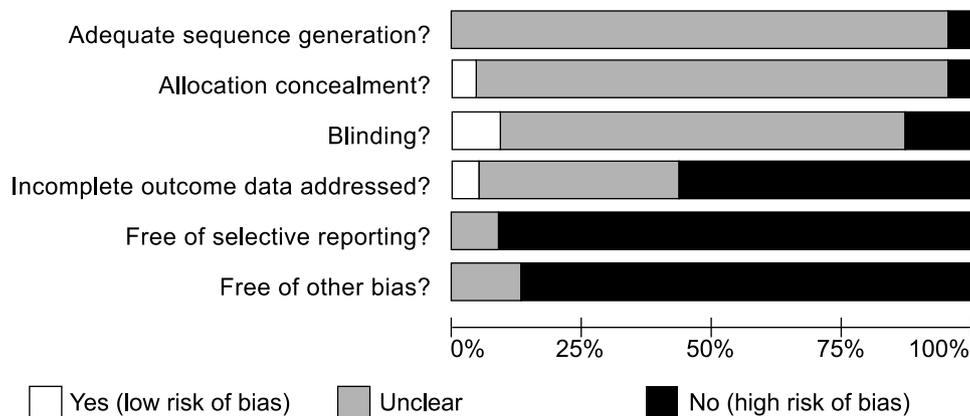

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all studies.

treatment arms. One study, Ekstrand, *et al* 1981[32], reported a median pain score (0 to 100 VAS) over 3 weeks of 43 for those who received acetylsalicylic acid 2 g + indomethacin 50 mg compared with a score of 53 for those who received acetylsalicylic acid 2 g alone (no baseline values were reported; p < 0.05).

NSAID + neuromodulator versus NSAID (3 studies). All trials[37,44,48] reported no significant differences between combination therapy and monotherapy.

Opioid + NSAID versus NSAID (1 study). Bedi 1969[29] found no significant difference between the treatment arms.

Opioid + analgesic versus analgesic (1 study). Huskisson 1974[38] found no significant difference between the treatment arms.

Opioid + neuromodulator versus opioid (1 study). Saarialho-Kere, *et al* 1988[45] reported worse pain control with a combination of dextropropoxyphene 65 mg + amitriptyline 25 mg versus dextropropoxyphene 130 mg alone [mean pain score (0 to 100 VAS) at baseline 50 (SD 6.6) and at 4 hours 44 (SD 6.6) vs 46 (SD 6.0) and 34 (SD 4.8), respectively; p < 0.05]. However, participants in the monotherapy arm received double the dose of opioid compared to those in the combination therapy arm.

Function and withdrawals due to inadequate analgesia. Of the 3 trials that reported function[33,46,47], 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[38,39,40,41,42,44,45,47], 7 studies reported no withdrawals due to inadequate analgesia in both study arms, and the remaining 8 trials reported some withdrawals due to inadequate analgesia in at least 1 of the study arms[28,30,31,33,34,35,43,49]. 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[30]. 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, were incompletely reported in the trials. Eight trials did not report this outcome at all, 5 trials reported that there were no withdrawals due to adverse events, and the remaining 10 trials reported a few withdrawals due to adverse events in at least 1 of the study arms[28, 29, 30, 31, 33, 34, 37, 40, 43, 49]. For these 10 trials, there was no significant difference in the proportion of withdrawals due to adverse events between monotherapy and combination therapy arms (analysis performed by the authors of the review). No deaths were reported in the 18 trials that either directly or indirectly reported on this outcome.

Of the 10 trials that reported on the number of participants with adverse events[29,31,35,36,37,40,43,46,48,49] all but one reported no differences between the combination and monotherapy arms. Seideman and Melander 1988[46] reported that 55% (11/20) of those who received combination therapy (indomethacin 50 mg + paracetamol 4 g) had at least 1 adverse event compared to 20% (4/20) of those who received indomethacin 150 mg alone (p = 0.05). Due to a lack of data, subgroup or sensitivity analyses could not be performed.

DISCUSSION

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

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

The risk of bias of all trials was high. Generation of an adequate randomization sequence and concealment of treatment allocation were poorly performed and/or reported, and participants with missing data were often excluded from the analysis. Further, the included trials were very small, and statistically significant results from small trials can easily be wrong[52]; while 17 of the 23 included studies were crossover trials, which implies the possibility of carryover and period effects. The interventions studied were heterogeneous in terms of drug combinations, treatment duration, drug class, drugs, and dosages. The comparator was also a source of heterogeneity and in several studies the monotherapy drug was not part of the combination therapy, precluding meaningful comparison for the purpose of our review.

The outcomes measured, how and when they were measured, and how the results were reported also varied widely between trials. For example, some trials measured pain while others measured improvement in pain; some used VAS for pain while others used a categorical scale; and some trials did

not report baseline and/or end values and/or change scores. None of the included trials reported any of the 4 dichotomous pain outcomes we had planned to assess as recommended by the Cochrane Pain, Palliative and Supportive Care Systematic Review Group editors and others for systematic reviews on chronic pain[25]. Group means for continuous measures of pain are difficult to interpret in terms of their clinical relevance as the underlying distribution is often skewed[25].

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

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

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

REFERENCES

1. Bergman MJ. Social and economic impact of inflammatory arthritis. Postgrad Med 2006;Spec No:5-11.
2. Gabriel SE. The epidemiology of rheumatoid arthritis. Rheum Dis Clin North Am 2001;27:269-81.
3. Braun J, Bollow M, Remlinger G, Eggens U, Rudwaleit M, Distler A, et al. Prevalence of spondylarthropathies in HLA-B27 positive and negative blood donors. Arthritis Rheum 1998;41:58-67.
4. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964-75.
5. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: Recommendations of an international task force. Ann Rheum Dis 2010;69:631-7.
6. Kvien TK. Epidemiology and burden of illness of rheumatoid arthritis. Pharmacoeconomics 2004;22:1-12.
7. Kazis LE, Meenan RF, Anderson JJ. Pain in the rheumatic diseases. Investigation of a key health status component. Arthritis Rheum 1983;26:1017-22.
8. Minnock P, Fitzgerald O, Bresnihan B. Quality of life, social support, and knowledge of disease in women with rheumatoid arthritis. Arthritis Rheum 2003;49:221-7.
9. da Silva JA, Ramiro S, Pedro S, Rodrigues A, Vasconcelos JC, Benito-Garcia E. Patients — and physicians — priorities for improvement. The case of rheumatic diseases. Acta Reumatol Port 2010;35:192-9.
10. Heiberg T, Kvien TK. Preferences for improved health examined in 1,024 patients with rheumatoid arthritis: Pain has highest priority. Arthritis Rheum 2002;47:391-7.
11. ten Klooster PM, Veehof MM, Taal E, van Riel PL, van de Laar MA. Changes in priorities for improvement in patients with rheumatoid arthritis during 1 year of anti-tumour necrosis factor treatment. Ann Rheum Dis 2007;66:1485-90.
12. Ramiro S, Radner H, van der Heijde D, van Tubergen A, Buchbinder R, Aletaha D, et al. Combination therapy for pain management in inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis). Cochrane Database Syst Rev 2011;10:CD008886.
13. Sidiropoulos PI, Hatemi G, Song IH, Avouac J, Collantes E, Hamuryudan V, et al. Evidence-based recommendations for the management of ankylosing spondylitis: Systematic literature search of the 3E Initiative in Rheumatology involving a broad panel of experts and practising rheumatologists. Rheumatology 2008;47:355-61.
14. Visser K, Katchamart W, Loza E, Martinez-Lopez JA, Salliot C, Trudeau J, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: Integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis 2009;68:1086-93.
15. Machado P, Castrejon I, Katchamart W, Koevoets R, Kuriya B, Schoels M, et al. Multinational evidence-based recommendations on how to investigate and follow-up undifferentiated peripheral inflammatory arthritis: Integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis 2011;70:15-24.
16. Whittle SL, Colebatch AN, Buchbinder R, Edwards CJ, Adams K, Englbrecht M, et al. Multinational evidence-based recommendations for pain management by pharmacotherapy in inflammatory arthritis: Integrating systematic literature research and expert opinion of a broad panel of rheumatologists in the 3e Initiative. Rheumatology 2012 Mar 24. [Epub ahead of print]
17. Higgins J, Green S, editors. Cochrane handbook for systematic reviews of interventions, Version 5.0.2. Chichester: The Cochrane Collaboration and John Wiley & Sons Ltd.; 2009.
18. Sackett DL, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine: How to practice and teach EBM. London: Churchill Livingstone; 1997.
19. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45.
20. Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. Arthritis Rheum 1983;26:1346-53.
21. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: The development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281-5.
22. Ware JE, Kosinski M. SF-36 Physical and Mental Health Summary Scales: manual for users. Version 1. 2nd ed. Lincoln, RI: Quality Metric; 2001.
23. de Jong Z, van der Heijde D, McKenna SP, Whalley D. The reliability and construct validity of the RAQoL: A rheumatoid arthritis-specific quality of life instrument. Br J Rheumatol

1997;36:878-83.

24. Doward LC, Spoorenberg A, Cook SA, Whalley D, Helliwell PS, Kay LJ, et al. Development of the ASQoL: A quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis 2003;62:20-6.

25. Andrew Moore R, Eccleston C, Derry S, Wiffen P, Bell RF, Straube S, et al. "Evidence" in chronic pain — establishing best practice in the reporting of systematic reviews. Pain 2010;150:386-9.

26. Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions, Version 5.0.1 (updated September 2008). The Cochrane Collaboration; 2008. Available from: www.cochrane-handbook.org.

27. Higgins J, Altman D. Assessing risk of bias in included studies. Ch. 8. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. The Cochrane Collaboration; 2008.

28. Beales D, Burry H, Grahame R. Comparison of aspirin and benorylate in the treatment of rheumatoid arthritis. Br Med J 1972;2:483-5.

29. Bedi S. Comparison of aspirin and dextropropoxyphene-with-aspirin as analgesics in rheumatoid arthritis. Br J Clin Pract 1969;23:413-7.

30. Brooks P, Walker J, Lee P, Bell A, Buchanan W, Fowler P, et al. Clinical study on a new acetylsalicylic acid/paracetamol preparation with gastric acid resistant coating (Safapryn), and on two various phenylbutazone dosages in patients with primary chronic polyarthritis as based on a new evaluation method. Z Rheumatol 1975;34:350-65.

31. Coigley M. Comparison of benorylate and indomethacin in the symptomatic control of arthritic disorders. Practitioner 1975;215:348-52.

32. Ekstrand R, Alvan G, Magnusson A, Oliw E, Palmer L, Rane A. Additive clinical effect of indomethacin suppositories during salicylate therapy in rheumatoid patients. Scand J Rheumatol 1981;10:69-75.

33. Furst DE, Blocka K, Cassell S, Harris ER, Hirschberg JM, Josephson N, et al. A controlled study of concurrent therapy with a nonacetylated salicylate and naproxen in rheumatoid arthritis. Arthritis Rheum 1987;30:146-54.

34. Grennan DM, Ferry DG, Ashworth ME, Kenny RE, Mackinnon M. The aspirin-ibuprofen interaction in rheumatoid arthritis. Br J Clin Pharmacol 1979;8:497-503.

35. Haslock D, Nicholson P, Wright V. A comparison of phenylbutazone and benorylate. Clin Trials J 1971;8:43-50.

36. Hingorani K. Double blind study of benorylate and ibuprofen in rheumatoid arthritis. Rheumatol Rehabil 1973;12:39-47.

37. Hobkirk D, Rhodes M, Haslock I. Night medication in rheumatoid arthritis: II. Combined therapy with indomethacin and diazepam. Rheumatol Rehabil 1977;16:125-7.

38. Huskisson EC. Simple analgesics for arthritis. Br Med J 1974;4:196-200.

39. Kean WF, Kraag GR, Rooney PJ, Capell HA. Clinical therapeutic trial of aspirin and azapropazone in rheumatoid arthritis when prescribed singly and in combination. Curr Med Res Opin 1981;7:164-7.

40. Malcolm A. A comparative clinical trial of benorylate and indomethacin in the treatment of active rheumatoid arthritis in general practice. J Int Med Res 1974;2:66-70.

41. Mavrikakis M, McLeod M, Hernandez L, El-Ghobarey A, Cappel H. Comparison of benorylate tablets with ibuprofen in rheumatoid arthritis. Pharmatherapeutica 1977;1:621-4.

42. Mavrikakis M, Madkour M, Spencer D, Balint G. Double-blind study comparing the therapeutic effect of a new non-steroidal anti-inflammatory drug, sulindac, with benorylate in tablet form in rheumatoid arthritis. Pharmatherapeutica 1977;1:681-5.

43. Mowat AM, Mowat AG. A comparative trial of naproxen and benorylate suspensions in the treatment of rheumatoid arthritis. Eur J Rheumatol Inflamm 1979;2:74-8.

44. Puttini P, Cazzola M, Boccassini L, Ciniselli G, Santandrea S, Caruso I, et al. A comparison of dothiepin versus placebo in the treatment of pain in rheumatoid arthritis and the association of pain with depression. J Int Med Res;16:331-7.

45. Saarialho-Kere U, Julkunen H, Mattila M, Seppälä T. Psychomotor performance of patients with rheumatoid arthritis: Cross-over comparison of dextropropoxyphene, dextropropoxyphene plus amitriptyline, indomethacin, and placebo. Pharmacol Toxicol 1988;63:286-92.

46. Seideman P, Melander A. Equianalgesic effects of paracetamol and indomethacin in rheumatoid arthritis. Br J Rheumatol 1988;27:117-22.

47. Seideman P. Additive effect of combined naproxen and paracetamol in rheumatoid arthritis. Br J Rheumatol 1993;32:1077-82.

48. Sharma BK, Haslock I. Night medication in rheumatoid arthritis. III. the use of sulindac. Curr Med Res Opin 1978;5:472-5.

49. Sperryn PN, Hamilton EB, Parsons V. Double-blind comparison of aspirin and 4-(acetamido) phenyl-2-acetoxy-benzoate (benorylate) in rheumatoid arthritis. Ann Rheum Dis 1973;32:157-61.

50. Staunton S, Moran C. Diflunisal plus indomethacin as concomitant therapy in rheumatoid arthritis. Eur J Rheumatol Inflamm 1980;3:187-93.

51. Dougados M, Simon P, Braun J, Burgos-Vargas R, Maksymowych WP, Sieper J, et al. ASAS recommendations for collecting, analysing and reporting NSAID intake in clinical trials/epidemiological studies in axial spondyloarthritis. Ann Rheum Dis 2011;70:249-51.

52. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. Br J Cancer 1976;34:585-612.

53. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain 2010;150:573-81.