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USO DE ANTI-INFLAMATÓRIOS ESTEROIDES E NÃO ESTEROIDES NO TRATAMENTO DA ARTRITE REUMATOIDE: REVISÃO SISTEMÁTICA E META-ANÁLISE

Sorocaba/SP
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Tese apresentada à Banca Examinadora do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba, como exigência parcial para obtenção do título de Doutor em Ciências Farmacêuticas.

Orientadora: Profa. Dra. Cristiane de Cássia Bergamaschi Motta

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À Deus, por ser essencial. Seu fôlego de vida me dá coragem para propor sempre υm novo mundo de possibilidades.

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"Ninguém escapa ao sonho de voar, de ultrapassar os limites do espaço onde nasceu, de ver novos lugares e novas gentes. Mas saber ver em cada coisa, em cada pessoa, aquele algo que a define como especial, um objeto singular, um amigo, é fundamental. Navegar é preciso, reconhecer o valor das coisas e das pessoas, é mais preciso ainda."

(Antoine de Saint-Exupery)

RESUMO

Sintomas incapacitantes da artrite reumatoide afetam aproximadamente 1% da população mundial e são frequentemente multifatoriais. Anti-inflamatórios não esteroides (AINES) e esteroides (AIES) são coadjuvantes usados no tratamento da doença; entretanto, as evidências são inconclusivas e não estão atualizadas sobre quais anti-inflamatórios são mais eficazes e seguros. O objetivo do estudo foi avaliar a efetividade e a segurança dos AINES e AIES no tratamento da artrite reumatoide, por meio de uma revisão sistemática com meta-análise. As bases de dados eletrônicas pesquisadas foram: CENTRAL; MEDLINE; EMBASE, CINAHL; *Web of Science*; entre outros. Os ensaios clínicos randomizados que compararam os anti-inflamatórios com placebo ou controles ativos foram avaliados. Revisores, aos pares e independentemente, selecionaram os estudos, realizaram extração dos dados e avaliaram o risco de viés. Desfechos primários incluíram dor, função física, rigidez matinal, número de articulações inchadas e doloridas, força de preensão, progressão da doença por imagem radiológica e qualidade de vida. Desfechos secundários incluíram eventos adversos e sua gravidade, satisfação com o tratamento e consumo de medicamentos de resgate. A qualidade da evidência foi aferida pelo *Grading of Recommendatons Assessment, Development and Evaluaton.* Meta-análises de rede foram realizadas para AINES, usando o Stata v.14.2. Dos 26 estudos selecionados, 21 reportaram o uso de AINES e 5 o uso de AIES. Naproxeno 1.000 mg melhorou a função física, reduziu a dor e o número de articulações dolorosas em comparação com o placebo (evidência de qualidade muito baixa). O etoricoxibe 90 mg comparado ao placebo reduziu o número de articulações dolorosas (evidência de baixa qualidade). Naproxeno 750 mg foi mais efetivo na redução do número de articulações edemaciadas quando comparado a todos os medicamentos, exceto o etoricoxibe 90 mg (evidência de qualidade muito baixa). Naproxeno 1.000 mg, etoricoxibe 90 mg e diclofenaco 150 mg foram melhores que o placebo na avaliação geral dos pacientes (evidências de qualidade muito baixa, baixa e alta, respectivamente). A avaliação geral do médico mostrou que qualquer AINE era melhor que o placebo, exceto celecoxibe 400 mg (evidência de qualidade muito baixa). Etoricoxibe 90 mg foi melhor que celecoxibe 400 mg (evidência de qualidade muito baixa) e naproxeno 1.000 mg (evidência de baixa qualidade). O etoricoxibe 90 mg foi o AINE com mais eventos adversos e o celecoxibe 200 mg o que apesentou menos eventos adversos, no entanto, a evidência é de qualidade muito baixa. Meta-análises não foram realizadas para AIES. Prednisolona 10 mg associada à ciclosporina reduziu a erosão articular em comparação com o metotrexato ou o uso de prednisolona com o metotrexato. Prednisona 5 mg com metotrexato reduziu o dano articular e a atividade da doença. A progressão radiográfica foi menor no grupo da prednisona 7,5 mg em comparação ao placebo. Naproxeno foi o medicamento mais efetivo e celecoxibe o que apresentou menos eventos adversos. No entanto, a baixa qualidade das evidências observadas nos resultados com AINEs; a ausência de meta-análises para avaliar os resultados com a AIES, bem como o risco de viés observado nos estudos, indica que novos ensaios clínicos randomizados podem confirmar esses achados.

Palavras-chave: Artrite reumatoide. Anti-inflamatórios não esteroides. Anti-inflamatórios esteroides. Corticoides. Revisão sistemática. Meta-análises de rede.

ABSTRACT

Rheumatoid arthritis (RA) affects approximately 1% of the world population. Symptoms of the disease are disabling and often multifactorial. Non-steroidal anti-inflammatory drugs (NSAIDS) and steroids (SAIDS) are co-adjuvants used for treatment of the disease; however, evidence is inconclusive and not up to date as to which anti-inflammatories are most effective and safe. The aim of this study was to evaluate effectiveness and safety of SAID and NSAID on the treatment of RA by carrying out a systematic review and meta-analysis. The following electronic databases were searched: CENTRAL; MEDLINE; EMBASE, CINAHL; Web of Science; among others. Randomized controlled trials (RCTs) which compared NSAIDs or SAIDS therapies with placebo or active controls were assessed. Reviewers, in pairs selected studies performed data extraction and assessed risk of bias. Primary outcomes of interest included pain, physical function, morning stiffness, number of swollen and painful joints, grip strength, disease progression as assessed by radiological imaging and quality of life. Secondary outcomes included frequency of patient reporting adverse events and their severity, satisfaction with current treatment and use of rescue medication. Quality of evidence was assessed according to Grading of Recommendations Assessment, Development and Evaluation. Network meta-analyses were performed using STATA software (version 14.2). Twenty-six articles were selected, 21 reporting use of NSAIDS and 5 the use of SAIDS. Naproxen 1,000 mg improved physical function and significantly reduced overall pain and the number of painful joints compared to placebo (evidence of very low quality). Etoricoxib 90 mg when compared to placebo was also able to reduce the number of painful joints (evidence of low quality). Naproxen 750 mg proved to be better than other drugs at reducing the number of swollen joints, except for etoricoxib 90 mg (evidence of very low quality). Naproxen 1,000 mg, etoricoxib 90 mg and diclofenac 150 mg were better than placebo regarding overall patient assessment (evidences of very low, low and high qualities, respectively). Overall assessment carried out by a physician showed that all NSAIDs were better than placebo, except celecoxib 400 mg (evidence of very low quality). Etoricoxib 90 mg was better than celecoxib 400 mg and naproxen 1,000 mg (evidence of low quality). Etoricoxib 90 mg was the NSAID associated with the most adverse events, while celecoxib 200 mg was associated with the fewest, but the evidence is of very low quality. Meta-analyses were not carried out for SAIDs. Prednisolone 10 mg associated with cyclosporine reduced joint erosion compared to the methotrexate alone group or to the methotrexate alongside prednisolone group. Methotrexate alongside prednisone 5 mg reduced joint damage and disease activity. Radiographic progression was lower in the prednisone 7.5 mg group compared to placebo. Naproxen was the most effective drug and celecoxibe the one with the fewest adverse events. However, the low quality of the evidence observed for the results with NSAIDS and the absence of meta-analyses to assess the outcomes with the SAIDS as well as the risk of bias observed in the studies allow us to conclude that further RCTs are needed to confirm such findings.

K**ey words:** Rheumatoid arthritis. Nonsteroidal anti-inflammatories. Steroid anti-inflammatories. Corticoids. Systematic review. Network meta-analyzes.

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LISTA DE ABREVIATURAS

ACR - *American College of Rheumatology* (Colégio Americano de Reumatologia)

AINEs- anti-inflamatórios não esteroides

AIEs - anti-inflamatórios esteroides

Anti-CCP - *anti-cyclic citrullinated peptides* (anticorpo do peptídeo citrulinado cíclico)

ARA - *American Association of Rheumatology* (Associação Americana de Reumatologia)

CENTRAL - *Cochrane Central Register of Controlled Trials*

CINAHAL - *Cumulative Index to Nursing and Allied Health Literature*

COX-2 - ciclooxigenase-2

DMP - diferença média padronizada

DMARDs - *Disease modifying antirheumatic drugs* (drogas antirreumáticas modificadoras de doença)

EMBASE - *Excerpta Medica Database*

EULAR - *European League Against Rheumatism* (Liga Europeia contra o Reumatismo)

GRADE - *Grading of Recommendatons Assessment, Development and Evaluaton*

HLA - *human leukocyte antigen* (Antígeno Leucocitário Humano)

CI - *Confidence interval*

Mesh - *Medical Subject Headings*

NR - *not reported*

NSAID - *non-steroidal anti-inflammatory drug*

PCR - proteína C reativa

PRISMA - *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*

PROSPERO - *International Prospective Register of Systematic Reviews*

RCT - *randomized clinical trials*

RR - *relative risk*

SAID - *steroid anti-inflammatory*

SD - *standard deviations*

SE - *standard error*

SMD - *standardized mean difference*

SUCRA - *Surface Under the Cumulative Ranking*

SUS - Sistema Único de Saúde

VHL - *Virtual Health Library*

WHO - *World Health Organization*

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1 APRESENTAÇÃO

Os sintomas incapacitantes da artrite reumatoide são comuns e frequentemente multifatoriais. Dentre os medicamentos utilizados em seu tratamento, os anti-inflamatórios não esteroides (AINEs) e esteroides (AIEs) são coadjuvantes no tratamento da dor e inflamação causadas pela doença.

As evidências a respeito do uso de AINEs e AIEs para o tratamento da artrite reumatoide não estão atualizadas e há incerteza a respeito de qual(is) anti-inflamatório(s) e em que dose, tempo de uso ou via de administração deve(m) ser recomendado(s). Embora pareça haver menor interesse atual em desenvolver ensaios clínicos envolvendo tais medicamentos, eles são prescritos e utilizados por pacientes com artrite reumatoide. Desta forma, a metanálise indireta pode ser uma estratégia que auxilie na avaliação das evidências de efetividade e segurança destes medicamentos e portanto, na tomada de decisão daqueles que se benficiariam com tais achados.

Em vista disso, a presente tese abordou o tema "Uso de anti-inflamatórios esteroides e não esteroides no tratamento da artrite reumatoide: revisão sistemática e meta-análise". O texto discute a efetividade e segurança desses medicamentos por meio de uma revisão sistemática e meta-análise de rede de ensaios clínicos randomizados.

Para maior clareza e organização, este trabalho foi estruturado em: referencial teórico, justificativa, objetivos, resultados e considerações finais.

O tópico "Referencial teórico" define a artrite reumatoide, apresenta sua prevalência, métodos de diagnóstico, métodos estimados para classificação da atividade da doença e as estratégias de tratamento. Dentre as possíveis opções terapêuticas, inclui-se a medicamentosa, sendo consideradas as classes dos medicamentos utilizados (com ênfase nos anti-inflamatórios), as vias de administração, as doses prescritas e o tempo de utilização.

O tópico "Objetivos" faz referência aos objetivos "geral" e "específicos" traçados por esse estudo.

O tópico "Resultados" está estruturado em um dos formatos adotado pelo Programa de Pós-graduação em Ciências Farmacêuticas da Uniso, o qual consiste em descrever os produtos desenvolvidos ao longo do curso de doutorado. Desta forma, o tópico 6.1 refere-se ao protocolo do estudo, publicado no periódico *Medicine*: "*Use of steroid and nonsteroidal anti-inflammatories in the treatment of rheumatoid arthritis systematic review protocol*" e o item 6.2, ao artigo com os dados completos deste protocolo intitulado: *"Use of steroid and non-*

steroidal anti-inflammatories in the treatment of rheumatoid arthritis: systematic review and network meta-analysis".

No tópico resultados, optou-se por inserir os textos na língua original da publicação ou submissão. A sequência numérica das tabelas e figuras foi reiniciada de acordo com o artigo científico.

O tópico "Considerações finais" discorre sobre os achados e conclusões da presente tese.

2 DECLARAÇÃO DE POTENCIAIS CONFLITOS DE INTERESSE

Autores: Mariana Del Grossi Paglia / Cristiane De Cassia Bergamaschi Motta

1. Você já aceitou de uma instituição, que pode se beneficiar ou se prejudicar financeiramente, algum dos benefícios abaixo?
a) Reembolso por comparecimento a eventos na área de sua pesquisa
Não / Não
b) Honorários por apresentação, consultoria, palestra ou atividades de ensino
Não / Não
c) Financiamento para redação de artigos ou editorias
Não / Não
d) Suporte para realização ou desenvolvimento de pesquisa na área
Não / Não
e) Recursos ou apoio financeiro para membro da equipe
Não / Não
f) Algum outro benefício financeiro
Não / Não

2. Você possui apólices ou ações de alguma empresa que possa de alguma forma ser beneficiada ou prejudicada?
Não / Não

3. Você possui algum direito de propriedade intelectual (patentes, registros de marca, royalties)?
Não / Não

4. Você já atuou como perito judicial?
Não / Não

5. Você participa, direta ou indiretamente, de algum grupo citado abaixo cujos interesses possam ser afetados pela sua atividade?
a) Instituição privada com ou sem fins lucrativos
Não / Não
b) Organização governamental ou não-governamental
Não / Não
c) Produtor, distribuidor ou detentor de registro
Não / Não
d) Partido político
Não / Não
e) Comitê, sociedade ou grupo de trabalho
Não / Não
f) Outro grupo de interesse
Não / Não

6. Você poderia ter algum tipo de benefício clínico?
Não / Não

7. Você possui uma ligação ou rivalidade acadêmica com alguém cujos interesses possam ser afetados?
Não / Não

8. Você possui profunda convicção pessoal ou religiosa que pode comprometer o que você irá escrever e que deveria ser do conhecimento público?
Não / Não

9. Existe algum aspecto do seu histórico profissional, que não esteja relacionado acima, que possa afetar sua objetividade ou imparcialidade?
Não / Não

10. Sua família ou pessoas que mantenha relações próximas possui alguns dos conflitos listados acima?
Não / Não

Confirmamos que todas as informações declaradas são verdadeiras e completas. Comprometemo-nos a informar se houver qualquer mudança em algumas das questões desta declaração que possa influenciar o interesse durante o desenvolvimento das atividades do Programa de Pós-Graduação em Ciências Farmacêuticas – Nível Mestrado da Universidade de Sorocaba.

Sorocaba, _____ de _____ de _____.

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3 REFERENCIAL TEÓRICO

3.1 Artrite reumatoide

Há mais de 200 doenças reumáticas e osteomusculares que compõem um grupo diversificado de doenças que acometem principalmente as articulações, mas podem afetar qualquer órgão do corpo. Geralmente, são causadas por problemas do sistema imunológico, inflamações e infecções, sendo progressivas e limitantes (VAN DER HEIJDE *et al.*, 2018).

Artrite reumatoide é a forma inflamatória autoimune mais comum de artrite. É uma doença crônica e progressiva, caracterizada por artralgia, rigidez matinal e edema, com potencial dano ósseo e cartilaginoso irreversível. Algumas vezes pode ter acometimento multissistêmico causando comorbidades como pleurite, doença pulmonar intersticial e doença ocular inflamatória e principalmente, comprometimentos cardiovasculares (KLARENBEEK *et al.*, 2010; SCOTT *et al.*, 2010).

As condições mais frequentes que levam as pessoas com artrite apresentarem tais comorbilidades são infeções, insuficiência renal, doenças cardiovasculares e linfomas (AMERICAN COLLEGE OF RHEUMATOLOGY, 2017; VENTADES et al., 2018).

Trata-se de uma condição que afeta aproximadamente 1 em 100 pessoas em todo o mundo (CROSS *et al.*, 2014). No Brasil, um estudo publicado em 2004 mostrou prevalência de 0,46%, representando quase um milhão de pessoas com essa doença (SENNA *et al.*, 2004; DA MOTA *et al.*, 2018). Afeta mulheres três vezes mais do que homens, em seus anos mais produtivos (WALLENIUS *et al.*, 2014). Embora haja registro de artrite reumatoide em todas as faixas etárias, a idade média para início dos sintomas geralmente é entre 40 e 60 anos (SILMAN; PEARSON, 2002).

Os custos relacionados à artrite reumatoide são elevados, licenças médicas e aposentadoria precoce são os principais responsáveis pela maioria dos custos indiretos (DE AZEVEDO; FERRAZ; CICONELLI, 2008). As consequências da doença na qualidade de vida dos pacientes são importantes e geram impacto econômico na sociedade (KOBELT *et al.*, 2008; SCHOELS *et al.*, 2010).

A etiologia da artrite reumatoide é complexa e em grande parte desconhecida. Há forte relação com fatores genéticos devido a presença de um antígeno leucocitário humano ou *Human Leukocyte Antigen (HLA*) ser mais comum em pacientes com esta condição. Estes alelos HLA codificam para uma sequência de aminoácidos que pode estar envolvida na patogênese desta

doença (AREND; FIRESTEIN, 2012). Fatores ambientais como tabagismo e infecções periodontais podem estar relacionados ao surgimento da doença (SZODORAY et al., 2010; AREND; FIRESTEIN, 2012).

A reposta inflamatória exagerada, padrão de infiltração de leucócitos e produção de citocinas, sugerem que a infecção pelo vírus Chikungunya pode estar relacionada como fator etiológico para doenças articulares crônicas e aumenta as chances de desenvolvimento associado de artrite reumatoide (NAKAYA et al., 2012; BURT; CHEN; MAHALINGAN, 2014).

O diagnóstico é realizado com base em manifestações clínicas, dessa forma, testes laboratoriais e radiográficos podem ser úteis na determinação de informações prognósticas, mas não são essenciais (DA MOTA *et al.*, 2013).

Para o diagnóstico deve-se considerar o tempo de evolução da artrite, a presença de auto anticorpos (quando disponível), a elevação de provas de atividade inflamatórias (proteína C-reativa, velocidade de hemossedimentação ou eletroforese de proteínas) e as alterações compatíveis em exames de imagem (CONITEC, 2019).

Os critérios para o diagnóstico da artrite reumatoide foram criados em 1987 pela Associação Americana de Reumatologia (*American Rheumatism Association* - ARA) (ARNETT *et al.*, 1988) (quadro 1) e revisados em 2010 pelo Colégio Americano de Reumatologia (*American College of Rheumatology* - ACR) e Liga Europeia Contra o Reumatismo (*European League Against Rheumatism* - EULAR) (ALETAHA *et al.*, 2010), a fim de auxiliar o diagnóstico precoce e orientar a terapia (quadro 2); desde que estudos sugerem forte correlação entre o tempo de início da doença e o alcance à remissão (VAN NIES *et al.*, 2014; VAN NIES *et al.*, 2015).

Os exames laboratoriais mais úteis para o diagnóstico da artrite reumatoide são: anticorpos anti-citrulina (anti-CCP), fator reumatóide, taxa de sedimentação dos eritrócitos, proteína C-reativa. O doseamento dos anticorpos anti-CCP apresenta uma elevada sensibilidade e especificidade diagnóstica (RUBENSTEIN; WAYNE; BRADLEY, 2010).

O diagnóstico precoce da artrite reumatoide pode ser preditor de remissão radiológica (BOSELLO *et al.*, 2011; MOUTERDE *et al.*, 2011), trazer impacto prognóstico funcional (WELSING; FRANSEN; VAN RIEL, 2005) e remissão sustentada do tratamento (VAN DER LINDEN *et al.*, 2010).

Quadro 1 - Critérios para diagnóstico da artrite reumatoide segundo Associação Americana de Reumatologia de 1987.

Critério / Definição
1. Rigidez matinal das articulações: duração de pelo menos 1 hora antes da melhora máxima
2. Artrite de 3 ou mais articulações: ao menos 3 articulações apresentam concomitantemente edema de partes moles ou derrame articular (e não supercrescimento ósseo isolado) identificados pelo médico. As 14 áreas articulares possíveis (direita e esquerda) são as articulações interfalangeanas proximais, metacarpofalangeanas, punho, cotovelo, joelho, tornozelo e articulações metatarsofalangeanas
3. Artrite nas articulações da mão: ao menos uma área articular apresenta o edema (punho, articulações metacarpofalangeanas ou interfalangeanas proximais)
4. Artrite simétrica: envolvimento simultâneo das mesmas áreas articulares em ambos os lados do corpo
5. Nódulos reumatoides: nódulos subcutâneos sobre as proeminências ósseas, superfícies extensoras ou regiões justa-articulares, que sejam identificados pelo médico
6. Fator reumatoide sérico: demonstração de quantidades anormais de fator reumatoide sérico
7. Alterações radiográficas: alterações radiográficas típicas da artrite reumatoide (erosões ou descalcificação óssea) detectadas por radiografia da mão e do punho

Nota: Para fins de classificação, um paciente é considerado portador de artrite reumatoide quando atende a pelo menos 4 dos 7 critérios descritos. Os primeiros 4 critérios devem ter duração mínima de 6 semanas.
Fonte: ARNETT, F. C. et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. **Arthritis & Rheumatism: Official Journal of the American College of Rheumatology**, v. 31, n. 3, p. 315-24, Mar 1988.

Quadro 2 - Critérios para diagnóstico da artrite reumatoide segundo os critérios Colégio Americano de Reumatologia e a Liga Europeia Contra o Reumatismo de 2010.

Critério / Definição	Pontos
Envolvimento articular	**(0-5)**
1 articulação média ou grande (ombros, cotovelos, quadril, joelhos e tornozelos)	0
2 a 10 articulações médias a grandes (ombros, cotovelos, quadril, joelhos e tornozelos)	1
1 a 3 articulações pequenas (articulações metacarpofalangeanas, interfalangeanas proximais, metatarsofalangeanas (2 a 5), interfalângicas do polegar e punhos - com ou sem envolvimento de articulações grandes)	2
4 a 10 articulações pequenas (articulações metacarpofalangeanas, interfalangeanas proximais, metatarsofalangeanas (2 a 5), interfalângicas do polegar e punhos - com ou sem envolvimento de articulações grandes)	3
>10 articulações (ao menos uma articulação pequena)	5
Sorologia	**(0-3)**
Negativa para fator reumatoide	0
Positiva baixa para fator reumatoide	2
Positiva alta para fator reumatoide	3
Reagentes de fase aguda	**(0-1)**
Normal para proteína C reativa e velocidade de sedimentação eritrocitária	0
Anormal para proteína C reativa e velocidade de sedimentação eritrocitária	1
Duração dos sintomas relatados pelo paciente	**(0-1)**
< 6 semanas	0
6 semanas	1

Nota: Para fins de classificação, um paciente é considerado portador de artrite reumatoide quando soma pelo menos 6 pontos do total de 10 descritos.
Fonte: ALETAHA, D. et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. **Arthritis & Rheumatology**, v. 62, n. 9, p. 2569-81, Sep 2010.

3.2 Estratégias terapêuticas

O gerenciamento ideal da artrite reumatoide implica que o tratamento seja iniciado o mais breve possível após a confirmação do diagnóstico, para evitar a progressão da doença e manter a capacidade funcional e qualidade de vida dos pacientes (BOMBARDIER *et al.*, 2012; DA MOTA *et al.*, 2012).

Alívio da dor, supressão do processo inflamatório, inibição da destruição da cartilagem articular e prevenção de deformidades articulares devem ser os objetivos do tratamento (WILLIAMS et al., 2015).

O tratamento multidisciplinar da artrite reumatoide é indispensável para o paciente, sendo composto por terapêutica medicamentosa e não medicamentosa (DA MOTA *et al.*, 2012).

3.2.1 Tratamento farmacológico da artrite reumatoide

O uso de medicamentos antirreumáticos modificadores de doença ou *Disease Modifying Antirheumatic Drugs* (DMARDs), sintéticos ou biológicos, para o manejo da artrite reumatoide é capaz de reduzir ou reverter sinais e sintomas, incapacidade, comprometimento da qualidade de vida, incapacidade para o trabalho e progressão do dano articular e, assim, interferir com todo o processo da doença (SMOLEN *et al.*, 2014).

O metotrexato é o DMARD sintético usado como primeira estratégia de tratamento por ter ação mais rápida (VERSCHUEREN *et al.*, 2015) e menor custo (ISHAQ *et al.*, 2011). No entanto, pacientes que possuem falha ou toxicidade a este tratamento, podem se beneficiar com outros fármacos do grupo, como sulfassalazina ou leflunomida (SMOLEN *et al.*, 2017).

A terapia tripla de DMARDs (metotrexato, sulfasalazina e hidroxicloroquina) ou dupla (metotrexato e leflunomida) podem ser mais eficazes do que iniciar com a monoterapia com metotrexato (OSIRI *et al.*, 2003; DONAHUE *et al.*, 2012; DE JONG *et al.*, 2013; HAZLEWOOD *et al.*, 2016). Se o benefício esperado não for obtido dentro de 6 meses, o tratamento deve ser modificado para outro DMARD sintético ou biológico, como os inibidores do fator de necrose tumoral, abatacepte ou tocilizumabe (STREHL *et al.*, 2016; SMOLEN *et al.*, 2017).

Para pacientes que não respondem ao tratamento inicial, a adição de um DMARD biológico (abatacepte, adalimumabe, certolizumabe pegol, etanercepte, golimumabe, infliximabe, rituximabe ou tocilizumabe) ao metotrexato pode ser considerada (VAN VOLLENHOVEN *et al.*, 2012; SINGH, *et al.*, 2016; CONITEC, 2019).

Em situações em que a terapia precise ser modificada, é recomendado que além da atividade da doença, sejam avaliados outros fatores, como por exemplo, progressão de danos estruturais, comorbidades e questões relacionadas à segurança no uso dos medicamentos (SMOLEN *et al.*, 2014). Atualmente os agentes biológicos disponíveis no Sistema Único de Saúde (SUS) para o tratamento da artrite reumatoide são infliximabe, adalimumabe e etanercepte (TERAPÊUTICAS, 2017).

Os anti-inflamatórios esteroides (AINEs) e não esteroides (AIEs) são coadjuvantes no tratamento da dor e inflamação causadas pela artrite reumatoide e a literatura têm reportado benefícios destes medicamentos na melhoria dos sintomas desta doença (SMOLEN *et al.*, 2014; VAN WALSEM *et al.*, 2015; SMOLEN *et al.*, 2017).

A dor em pessoas com artrite reumatoide faz com que estas recorram para o uso de analgésicos e anti-inflamatórios (COLEBATCH *et al.*, 2011). Os AINEs não são capazes de modificar ou impedir a progressão da doença, mas podem ser prescritos para controle sintomático, enquanto espera-se os efeitos das DMARDs sintéticos ou biológicos, optando-se pelo uso da menor dose pelo menor tempo possível (EMERY, 2006; CONITEC, 2019).

A combinação de DMARD sintética com um AIE (corticoide) é recomendada como terapia de primeira escolha e deve ser iniciada logo que o diagnóstico de artrite reumatoide for estabelecido (SINGH, *et al.*, 2016; STREHL *et al.*, 2016; CHATZIDIONYSIOU *et al.*, 2017; SMOLEN *et al.*, 2017).

3.2.1.1 Uso de anti-inflamatórios não esteroides (AINES) e os riscos associados

Os AINEs estão entre os medicamentos mais utilizados no mundo. As principais causas destacam-se a grande facilidade de acesso, pois o receituário médico não é necessário para compra e também ao fato da população idosa possuir concomitantes doenças reumatológicas (BATLOUNI, 2010; MELGAÇO *et al.*, 2010).

Os AINES possuem ação terapêutica anti-pirética, analgésica e anti-inflamatória, suas propriedades são utilizadas na artrite reumatoide principalmente na redução da dor e edema articulares (WALKER; WHITTLESEA, 2012).

O principal mecanismo de ação dos AINEs é a inibição das enzimas ciclooxigenases, que são descritas em dois tipos: COX-1 e COX-2. A COX-1 regula a produção de muco protetor gástrico, a inibição da secreção gástrica, a homeostase vascular e a função renal; já a COX-2 é ativada nos processos inflamatórios, participando da ativação de mastócitos, macrófagos e células endoteliais (RAHMAN *et al*., 2006). A inibição da COX-2 está mais associada às propriedades anti-inflamatórias enquanto que a inibição da COX-1 relaciona-se em maior proporção com efeitos indesejáveis, principalmente gastrointestinais (KUMMER; COELHO, 2002; BOSWELL*;* KWONG; KAVANAGH, 2010; NG; CHAN, 2010; CONAGHAN, 2012).

O risco de efeitos adversos especialmente em pacientes com comprometimento hepático é grande, pois alguns medicamentos são metabolizados pelo fígado. Dessa forma, a recomendação é de que os AINEs sejam utilizados pelo menor tempo e dose necessária (RADNER *et al.*, 2012).

Na tentativa de diminuir os efeitos adversos, AINES inibidores seletivos da COX-2, como celecoxibe e etoricoxibe, foram desenvolvidos. Porém, no endotélio, a COX-2 leva à

formação de prostaglandina que possui um efeito vasodilatador e inibidor da agregação plaquetária, gerando maior risco cardiovascular, trombótico e aumento da pressão arterial (QUAN *et al*., 2009; ROUBILLE *et al.*, 2015).

Tanto a COX-1 como a COX-2 estão presentes nos rins, dessa forma, todas as classes de AINEs podem causar toxicidade renal, resultando em síndrome nefrótica e nefrite intersticial (QUAN *et al*., 2009).

Vários são os AINEs que podem ser usados no tratamento da artrite reumatoide. Recomenda-se como primeiras opções ibuprofeno, naproxeno, diclofenaco de potássio ou diclofenaco de sódio em pacientes com leve, moderada ou alta atividade da doença (BMJ BEST PRATICE, 2018). No âmbito do SUS, ibuprofeno e naproxeno estão disponibilizados (CONITEC, 2019). O uso simultâneo de AINEs com metotrexato parece ser seguro, no entanto, autores não conseguiram responder qual AINE seria o mais indicado (COLEBATCH et al., 2011).

Embora a qualidade das evidências disponíveis seja classificadas como moderadas, o uso de piroxicam ou etodolaco não parece apresentar eventos adversos clinicamente significativos, já o uso de celecoxibe ou etoricoxibe foi associado a eventos adversos leves como náusea, vômito e dores de cabeça (COLEBATCH et al., 2011).

O risco de complicações gastrointestinais, especialmente sangramentos, foi relatado como efeito adverso relacionado ao uso de coxibes e AINEs em uma meta-análise. Houve aumento do risco cardiovascular com altas doses de diclofenaco e ibuprofeno, assim como de coxibes, enquanto altas doses de naproxeno estão associados a menor risco comparado aos outros AINEs (BHALA *et al.*, 2013).

3.2.1.2 Uso de anti-inflamatórios esteroides (AIES) e os riscos associados

Os corticoides são potentes anti-inflamatórios e possuem ação rápida (GOTZSCHE; JOHANSEN, 2005) quando administrados em associação com DMARDs. O uso sistêmico de prednisona ou prednisolona, em baixas doses (≤10 mg/dia) e por curtos períodos de tempo (<3 meses), podem contribuir para redução sintomas e progressão radiográfica (CHOY *et al.*, 2008; BAKKER *et al.*, 2012; BIJLSMA, 2012; MONTECUCCO *et al.*, 2012; KUME *et al.*, 2013; SAFY *et al.*, 2017; DA MOTA *et al.*, 2018).

Os corticoides atuam inibindo a libertação de citocinas que auxiliam no alívio dos sintomas e a redução da inflamação. A administração pode ser feita através da via oral,

intramuscular ou intra-articular (WALKER; WHITTLESEA, 2012). O tratamento recomendado geralmente envolve doses diárias baixas de prednisona oral (1 a 10 mg/dia), sendo que doses maiores que 10 mg são necessárias apenas em casos de alta atividade da doença (BMJ BEST PRATICE, 2018; VERSCHUEREN *et al.*, 2015). Regimes de diminuição gradual com a finalidade de atingir a menor dose de manutenção possível devem ser idealizados (WALKER; WHITTLESEA, 2012).

Os sintomas matinais da artrite reumatoide estão ligados ao aumento circadiano da inflamação noturna e pela secreção inadequada de cortisol na doença ativa. Diante disso, o uso diário de formulações de corticoides de liberação noturna, como prednisona 5 mg (BUTTEGEREIT *et al.*, 2013) ou prednisolona <5 mg (PAOLINO; CUTOLO; PIZZORNI, 2017) mostraram-se eficazes para o tratamento da artrite reumatoide em alguns ensaio clínicos randomizados, pois possibilitam um melhor aproveitamento do fármaco pelo organismo.

Segundo a Sociedade Brasileira de Reumatologia, se os sintomas da doença estiverem ativos em uma ou algumas articulações, corticoides intra-articulares podem aliviar temporariamente os sintomas, mas não devem ser aplicados mais de três a quatro vezes por ano em uma mesma articulação (DA MOTA *et al.*, 2012).

A prednisolona é efetiva em doses baixas (não excedendo 15 mg/dia) em pacientes com artrite reumatoide. Este fármaco apresenta melhores efeitos quando comparada ao tratamento com AINEs para a redução da sensibilidade articular (diferença de média padronizada - DMP: -0,63, IC 95%: -1,16 a -0,11) e dor (DMP: -1,25, IC 95%: -2,24 a -0,26). No entanto, a heterogeneidade das evidências disponíveis e as informações escassas sobre os medicamentos e doses utilizadas, impossibilita chegar à conclusão sobre o anti-inflamatório mais indicado para esta condição (GOTZSCHE; JOHANSEN, 2005).

A dose e frequência de injeção intra-articular varia de acordo com o local aplicado, mas é sugerido seu emprego para atividade leve, moderada ou alta da doença. Recomenda-se o uso de metilprednisolona 40-80 mg/dose a cada 1 à 5 semanas ou fosfato de sódio de dexametasona 0,2 à 6 mg/dose a cada 3 à 5 dias ou a cada 2 à 3 semanas (BMJ BEST PRATICE, 2018). As injeções são administradas localmente nas articulações alvo resultam em uma ação anti-inflamatória com alívio dos sintomas (WALKER; WHITTLESEA, 2012).

No Brasil, prednisona, prednisolona e metilprednisolona estão disponíveis no SUS para o tratamento da artrite reumatoide, sendo que a prednisolona oral é preferível em pacientes com disfunção hepática, pois não é metabolizada no fígado (CONITEC, 2019).

Tanto o uso de corticoides como de AINES está associado a um aumento de 47% e 18% no risco de todos eventos cardiovasculares, respectivamente, segundo uma revisão sistemática (ROUBILLE et al., 2015). Há dificuldade em concluir qual medicamento promoveu menos eventos adversos, pois muitos estudos incluídos apresentaram tratamento conjunto o que prejudica a relação risco-benefício dos corticoides e AINES separadamente (ROUBILLE *et al.*, 2015).

Eventos adversos como osteoporose, diabetes *mellitus*, doenças cardiovasculares, acidente vascular cerebral, infecções, ganho de peso e miopatias são relacionados ao uso de corticoides, especialmente quando usados em doses inadequadas e por períodos prolongados (VAN DER GOES *et al.*, 2010; ROUBILLE *et al.*, 2015).

3.2.2 Tratamento não farmacológico da artrite reumatoide

As ações de educação devem ser parte do tratamento para as artrites inflamatórias e podem melhorar a adesão ao tratamento (EL MIEDANY *et al.*, 2012), as habilidades de enfrentamento por meio do maior conhecimento sobre a doença (NETO *et al.*, 2009; KNITTLE; MAES; DE GUCHT, 2010), a saúde psicológica (BARSKY *et al.*, 2010; SHARPE; SCHRIEBER, 2012) e o envolvimento dos pacientes no tratamento da doença (LEUNG *et al.*, 2008).

Alterações na dieta e hábitos de vida são fundamentais, pois o uso de corticoides favorece a conservação de sódio e a excreção de grandes quantidades de potássio, por isso a dieta deve ser hipossódica e rica em potássio. Como a utilização de medicamentos pode comprometer a função hepática, o consumo de álcool deve ser restrito (QUEIROZ; 2011).

Pessoas que sofrem com artrite reumatoide possuem tendência a apresentar diminuição da funcionalidade (HAGEN et al., 2012) e são frequentemente encaminhadas aos fisioterapeutas e terapeutas ocupacionais para gerenciar os danos nas articulações, melhorar a função e reduzir a dor (HAMMOND, 2004; TUNTLAND *et al.*, 2009).

Uma revisão sistemática (KNOB *et al.*, 2016) mostrou que há poucas evidências sobre a efetividade da atividade física nesse grupo de pacientes. No entanto o que se sabe é que a prática de atividade física de moderada intensidade, por pelo menos 150 minutos semanais, e atividades de fortalecimento muscular, pelo menos duas vezes por semana, é recomendado para todos os indivíduos adultos. Assim é possível que gere bons resultados no tratamento de pacientes com essa doença.

O exercício físico também foi associado com reduções nos sintomas depressivos em adultos com artrite reumatoide, entre outras condições inflamatórias (KELLEY; KELLEY; HOOTMAN, 2015).

O treinamento físico pode ser benéfico para reverter a caquexia e melhorar a função física sem exacerbar a atividade da doença e é sugerido que o mesmo reduza o risco cardiovascular (COONEY *et al*., 2011). Hidroterapia, treino de força muscular e de resistência, alongamento e ciclismo são modalidades de exercícios recomendadas para os pacientes com artrite reumatoide (DA ROSA *et al*., 2018).

Revisão sistemática sobre intervenções não farmacológicas para estes pacientes retrata que a atividade física pode ser incluída para pacientes com esta condição, como estratégia para aumentar o nível diário geral de atividade ou como um regime específico de exercícios, por exemplo, caminhar ou andar de bicicleta por um período determinado e na intensidade desejada (CRAMP *et al*., 2013). Além disso, intervenções psicossociais como terapias comportamentais também podem ser orientadas a esse grupo de pacientes, pois proporcionam benefícios significativos em relação à fadiga (CRAMP *et al*., 2013).

4 OBJETIVOS

4.1 Geral

Avaliar a efetividade e a segurança dos anti-inflamatórios esteroides e não esteroides no tratamento da artrite reumatoide, por meio de uma revisão sistemática com meta-análise.

4.2 Específicos

Comparar desfechos de efetividade e segurança dos anti-inflamatórios com placebo ou outros tratamentos;

Estimar os eventos adversos decorrentes do uso dos fármacos estudados;

Definir a qualidade da evidência dos dados produzidos nesta revisão;

Identificar lacunas nas evidências atuais, avaliar suas implicações e fazer recomendações para pesquisas futuras.

5 RESULTADOS

Esta tese é apresentada no formato de artigo científico, elaborado conforme as recomendações do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba (anexo A).

O protocolo do estudo foi publicado no periódico *Medicine Journal* e é intitulado: "Use of steroid and nonsteroidal anti-inflammatories in the treatment of rheumatoid arthritis: systematic review protocol". O artigo científico que contém os resultados do protocolo é apresentado na sequência. Este artigo foi submetido ao periódico *Annals of the rheumatic diseases*, cujo comprovante segue abaixo.

Submission Confirmation

Thank you for your submission

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Use of steroid and non-steroidal anti-inflammatories in the treatment of rheumatoid arthritis: systematic review and network meta-analysis

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5.1 Title: Use of steroid and nonsteroidal anti-inflammatories in the treatment of rheumatoid arthritis: systematic review protocol.

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Abstract

Background Rheumatoid arthritis affects 1% of the world's population and its current treatment options are costly. There are not enough studies that evaluated the efficacy and safety of anti-inflammatory drugs medications used to reduce rheumatoid arthritis's symptoms. This study will evaluate the effectiveness and the safety of steroid and nonsteroidal anti-inflammatory drugs for the treatment of patients with rheumatoid arthritis. Methods Randomized clinical trials eligible for our systematic review will enroll adults with rheumatoid arthritis treated with anti- inflammatory drugs compared with a control group (placebo or active control) at any dose, duration, and route of administration and double blind studies. In order to include all forms of rheumatoid arthritis and anti-inflammatory drugs, we will search the following electronic databases: Cochrane Central Register of Controlled Trials, MEDLINE (via Ovid); ExcerptaMedica Database (via Ovid); Cumulative Index to Nursing and Allied Health Literature (via Ovid); Web of Science; ClinicalTrial.gov; and WHO International Clinical Trials Registry Platform. We will not impose any language restrictions or publication status. Outcomes of interest include are pain, physical function, swelling, stiffness, grip force, radiological image of the joint, quality of life, adverse events, discontinuation due to adverse events, satisfaction with the treatment, and rescue medication for pain. A team of reviewers will independently screen search results, extract data from eligible trials, and assess risk of bias. We will use the Grading of Recommendations Assessment, Development and Evaluation approach to rate overall certainty of the evidence by outcome. Dichotomous data will be summarized as risk ratios; continuous data will be given as standard average differences with 95% confidence intervals. Results The evidence derived by this study will increase awareness of the effectiveness and safety of steroid and nonsteroidal anti-inflammatory drugs for the treatment of rheumatoid arthritis. Conclusion The results could guide patients and healthcare practitioners and help facilitate evidence-based shared care decision making.

Keywords: corticosteroids, nonsteroidal anti-inflammatories, rheumatoid arthritis, steroid anti-inflammatories.

1. Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune, and systemic inflammatory disease of unknown etiology, which mainly affects joints and is characterized by symmetrical synovial inflammation, resulting in destruction of joint cartilage, signifi- cant pain,[1,2] and severe disability.[3] RA affects 1% of the population[4,5] and is more prevalent in women over 65 years.[1]

Arthritis in general has a significant impact on the quality of life of patients and society in terms of medical costs and disillusion- ment at work.[6] The chronic inflammatory process in uncon- trolled RA often results in functional disability. It is estimated that only 40% of these patients are able to work after 15 years of diagnosis. In addition to the associated morbidity, there is an increase in mortality; since the patients affected have a lower life expectancy compared the general population, mainly due to cardiovascular changes, the most common cause of death.[7]

Treatment of RA is based on pain relief, improvement of function, and prevention of joint damage.[8] Despite the significant advances in disease management, a study conducted in Europe and the United States with 2795 adults with RA showed that although patients presented the disease at a controlled stage, most reported dissatisfaction with the level of pain, predominantly classified as moderate to severe.[9]

According to the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), the current approach focuses on disease early treatment with synthetic or biological disease-modifying anti-rheumatic drugs (DMARDs) as soon as the diagnosis is completed.[10,11] The recommendation is to initiate the use of synthetic DMARD while the biological DMARD is usually recommended after its failure.[12] It is recommended during the first 3 months after the diagnosis of RA.[13]

As adjunctive therapy in the treatment of RA, symptomatic drugs that act in the control of pain and inflammation such as analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and steroids (corticosteroids) are recommended.[14]

NSAIDs inhibit cyclooxygenase enzymes (COX-1 and COX-2) and reduce pain and inflammation by restraining the formation of prostaglandins.[15] Due to the reduction of prostaglandins production in the gastrointestinal mucosa, NSAIDs can cause gastric damage and compromise cardiovascular safety.[16]

Corticosteroids exert a potent anti-inflammatory effect. The recommendation is to

use of a low-dose and short-term corticosteroid if the disease is classified as moderate or high activity, in conjunction with current therapy.[11] The EULAR recommends the use of a low-dose corticosteroid as part of the initial treatment strategy in combination with DMARD for up to 6 months, decreasing the dose as clinically as possible.[10]

Considered as adjuvants in the treatment of RA, the literature has reported that the use of anti-inflammatories is of the common use in these patients[17] and may bring benefit to the improvement of symptoms.[10,18–20] Systematic reviews found benefit of using corticosteroids administered in addition to standard therapy in inhibiting the progression of radiological damage caused by RA[21]; however, they point to gaps regarding the effectiveness and safety of these drugs for the treatment of RA.

Systematic review published in 2004 found that the use of low- dose prednisolone (maximum 15 mg/d) was superior to placebo and NSAIDs in improving joint sensitivity and pain in patients with RA, but the authors reported some limitations of the study as poor description of adverse effects, substantial heterogeneity between clinical trials and restriction of findings only at the first month of treatment initiation.[19]

Another systematic review study also published in 2004 verified that NSAIDs were more effective and often more preferred than paracetamol by patients with RA; however, the low methodological quality of clinical trials included compro- mised the confidence in findings.[22]

Some clinical trials evaluated the efficacy of new corticosteroid formulations for the treatment of RA, as example of sustained release formulations[23–25] and the intraarticular use of this class of drugs,[26] in addition, the authors warned about the need for further studies evaluating aspects related to the safety of long- term use of these drugs.[21]

In view of this, this study aims to update the available evidence to verify the effectiveness and the safety of the use of steroid and NSAIDs for the treatment of RA by means of a systematic review and meta-analysis.

2. Methods

2.1 Standards

The systematic review will be performed according to the recommendations specified in the Cochrane Handbook for Interventional Reviews [27,28] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta- Analyses

(PRISMA) statement.[28,29]

2.2. Protocol and registration

We registered our review protocol with the International Prospective Register of Systematic Reviews (https://www.crd. york.ac.uk/prospero/, PROSPERO-CRD42017073532). Ethical approval is not required because this is a literature-based study.

2.3. Eligibility criteria

2.3.1. Inclusion criteria

Adults patients (>18 years old) with RA diagnosis according to the criteria of ACR[30] or the equivalent criterion[31] in treatment with steroid (beclometha- sone, betamethasone, budesonide, dexamethasone, flunisolide, fluticasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, prednisoneand triamcinolone) and NSAIDs (aceclofenac, acetylsalicylic acid, bufexamac, diclofenac, etodo- lac, fenclofenac, fenoprofen, flurbiprofen, ibuprofen, indometh- acin, ketoprofen, ketorolac, meclofenamicacid, mefenamicacid, naproxen, niflumic acid, oxaprozin, oxyphenbutazone, phenyl- butazone, piroxicam, sulfasalazine, sulindac, suprofen, tenoxicam, tiaprofenic acid, tolfenamic acid, nabumetone, celecoxib andetoricoxib) at any dose, duration, and route of administration compared to placebo or active control. The type of study included will be randomized controlled trials (RCT) and double blind.

2.3.2. Exclusion criteria.

Studies in which more than 20% of patients have other disease, with sample below 200 and studies with participants with mild pain.

2.4. Measure outcomes

We will include studies that report any of the following outcomes.

2.4.1. Primary outcomes.

- decreased pain (visual analog scale [VAS] and other scales and patient global impression) in patients with initial pain moderate or severe;
- improvement of physical function (scales);

- decreased swelling (VAS and other scales);
- decreased stiffness (time in minutes or other scales);
- improvement of grip force (indicator of general strength and general health);
- progression of the disease through the radiological image of the joints; and
- improvement of quality of life (Short Form-36 and other scales).

2.4.2. Secondary outcomes.

- reports of adverse events including serious adverse events (that cause death, life-threatening, hospitalization, disability, or permanent damage);
- number of patients reporting any adverse effects;
- withdrawal of the study due to adverse events or treatment ineffectiveness;
- satisfaction with the treatment; and
- consume of rescue medication.

2.5. Search methods for primary studies

We will not impose any language restrictions or publication status.

2.5.1. Electronic searches.

We will search the following electronic databases without publication status restrictions: Cochrane Central Register of Controlled Trials, MEDLINE; ExcerptaMedica Database; Cumulative Index to Nursing and Allied Health Literature; Web of Science; ClinicalTrial.gov; and WHO International Clinical Trials Registry Platform.

2.5.2. Searching other resources.

The grey literature will be identified by searching by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

2.6. Search strategy

The search strategy will be comprised of both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings (MeSH) and keywords. The search strategy will be designed with the assistance of a trained librarian.

We will use the following MeSH terms, with associated keywords: intervention (anti-inflammatory agents); condition (arthritis Rheumatoid), and methodological filters will be applied to limit retrieval to RCT. The search strategy will be adapted for each database. MEDLINE (via Ovid) search strategy is provided in Table 1.

2.7. Eligibility determination

Six reviewers, working in pairs, will independently monitor potentially relevant citations and abstracts and apply the selection criteria. We will obtain full texts of any article that is considered eligible. The same reviewers will independently evaluate the eligibility of each full-text article. In case of duplicate publication, we will use the article with the most complete data.

The agreement between evaluators will be evaluated using the kappa coefficient (k) of Cohen. Values of kappa between 0.40 and 0.59 will be considered to reflect fair agreement, values between 0.60 and 0.8 reflect good agreement, and values that are 0.75 or more reflect excellent agreement.[32]. Disagreement will be resolved through arbitration by a third-party investigator.

2.8. Data extraction

The same reviewers, working in pairs, will independently extract the data and will record information regarding patients, methods, interventions, outcomes, and missing outcome data using standardized and pretested data extraction forms with instruc- tions. Before starting data abstraction, we will conduct calibration exercises to ensure consistency between reviewers. We will contact study authors to resolve any uncertainties. Disagreements will be resolved by consensus with any unresolved issues referred to another reviewer.

2.9. Risk of bias in individual studies

Using a modified version of the Cochrane collaboration risk of bias tool,[28] the same pairs of reviewers will independently assess the risk of bias for each randomized trial, according to the following criteria: random sequence; allocation concealment; blinding of the patient, healthcare professionals, outcome assessors, data collectors, and data analysts; incomplete outcome data; selective outcome reporting; and major baseline imbalance. Reviewers will assign response options of “definitely yes,” “probably yes,”

"probably no," and "definitely no" for each of the domains, with "definitely yes" and "probably yes" ultimately being assigned a low risk of bias and "definitely no" and "probably no" a high risk of bias.[33] Reviewers will resolve disagreements by discussion, and 1 arbitrator will adjudicate unresolved disagreements. For incomplete outcome data, loss to follow-up of <10% and a difference of <5% in missing data in intervention and control groups is considered low risk of bias.

2.10. Confidence in pooled estimates of effect

We will also independently rate the quality of evidence from randomized trials for each of the outcomes by using Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[33] In the GRADE approach, randomized trials begin as high-quality evidence but may be rated down by 1 or more of 5 categories of limitations: risk of bias, inconsistency, indirectness, imprecision, and reporting bias. The consensus will be established by discussion and by a third-party critic as needed. The final results will be summarized in an evidence profile.

2.11. Data synthesis

We will conduct analyses for each anti-inflammatory drug and for each outcome of interest. We will determine the confidence in estimates for each body of evidence and conduct an analysis for the body of evidence that warrants greater confidence.

Meta-analyses will be conducted using Stata software (version 14.2). We will use random-effects meta-analyses,[34] which are conservative in that they consider within-studies and between-studies differences in calculating the error term used in the analysis.

For trials that report dichotomous outcomes, we will calculate the pooled relative risk with associated 95% confidence interval (CI). For continuous outcomes, we will use weighted mean differences (WMD) and its 95% CI as effect measure after we convert them into same scale. Once the WMD has been calculated, we will contextualize this value by noting, when available, the corresponding anchor-based minimally important difference (MID), the smallest change in instrument score that patients perceive is important.

If studies reported the same construct using different measurement instruments, we will calculate the standardized mean difference (SMD) as sensitivity analysis. The SMD expresses the intervention effect in standard deviation units, rather than the original

units of measurement, with the value of an SMD depending on the size of the effect (the difference between means) and the standard deviation of the outcomes (the inherent variability among participants). For outcome measures that have an established anchor-based MID, we will use this measure to convert the SMD into an odds ratio and risk difference.[35]

To facilitate the interpretation of the effects of continuous outcomes, we will substitute the MID, when MID is available for different scales, for the standard deviation (denominator) in the SMD equation, which will result in more readily interpret- able MID units instead of standard deviation units.[36] If an estimate of the MID is not available, we will use a statistical approach developed by Suissa[37] to provide a summary estimate of the proportion of patients who benefit from treatment across all studies. Statistical approaches to enhance the interpretability of results of continuous outcomes outlined in this paragraph will use methods cited as well as those described by Thorlund et al. [38] The publication bias will be explored by statistical techniques (Egger and Peters tests). In both tests, we will consider as significant probabilities below 0.10.[39] Another strategy will include visual inspection of the asymmetry in 2 funnel graphs (at least 10 studies contributed to a pooled analysis), obtained by sample size and logarithm of chance, and another by logarithm and standard error.[40] Therefore, we will determine the smaller weight for studies with a small sample size, in order to avoid this type of risk of bias.

We will use recently developed approaches to address missing participant data for dichotomous outcomes[39] and continuous outcomes.[39] We will only apply these approaches to outcomes that show a significant treatment effect and report sufficient missing participant data to potentially introduce clinically important bias.

Thresholds for important missing participant data will be determined on an outcome-by-outcome basis.

We will estimate heterogeneity associated with pooled effect estimates with the use of a chi-squared test and the I2 statistic.[40] The following heterogeneity was considered: 0% to 25% (low heterogeneity); 50% (moderate heterogeneity); and 75% (high heterogeneity).[41]

We will also perform the meta-regression of the measures of outcomes identified in double-arcosene model of moments with the maximum likelihood restricted with the modification of the variance of the coefficients suggested by Knapp and Har-tung. [42,43]

The coefficient (b), the probability (P value), and the residual heterogeneity will be calculated. Values of $P < .05$ will be considered significant.

Analysis of subgroups will be performed and possible explanations for heterogeneity will include the following: doses (higher vs lower) with an expected larger effect with higher doses, duration of the treatment (longer vs shorter) with an expected larger effect with longer duration of the treatment; risk of bias (high vs low) with an expected larger effect in trials at high or unclear risk of bias versus trials at low risk of bias, blinding (absence vs presence) with an expected larger effect in trials with absence blinding versus trials with blinding, and study size (large vs small studies) with larger studies provide better estimates of effect.

We will provide summary tables and a narrative synthesis if the meta-analysis is not appropriate due to excessive heterogeneity in populations, interventions, comparators, outcomes, or method- ologies.

2.12. Summarizing evidence

We will follow the recommendation by the GRADE Working Group, presenting cumulative findings in evidence profiles.[42,44] Evidence profiles provide succinct, easily digestible presentations of quality of evidence and magnitude of effects. The evidence profiles will be constructed with the following elements: a list of until 7 important outcomes, both desirable and undesirable; a measure of the typical burden of these outcomes (e.g., control group, estimated risk); a measure of the difference between risks with and without intervention; the relative magnitude of effect; numbers of participants and studies addressing these outcomes, as well as follow-up time; and a rating of the overall confidence in the estimate of effect for each outcome and comments, which will include the MID if available.

2.13. Ethics and dissemination

Ethical approval is not needed for a systematic review that does not involve privacy concerns due to collection or presentation of data from individual patients. The systematic review will be submitted to journals and presentations with scores in related research conferences.

3. Discussion

Our review will evaluate the available evidence for the treatment with steroid and NSAIDs for adult with RA, provide estimates of the effectiveness of treatments and their associated harms, and evaluate the quality of the evidence in a rigorous and consistent manner using the GRADE approach.[43] The results of our systematic review will be of interest to public health and practitioners worldwide, particularly in Brazil.

The compiled information about these medications will inform patients and healthcare practitioners about their effectiveness and safety, and help facilitate evidence-based shared care decision making. This study will also identify key areas for future research.

3.1. Strengths and limitations of this study

This systematic review will assess the effectiveness and the safety of the use of steroid and NSAIDs for the treatment of RA. The method of this review includes explicit eligibility criteria, comprehensive and extensive search in database, independent and paired evaluation to selection of studies.

We will utilize robust statistical techniques and assess risk of bias of included studies. In addition, the GRADE approach will evaluate the strength and quality of the evidence body concerning the estimate of the effect for each outcome, including independent analysis of the risk bias, precision, consistency, publication bias, and indirect evidence.

The quality of the primary studies to be included in this review may be a limiting factor if there is heterogeneity in study design, in doses, and in outcome measurements and thus they will have high bias risk. These limitations may decrease the quality of the evidence from the study findings regarding the effectiveness and safety of steroid and NSAIDs in RA.

The results could guide patients and healthcare practitioners about the effectiveness and safety of the use of anti- inflammatory drugs and help facilitate evidence-based shared care decision making.

Author contributions

Mariana Del Grossi Moura is the principal investigator and led the writing of the manuscript. Luciane Cruz Lopes and Cristiane de Cássia Bergamaschi are the project managers and coinvesti- gators and contributed to the writing and revision of the

manuscript. Marcus Tolentino Silva, Sílvio Barberato-Filho, and Rogério Heládio Lopes Motta are coinvestigators and contrib- uted to the writing and revision of the manuscript. All authors read and approved the final manuscript.

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5.2 Title: Use of steroid and non-steroidal anti-inflammatories in the treatment of rheumatoid arthritis: systematic review and network meta-analysis

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ABSTRACT

Evidence on the use of non-steroidal anti-inflammatory drugs (NSAIDs) and corticoids for rheumatoid arthritis (RA) is inconclusive and is not up to date. This systematic review assessed the effectiveness and safety of these anti-inflammatories (AI) in the treatment of RA. The databases searched were: CENTRAL, MEDLINE, EMBASE, CINAHL, Web of Science and Virtual Health Library; to identify randomized controlled trials with adults which used AI (dose=mg/day) compared with placebo or active controls. Reviewers, in pairs and independently, selected studies, performed data extraction and assessed the risk of bias. The outcomes included pain, physical function, morning stiffness, number of swollen and painful joints, grip strength, disease progression based on radiological imaging of joints, quality of life, adverse events, satisfaction with the treatment and consumption of rescue medication. The quality of the evidence was assessed by GRADE. Network meta-analyses were performed using the Stata v.14.2. Twenty-six articles were selected (NSAIDs=21 and corticoids=5). Naproxen 1,000 improved physical function, reduced pain and the number of painful joints compared to placebo. Etoricoxib 90 compared to placebo reduced the number of painful joints. Naproxen 750 reduced the number of swollen joints, except for etoricoxib 90. Naproxen 1,000, etoricoxib 90 and diclofenac 150 were better than placebo regarding overall patient assessment. Assessment physician showed that NSAIDs were better than placebo; and etoricoxib 90 was better than celecoxib 400 and naproxen 1,000. Greater and lesser number of adverse events was observed for etoricoxib 90 and celecoxib 200, respectively. Prednisolone 10 associated with cyclosporine reduced erosion compared to methotrexate (MTX) alone or

prednisolone with MTX. Prednisone 5 with MTX reduced joint damage and disease activity compared to placebo. Radiographic progression was lower with prednisone 7.5 compared to placebo. No serious adverse events were observed for AI. Naproxen 1,000 was the most effective drug and celecoxib 200 showed fewer adverse events. However, the low quality of the evidence observed for the outcomes with NSAIDs, the absence of meta-analyses to assess the outcomes with corticoids, as well as the risk of bias observed, indicate that future randomized controlled trials can confirm such findings.

Key words: Rheumatoid arthritis. Non-steroidal anti-inflammatories. Corticoids. Steroid anti-inflammatories.

BACKGROUND

Rheumatoid arthritis is a chronic and progressive systemic inflammatory disease. During its course, the immune system, which combats infections at homeostatic conditions, attacks the lining of joints causing local inflammation characterized by pain, swelling, and joint stiffness(1-3). Its prevalence is about 5 in every 1,000 individuals(4), occurring often during their most productive years. It affects twice as many women than men(5, 6).

Patients suffering from rheumatoid arthritis usually require analgesic and anti-inflammatory drugs to control disease symptoms, making it vital to better understand effectiveness and safety of these drugs. Proper management of drug administration is important in determining the best practices for treatment of the disease(7, 8).

Non-steroidal anti-inflammatory drugs (NSAIDs) and corticoids (steroid anti-inflammatory drugs - SAIDs) are commonly used in patients as adjuvants to rheumatoid arthritis treatment, as they can promote benefits by reducing pain and inflammation caused by the disease(8-11).

Disease-modifying antirheumatic drugs (DMARDs) in combination with corticoids can be used as first choice therapy options and their administration should be started as soon as the diagnosis of rheumatoid arthritis has been confirmed, in an effort to achieve remission and prevent the increase of disease activity(7, 8, 12, 13).

DMARDs administered in combination with prednisone or prednisolone at lower doses (≤10 mg/day) and for short periods (<3 months) can help reduce symptoms and radiographic progression(14-20). NSAIDs can also be prescribed for symptomatic control

while the effects of synthetic or biological DMARDs take place, usually at the lowest dose for the shortest possible period(21, 22). NSAIDs recommended as first choices include ibuprofen, naproxen, potassium diclofenac and sodium diclofenac for patients with mild, moderate or high disease activity(9, 23).

Although there are systematic reviews evaluating the use of NSAIDs(9, 23) and corticoids (24-26) for the treatment of rheumatoid arthritis, no up-to-date evidence was found on this topic and these drugs are routinely used by patients suffering from this condition. Network meta-analysis can be a strategy for dealing with existing evidence. Published studies on this topic are old and safety data on long-term use are very unclear(9). Thus, this study performed a systematic review of randomized clinical trials on the effectiveness and safety of use of these anti-inflammatories in the treatment of rheumatoid arthritis.

METHODS

The systematic review was performed according to the recommendations specified in the Cochrane Handbook for Interventional Reviews(27, 28) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension for network meta-analysis(29) (Appendix A).

Protocol and registration

The review protocol was registered by the International Prospective Register of Systematic Reviews (PROSPERO) with protocol number CRD42017073532 and was previously published (30). Some adjustments to the protocol version needed to be made such as: i) eligibility criteria were altered to include clinical trials in which patients were diagnosed with rheumatoid arthritis regardless of diagnostic criteria, not including only the criteria of the American College of Rheumatology; ii) trials of cross-over design were excluded due to the difficulty of using their data to perform comparisons between initial and final results; iii) studies included in this review could not be compared directly, so network meta-analyses were performed.

Eligibility Criteria

Types of studies

Randomized controlled trials that compared NSAIDs or corticoids to another therapy (placebo or active control) for rheumatoid arthritis were considered eligible. Studies where only the abstract was available or if they had fewer than 200 participants or trials of cross-over design were excluded.

Types of participants

Studies involving adults (≥18 years old) diagnosed with rheumatoid arthritis were considered eligible. Studies in which more than 20% of the patients suffered from another inflammatory disease were excluded, except in cases where results for the studied population could be separated from other analyses.

Types of interventions

Experimental group**:** NSAIDs (aceclofenac, aspirin, bufexamac, diclofenac, etodolac, fenclofenac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, naproxen, niflumic acid, oxaprozin, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, suprofen, tenoxicam, tiaprofenic acid, tolfenamic acid, nabumetone, meloxicam, celecoxib and etoricoxib) and SAIDs/corticoids (beclomethasone, betamethasone, budesonide, dexamethasone, flunisolide, fluticasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone and triamcinolone) at any dose, duration and route of administration and that are commercially available;

Control group: placebo or any active control.

Types of outcome measures

Primary outcome measure: pain (Visual Analogue Scale – VAS, patient global impression or other scale); physical function (measured using the Health Assessment Questionnaire – HAQ or a modified HAQ)(31); number of swollen joints; number of painful joints; morning stiffness (time in minutes or hours); grip strength (indicator of general strength and general health); patients' and physicians' global assessment, disease progression as assessed based on radiological imaging of joints; quality of life (Short Form-36 and other scales).

Secondary outcome measures included adverse events and serious adverse events (such as death, life-threatening events, hospitalization, disability or permanent damage);

withdrawal from the study; satisfaction with current treatments and consumption of rescue medication.

Information sources

We searched the following electronic databases with no restrictions regarding publication status or language: CENTRAL, MEDLINE; EMBASE; CINAHL; Web of Science and Virtual Health Library. References for all included studies, other reviews, guidelines and related articles were searched examining reference lists. Ongoing studies were searched in the trial registry ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform. The searching was carried out in order to identify all relevant publications up to December of 2019.

Search

The search strategy was created using terms of the Medical Subject Headings (MeSH) and keywords (Appendix B). The associated keywords: i) intervention (anti-inflammatory agents); ii) condition (rheumatoid arthritis), and iii) methodological filters were applied to limit retrieval to randomized controlled trials.

The search strategy was adapted for each database and designed with the assistance of a trained librarian. Details of the strategies are provided in appendix C.

Study selection

Four reviewers (MDGP, SB-F, LGM, FCA), working in pairs and independently, screened titles and abstracts. The same reviewers, in pairs and independently, assessed eligibility of each full-text article. In case of duplicate publications, we would just include the article with most complete data, however this situation did not occur. Disagreements were resolved by consensus or by a third review author (CCB or LCL) if necessary.

Data collection process

All reviewers, in pairs and independently, extracted the data using standardized and pretested forms with instructions and contacted study authors to clarify any uncertainties.

In the studies where important data were incomplete or missing, we contacted the authors to seek further information; however, we have not received reply from any

authors. Whenever possible, we computed missing standard deviation (SD) from other statistics, such as standard error (SE)[27]. For the studies that did not provide enough data, we verified whether these values could be extracted from graphs using web based tools (https://automeris.io/WebPlotDigitizer/).

The following information were extracted: studies (year and country of the publication, register protocol, study design, characteristics of the population (diagnostic criteria, pain relief medications, number of patients, mean and standard deviation age, percentage of women)); interventions and comparators (drug, dose diary, via of administration, duration of the treatment in weeks); risk of bias and outcomes.

Geometry of the network

The data were summarized in a network meta-analysis. The model was proposed by Bucher et al.(32) and draws on both direct evidence (treatments compared in the same trial) and indirect evidence (different treatments studied in separate trials, but compared when they use a common comparator), with the benefit of randomization in each study retained.

Network meta-analysis using mixed treatment comparisons technique was carried out to unite in a single analysis direct and indirect evidences, the main objective being increasing precision of the estimation. The network diagram is made up of lines and nodes. In the diagram, the notes represent every intervention, and the size of the nodes means the number of participants. The lines indicate direct comparisons between different interventions and the thickness of the line means the amount of studies(33).

Risk of bias within individual studies

Using a modified version of the Cochrane collaboration risk of bias tool (27), the same reviewers assessed the risk of bias for each trial, in pairs and independently, according to the following criteria: random sequence; allocation concealment; blinding of the patients, care provider and outcome assessor for each outcome measure; incomplete outcome data; selective outcome reporting; and other biases.

To determine the risk of bias of a study, each criterion was rated as ‘definitely yes’, ‘probably yes’, being assigned a low risk of bias and ‘probably no’ and ‘definitely no’, assigned a high risk of bias(34). Disagreements were resolved by consensus.

Incomplete outcome data, lost follow-up less than 10% and a difference of less than 5% in missing data in intervention and control groups were considered low risk of bias. In order to determine whether there was reporting bias or not, we first determined whether the protocol for the assessed randomized controlled trials was published before recruitment of patients had started. For studies published after July 1st, 2005, we screened the Clinical Trial Register at the International Clinical Trials Registry Platform of the World Health Organization (http://apps.who.int/trialsearch)(35).

In cases where study protocol registration reports and safety results were not found, we used the classification for high risk of bias. The absence of a criterion for diagnosis of rheumatoid arthritis was identified as a possible source of bias and classified as high risk of bias in the criterion "other risks of bias".

The bias classification was done using the Review Manager 5 software and a third review author (CCB or MTS) carried out any final decisions when necessary.

Summary measures and methods of analyses

Analyses were carried out for each anti-inflammatory drug and for each outcome of interest. Estimates of comparative effectiveness were measured using standardized mean differences (SMD) with associated 95% confidence intervals (95% CI); and estimates of comparative safety were measured using odds ratio (OR) with 95% CI. Subgroup analysis could not be performed due to heterogeneity of the studies.

Analysis of subgroups for explanations for heterogeneity were intended for: doses (higher vs lower) with an expected larger effect with higher doses; duration of the treatment (longer vs shorter) with an expected larger effect with longer duration of the treatment; risk of bias (high vs low) with an expected larger effect in trials at high or unclear risk of bias versus trials at low risk of bias; blinding (absence vs presence) with an expected larger effect in trials with absence blinding versus trials with blinding; and study size (large vs small studies) with larger studies provide better estimates of effect.

We are provided summary tables when the meta-analysis was not appropriate due to excessive heterogeneity in populations, interventions, comparators, outcomes, or methods (Appendix D). The analyses were carried out using Stata software (version 14.2). We adopted a comparison of mixed treatment with mixed generalized linear models to analyze the indirect and direct comparisons between the networks. The comparisons

presented were derived from indirect comparison and direct comparison, if available. The maximum restricted likelihood method was used to estimate the random effect model.

We calculated the relative ranking of agents for induction of clinical remission as their surface under the cumulative ranking (SUCRA), which represents the percentage of efficacy or safety achieved by a drug compared to other that is always the best without uncertainty (SUCRA=100%)(36). This parameter was used to estimate the ranking probabilities for all treatments in order to obtain a treatment hierarchy. The trial nodes that were not connected to the network were excluded.

Quality of evidence

We followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to appraise the confidence in estimates derived from network meta-analysis of outcomes(37). Randomized controlled trials start at high confidence and can be rated down based on risk of bias, indirectness, imprecision, inconsistency and publication bias; they can then be graded at levels of moderate, low and very low confidence(38).

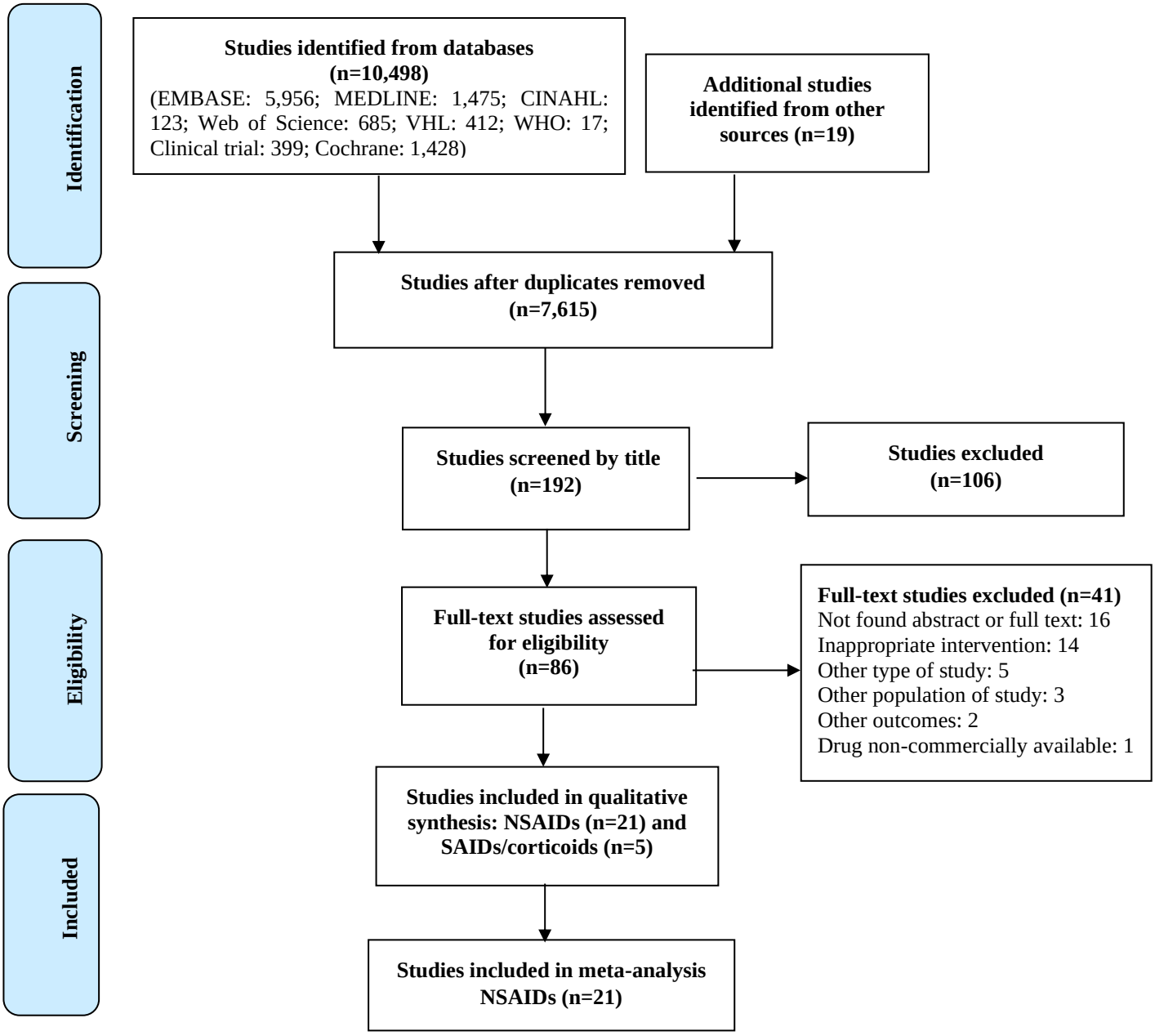
The risk of bias was evaluated for each outcome as low, moderate or high and is represented in figures of network meta-analysis in colors green, yellow and red, respectively. Publication bias was measured when more than 10 studies were included for the outcome of interest. If direct and indirect estimates were coherent, then the higher of their ratings was assigned to the network meta-analysis estimates. A summary of findings can be found in appendix E.

RESULTS

Study selection

Of a total of 10,498 publications (reasons for exclusion are detailed in appendix F), 26 studies met the inclusion criteria (21 for NSAIDs and 5 for corticoids) (Appendix G) (Figure 1).

Figure 1. Study flowchart



Notes: VHL: Virtual Health Library; WHO: World Health Organization; NSAIDs: Non-steroidal anti-inflammatory drugs; SAIDs: Steroidal anti-inflammatory drugs.

Non-steroidal anti-inflammatories for rheumatoid arthritis

Description of studies

Twenty-one trials involving 10,503 patients with rheumatoid arthritis were included in this review. These trials comprised ten NSAIDs: aceclofenac, aspirin, celecoxib, diclofenac, etodolac, etoricoxib, indomethacin, ketoprofen, meloxicam,

nabumetone, naproxen, piroxicam, tenoxicam. One study evaluated the use of a patch formulation, the others described oral administration. Follow-up time ranged from 14 to 182 days. Most studies (n=16) reported the use of rescue medication. The mean age of the patients varied between 46.9 and 58.7 years and 16 studies described concomitant use of DMARD therapy (table 1). More detailed description of the characteristics of these studies is given in appendix H.

Table 1 - Characteristics of the included studies on non-steroidal anti-inflammatories for rheumatoid arthritis (n=21)

Study	Interventions (dose in mg/day)	Outcomes reported	Sample size (N)	Loost follow-up (%)	Rescue medication	Duration (weeks)	Mean age (years)	Woman (%)
Bernhard et al., 1987(39)	nabumetone 1,000, aspirin 900	5,6,7,8, 10	234	49.1	acetaminophen	24	50.7	75
Collantes et al., 2002(40)	placebo, etoricoxib 90, naproxen 1,000	1,3,4,7,8,9,10	687	29.7	aspirin	12	52.3	NR
Emery et al., 1992(41)	nabumetone 2,000, naproxen 1,000	1,5,10	284	4.9	acetaminophen	12	53.2	NR
Emery et al., 1999(42)	celecoxib 400, diclofenac 150	1,2,3,4,5,7,8,10	497	31.8	NR	24	55.2	96.7
Furst et al., 2002(43)	placebo, meloxicam 7.5, 15, 22.5, diclofenac 150	1,2,3,4,7,8, 10	888	0.7	acetaminophen	12	55.4	NR
Geusens et al., 2002(44)	placebo, naproxen 1,000	3,4,5,7,8,10	1023	NR	acetaminophen	12	53.6	82.8
Geusens et al., 2004(45)	naproxen 500, placebo	1,3,4,7,8,9,10	726	54.9	acetaminophen	26	53.5	88
Gibofsky et al., 2007(46)	naproxen 1,000, placebo	1,2,3,4,5,7,8,9,10	340	49.4	acetaminophen	12	55.9	68.5
Jacob et al., 1986(47)	placebo, etodolac 50, 100, 200, aspirin 3,900	1,3,4,5,6,10	264	42.4	acetaminophen	6	52.9	60.2
Kawai et al., 2010(48)	placebo, ketoprofen 20	1,10	652	3.7	NR	2	58.7	85.8
Kornasoff et al., 1996(49)	aceclofenac 200, indomethacin 100	3,4,5,6,7,8,10	219	17.8	acetaminophen	12	56.0	70.7
Krug et al., 2000(50)	nabumetone 2,000, naproxen 1,000	3,4,7,8,10	344	0.6	acetaminophen	12	54.0	70.9
Lightfoot, 1997(51)	etodolac 400, 600, piroxicam 20	3,4,5,10	361	37.3	acetaminophen	12	57.0	84.2
Matsumoto et al., 2002(52)	placebo, etoricoxib 90, naproxen 1,000	1,3,4,7,8,9,10	448	68.7	aspirin	12	55.6	NR
Pasero et al., 1995(53)	aceclofenac 200, diclofenac 150	1,5,6,10	327	7.6	NR	24	50.7	81.3
Perez Ruiz; Alonso Ruiz; Ansoleaga, 1996(54)	aceclofenac 200, tenoxicam 20	1,5,6,10	237	13	acetaminophen	12	56.6	98.7
Shi et al., 2004(55)	diclofenac 100, meloxicam 15, nabumetone 1,000, celecoxib 200	10	407	31.2	NR	24	46.9	76.9
Vasey et al., 1987(56)	nabumetone 1,000, naproxen 500	5,6,7,8,10	318	54.4	acetaminophen	24	55.0	NR
Williams et al., 2006(57)	placebo, naproxen 500	7,8,10	1093	59.5	NR	12	56.2	76.4
Wojtulewski et al., 1996(58)	meloxicam 7.5, naproxen 750	1,3,4,5,6,7,8,10	306	23.8	acetaminophen	26	NR	NR
Zhao et al., 2000(59)	placebo, celecoxib 100, 200, 400, naproxen 1,000	2,9,10	688	67	acetaminophen	12	54.5	NR

Notes. Outcomes reported: 1:pain; 2:functional disability score; 3:swollen joint count; 4:tender joint count; 5:morning stiffness; 6: grip strength; 7:physician assessment; 8:patient assessment; 9:quality of life scale; 10:adverse events. NR:not reported.

Risk of bias of included studies (Figure 2)

One study had minimum risk of bias(43). Allocation concealment was insufficiently described in the majority of studies(40, 41, 44-48, 50-55, 58, 59). Shi et al. (2004)(55) did not describe the blinding of patients or healthcare professionals due to the fact the study was an open trial in which both researchers and participants were aware of which treatments were administered.

Most of the randomized controlled trials had attrition bias, since they did not report their results with the intention to analyse reported withdrawals >10% of sample and/or did not discuss the implications of patients lost follow-up(39, 40, 42, 44-47, 49, 51, 52, 54-59).

The study by Gibofsky et al. (2007)(46) and Zhao et al. (2000)(59), even though reported adverse events, did not evaluate other important outcomes (such as improvement of pain, swelling and duration of morning stiffness), and thus showed reporting bias. Also, two other clinical trials which described disease diagnostic did not cite the criteria used, generating doubts regarding how the diagnosis for participants inclusion was carried out(39, 56).

Figure 2 - Risk of bias for studies on non-steroidal anti-inflammatories (n=21)

Effect of interventions

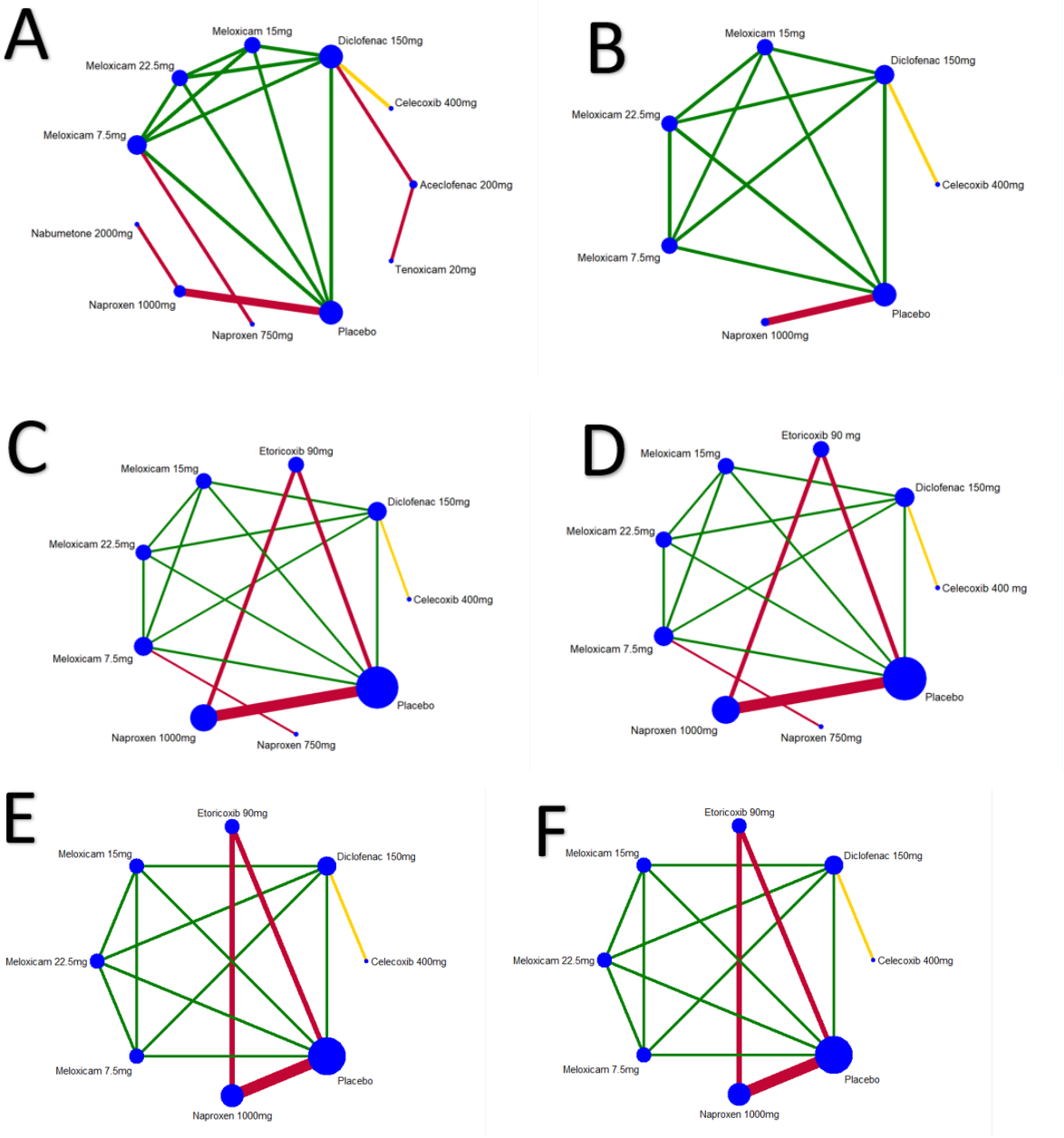
The doses of drugs were shown as milligrams per day (mg/day). Nine studies could not be included in the meta-analysis due to absence of standard deviation, standard error or confidence interval data(39, 47-50, 55-57, 59). All studies were included in the meta-analysis according to safety outcomes and none of the studies assessed the outcomes "disease progression based on radiological imaging of joints" or "satisfaction with current treatment". Subgroup analysis could not be performed due to heterogeneity of the studies.

Assessed outcomes and network meta-analysis

Nine NSAIDs were compared at 13 different dosages and placebo groups. Of the 12 trials, 8 (66.6%) were two-arm studies, whereas 4 (33.3%) were multiple-arm studies (Figure 3). Overall, regarding inclusion of patients by outcome, 4,016 patients were included for "improvement of pain" (Figure 3A); 2,447 patients for "improvement of physical function" (Figure 3B); 4,962 patients for "number of tender/painful joints" (Figure 3C); 4,962 for "number of swollen joints" (Figure 3D), 4,152 for "patient's global assessment" (Figure 3E); and 4,152 for "physician's global assessment" (Figure 3F).

The outcomes of studies that could not be included in the network meta-analysis are described in appendix D.

Figure 3 - Evidence structure of eligible comparisons for network meta-analysis: effectiveness outcomes.



Notes: 3A - Pain (9 studies, 10 non-steroidal anti-inflammatories - NSAIDs, 22 arms, 4,016 patients); 3B - Physical function (4 studies, 5 NSAIDs, 11 arms, 2,447 patients); 3C- Number of tender/painful joints (8 studies, 6 NSAIDs, 21 arms, 4,962 patients); 3D - Number of swollen joints (8 studies, 6 NSAIDs, 21 arms, 4,962 patients); 3E - Patient's Global Assessment (6 studies, 6 NSAIDs, 17 arms, 4,152 patients); 3F - Physician's Global Assessment (6 studies, 6 NSAIDs, 17 arms, 4,152 patients).

Pain

This outcome included data from 13 studies(40-48, 52-54, 58). Four studies did not provide data that could be extracted (Appendix D)(40, 47, 48, 52). Naproxen 1,000

reduced pain compared to placebo (SMD: -10.28, 95% CI: -20.39; -0.17) (evidence of very low quality) (Figure 4A and Appendix E).

Physical function

Emery et al. (1999)(42), Furst et al. (2002)(43), Gibofsky et al. (2007)(46) and Geusens et al. (2004)(45) were included in the meta-analysis for this parameter. Naproxen 1,000 improved physical function compared to placebo (SMD: -0.14, 95% CI: -0.24; -0.05) (evidence of very low quality) (Figure 4B and Appendix E).

Number of tender/painful joints and swollen joints

Eight studies were included in the meta-analysis(40, 42-46, 52, 58) while four studies could not be included(47, 49-51). The meta-analysis showed significant reduction in number of painful joints for naproxen 1,000 (SMD: -3.54, 95% CI: -5.15; -1.92) (evidence of very low quality) and etoricoxib 90 (SMD: -4.98, 95% CI: -7.13; -2.82) (evidence of very low quality) compared to placebo.

Naproxen 750 was better for reducing number of swollen joint than naproxen 1,000 (SMD: -5.21, 95% CI: -9.57; -0.85) (evidence of very low quality), meloxicam 7.5 (SMD: -5.24, 95% CI: -9.11; -1,37) (evidence of low quality), meloxicam 15 (SMD: -6.54, 95% CI: -10.83; -2.25) (evidence of very low quality), meloxicam 22.5 (SMD: -5.34, 95% CI: -9.63; -1.05) (evidence of very low quality), diclofenac 150 (SMD: -6.04, 95% CI: -10.33; -1.75) (evidence of very low quality) and celecoxib 400 (SMD: -5.74, 95% CI: -10.70; -0.78) (evidence of very low quality), (Figure 4C and Appendix E).

Morning stiffness

Twelve studies reported data on this outcome(39, 41, 42, 44, 46, 47, 49, 51, 53, 54, 56, 58) but it was not possible to perform a meta-analysis (Appendix D).

Grip strength

Grip strength changes were assessed in seven studies, but they could not be summarized in a meta-analysis due to improper reporting of data and to use of different drugs(39, 47, 51, 53, 54, 56, 58) (Appendix D).

Quality of life

Two studies(46, 59) investigated this outcome, but meta-analysis was not performed due to improper reporting of data and to measurements carried out with different scales (appendix D).

Patients' and physicians' global assessment

Six studies which investigated patient's global assessment were included in the meta-analysis(40, 42, 43, 45, 46, 52). Other studies were not included due to the manner they were reported (graphs, final percentage improvement or absence of standard deviation values)(39, 44, 47, 49, 50, 56-58) (Appendix D).

Naproxen 1,000 (SMD: -11.68, 95% CI: -15.68; -6.51) (evidence of very low quality), etoricoxib 90 (SMD: -14.32, 95% CI: -20.26; -8.38) (evidence of low quality) and diclofenac 150 (SMD: -10.08, 95% CI: -19.52; -0.63) (evidence of high quality) were better than placebo for patient's global assessment. For physician's global assessment, all drugs assessed were better than placebo, except celecoxib 400. In general, the evidence assessed was of very low to moderate quality; the only exception was for diclofenac 150 *vs* placebo, where the evidence was of high quality. Etoricoxib 90 was better than both celecoxib 400 (SMD: -6.28, 95% CI: -12.55; -0.01) (evidence of very low quality) and naproxen 1,000 (SMD: 4.43, 95% CI: 2.01; 6.84) (evidence of low quality) (Figure 4D and Appendix E).

Figure 4 - Comparative effectiveness outcomes between drugs using network meta-analysis. Comparisons should be read from left to right. Standardized mean difference (SMD) for comparisons are located in the common cell between the column-defining and row-defining treatment. Numbers on highlighted background are statistically significant.

A

Placebo	-15.91 (-41.49; 9.68)	-10.97 (-31.19; 9.25)	**-10.28 (-20.39; -0.17)**	-14.23 (-32.06; 3.60)	-6.68 (-20.58; 7.22)	-9.80 (-23.72; 4.12)	-10.60 (-24.52; 3.32)	-10.80 (-24.65; 3.05)	-8.77 (-28.70; 11.16)	-13.94 (-35.13; 7.25)
	Tenoxicam 20mg	4.94 (-24.91; 34.80)	5.63 (-21.90; 33.17)	1.68 (-29.52; 32.88)	9.23 (-16.76; 35.21)	6.11 (-19.88; 32.10)	5.31 (-20.68; 31.30)	5.11 (-16.51; 26.73)	7.14 (-18.83; 33.10)	1.97 (-12.43; 16.37)
		Naproxen 750mg	0.69 (-21.93; 23.31)	-3.26 (-30.23; 23.71)	4.28 (-10.43; 19.00)	1.17 (-19.50; 21.84)	0.37 (-20.30; 21.04)	0.17 (-20.48; 20.82)	2.19 (-22.95; 27.34)	-2.97 (-29.16; 23.21)
			Naproxen 1000mg	-3.95 (-18.67; 10.76)	3.59 (-13.60; 20.79)	0.48 (-16.74; 17.69)	-0.32 (-17.54; 16.89)	-0.52 (-17.69; 16.64)	1.50 (-20.86; 23.87)	-3.66 (-27.17; 19.84)
				Nabumetone 2000mg	7.55 (-15.07; 30.16)	4.43 (-18.20; 27.06)	3.63 (-19.00; 26.26)	3.43 (-19.16; 26.02)	5.46 (-21.30; 32.21)	0.29 (-27.42; 28.00)
					Meloxicam 7.5mg	-3.12 (-17.65; 11.41)	-3.92 (-18.45; 10.61)	-4.12 (-18.62; 10.39)	-2.09 (-22.49; 18.31)	-7.26 (-28.93; 14.41)
						Meloxicam 22.5mg	-0.80 (-15.34; 13.74)	-1.00 (-15.51; 13.51)	1.03 (-19.38; 21.44)	-4.14 (-25.82; 17.53)
							Meloxicam 15mg	-0.20 (-14.71; 14.31)	1.83 (-18.58; 22.24)	-3.34 (-25.02; 18.33)
								Diclofenac 150mg	2.03 (-12.34; 16.40)	-3.14 (-19.31; 13.03)
									Celecoxib 400mg	-5.17 (-26.80; 16.46)
										Aceclofenac 200mg

B

Placebo	-0.14 (-0.24; -0.05)	-0.07 (-0.22; 0.08)	-0.14 (-0.28; 0.00)	-0.13 (-0.27; 0.01)	-0.08 (-0.23; 0.07)	-0.08 (-0.31; 0.15)
	Naproxen 1,000 mg	0.07 (-0.10; 0.25)	0.00 (-0.17; 0.18)	0.01 (-0.16; 0.19)	0.06 (-0.11; 0.24)	0.06 (-0.18; 0.31)
		Meloxicam 7.5 mg	-0.07 (-0.22; 0.08)	-0.06 (-0.21; 0.09)	-0.01 (-0.16; 0.14)	-0.01 (-0.24; 0.22)
			Meloxicam 22.5mg	0.01 (-0.13; 0.15)	0.06 (-0.09; 0.21)	0.06 (-0.17; 0.29)
				Meloxicam 15mg	0.05 (-0.10; 0.20)	0.05 (-0.18; 0.28)
					Diclofenac 150mg	0.00 (-0.17; 0.17)
						Celecoxib 400 mg

C

Placebo	-5.34 (-12.22;1,54)	**-3.54 (-5.15; -1.92)**	-1.60 (-5.15; 1.95)	-1.60 (-5.15; 1.95)	-0.90 (-4.45; 2.65)	**-4.98 (-7.13; -2.82)**	-2.30 (-5.85; 1.25)	-2.80 (-8.47; 2.87)
6.74 (2.45; 11.03)	**Naproxen 750mg**	1.80 (-5.26; 8.87)	3.74 (-2.15; 9.63)	3.74 (-3.14; 10.62)	4.44 (-2.44; 11.32)	0.36 (-6.85; 7.57)	3.04 (-3.84; 9.92)	2.54 (-5.64; 10.72)
1.53 (0.72; 2.34)	-5.21 (-9.57; -0.85)	**Naproxen 1000mg**	1.94 (-1.96; 5.84)	1.94 (-1.97; 5.84)	2.64 (-1.27; 6.54)	-1.44 (-3.61; 0.72)	1.24 (-2.66; 5.14)	0.74 (-5.16; 6.64)
1.50 (-0.34; 3.34)	-5.24 (-9.11; -1.37)	-0.03 (-2.04; 1.98)	**Meloxicam 7.5mg**	-0.00 (-3.55; 3.55)	0.70 (-2.85; 4.25)	-3.38 (-7.53; 0.77)	-0.70 (-4.25; 2.85)	-1.20 (-6.87; 4.47)
1.40 (-0.40, 3.20)	-5.34 (-9.63; -1.05)	-0.13 (-2.14; 1.88)	-0.10 (-1.94; 1.74)	**Meloxicam 22.5mg**	0.70 (-2.85; 4.25)	-3.38 (-7.53; 0.78)	-0.70 (-4.25; 2.85)	-1.20 (-6.87; 4.47)
0.20 (-1.60, 2.00)	-6.54 (-10.83; -2.25)	-1.33 (-3.34; 0.68)	-1.30 (-3.14; 0.54)	-1.20 (-3.04; 0.64)	**Meloxicam 15mg**	-4.08 (-8.23; 0.08)	-1.40 (-4.95; 2.15)	-1.90 (-7.57; 3.77)
2.60 (1.70, 3.50)	-4.10 (-8.49; 0.28)	1.11 (0.13; 2.08)	1.14 (-0.92; 3.19)	1.24 (-0.82; 3.29)	2.44 (0.38; 4.49)	**Etoricoxib 90mg**	2.68 (-1.47; 6.83)	2.18 (-3.89; 8.25)
0.7 (-1.1, 2.5)	-6.04 (-10.33; -1.75)	-0.83 (-2.84; 1.18)	-0.80 (-2.64; 1.04)	-0.70 (-2.54; 1.14)	0.50 (-1.34; 2.34)	-1.94 (-3.99; 0.12)	**Diclofenac 150mg**	-0.50 (-4.92; 3.93)
1.0 (-2.1, 4.1)	-5.74 (-10.70; -0;78)	-0.53 (-3.74; 2.67)	-0.50 (-3.60; 2.60)	-0.40 (-3.50; 2.70)	0.80 (-2.30; 3.90)	-1.64 (-4.87; 1.60)	0.30 (-2.19; 2.79)	**Celecoxib 400mg**

D

Placebo	-11.10 (-15.68; -6.51)	-6.19 (-15.64; 3.26)	-9.09 (-18.54; 0.36)	-8.69 (-18.14; 0.76)	-14.32 (-20.26; -8.38)	-10.08 (-19.52; -0.63)	-10.07 (-22.76; 2.63)
5.60 (3.79; 7.41)	**Naproxen 1,000mg**	4.91 (-5.60; 15.41)	2.01 (-8.50; 12.51)	2.41 (-8.10; 12.91)	-3.22 (-8.96; 2.52)	1.02 (-9.48; 11.52)	1.03 (-12.47; 14.53)
5.00 (0.15; 9.85)	-0.60 (-5.78; 4.58)	**Meloxicam 7.5mg**	-2.90 (-12.35; 6.55)	-2.50 (-11.95; 6.95)	-8.13 (-19.29; 3.04)	-3.89 (-13.34; 5;56)	-3.88 (-16.58; 8.83)
6.00 (1.15; 10.85)	0.40 (-4.78; 5.58)	1.00 (-3.85; 5.85)	**Meloxicam 22.5mg**	0.40 (-9.05; 9.85)	-5.23 (-16.39; 5.94)	-0.99 (-10.44; 8.46)	-0.98 (-13.68; 11.73)
5.75 (0.90; 10.60)	0.15 (-5.03; 5.33)	0.75 (-4.10; 5.60)	-0.25 (-5.10; 4.60)	**Meloxicam 15mg**	-5.63 (-16.79; 5.54)	-1.39 (-10.84; 8.06)	-1.38 (-14.08; 11.33)
10.02 (7.90; 12.14)	4.43 (2.01; 6.84)	5.03 (-0.27; 10.32)	4.03 (-1.27; 9.32)	4.28 (-1.02; 9.57)	**Etoricoxib 90mg**	4.24 (-6.92; 15.40)	4.25 (-9.77; 18.27)
5.75 (0.90; 10.60)	0.15 (-5.03; 5.32)	0.75 (-4.10; 5.60)	-0.25 (-5.10; 4.60)	-0.00 (-4.85; 4.85)	-4.28 (-9.57; 1.02)	**Diclofenac 150mg**	0.01 (-8.49; 8.51)
3.75 (-2.15; 9.65)	-1.85 (-8.02; 4.32)	-1.25 (-7.15; 4.65)	-2.25 (-8.15; 3.65)	-2.00 (-7.90; 3.90)	-6.28 (-12.55; -0.01)	-2.00 (-5.36; 1.36)	**Celecoxib 400mg**

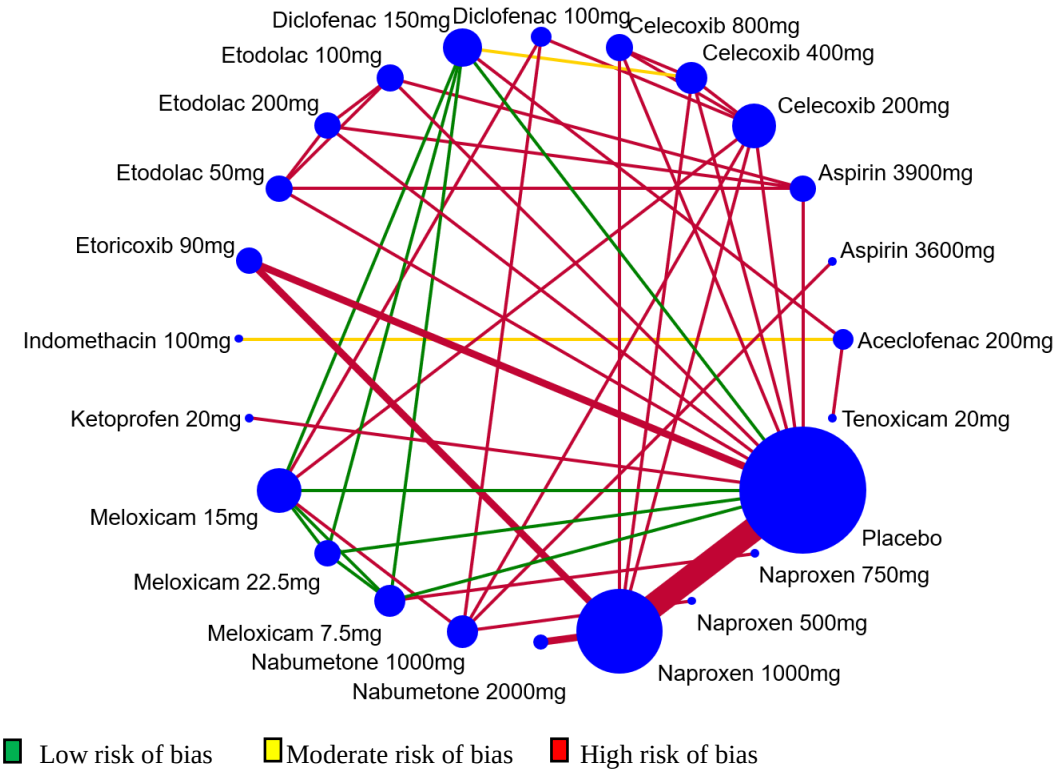
Notes. 4A. Pain; 4B. Physical function; 4C. Number of tender/painful joints (upper right quarter) and number of swollen joints (lower left quarter); 4D. Patient's global assessment (upper right quarter) and physician's global assessment (lower left quarter).

Safety of the interventions

All studies were included in the meta-analysis. Overall, 10,072 patients reported a number of adverse events for 12 different NSAIDs assessed in 56 arms. Of the 21 trials,

10 (41.6%) were two-arm studies and 11 (58.3%) were multiple-arm studies (Figure 5). Although adverse events were reported for most drugs, only etoricoxib 90 was associated with more adverse events compared to placebo (RR: 4.43, 95% CI: 1.22; 16.08) (evidence of low quality) (Figure 6).

Figure 5 - Evidence structure of eligible comparisons for network meta-analysis: adverse events.



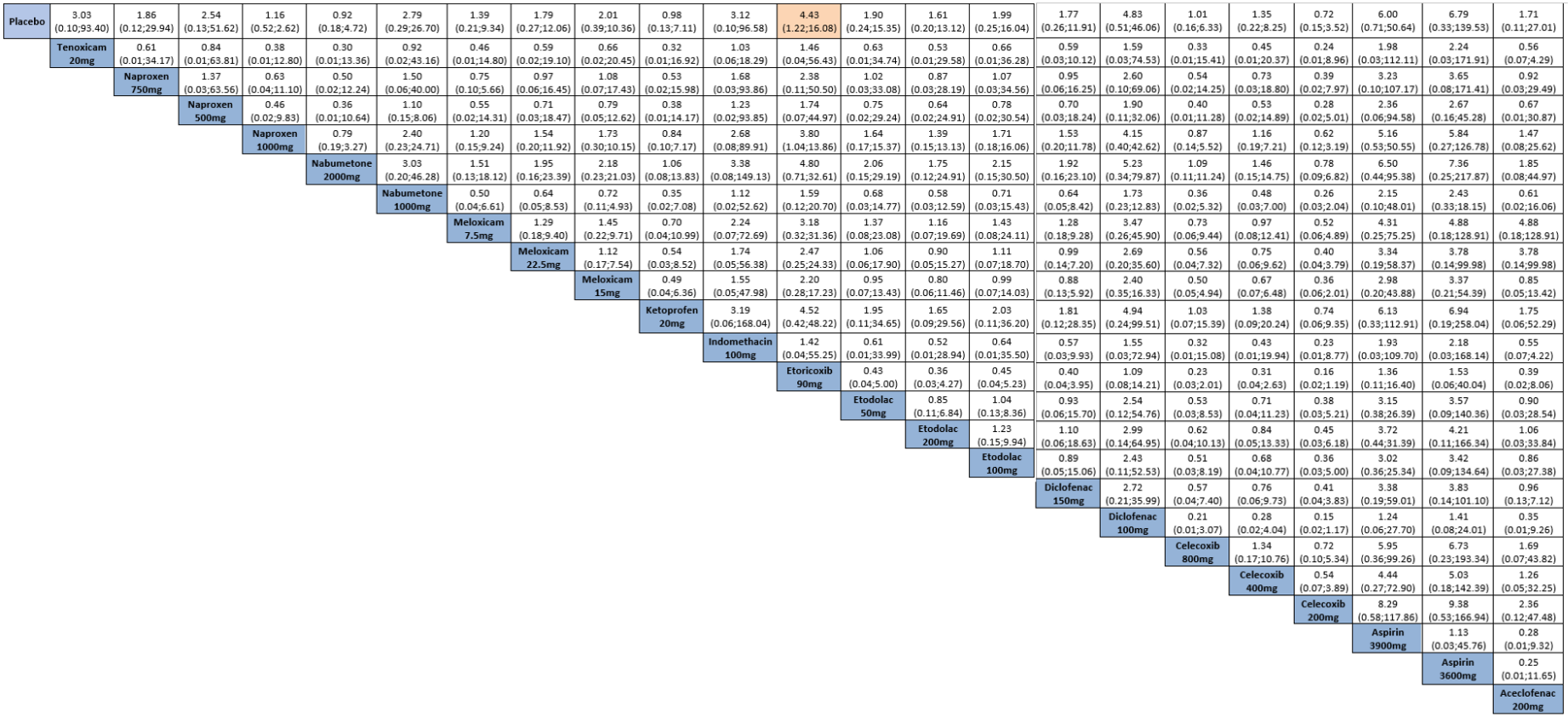
Notes. Lines connect the interventions that have been studied in head-to-head (direct) comparisons in the eligible randomized controlled trials. The width of the lines represents the cumulative number of randomized controlled trials for each pairwise comparison and the size of every node is proportional to the number of randomized participants (sample size).

In most of the studies, gastrointestinal adverse events were the issues most commonly reported by patients using NSAIDs. Abdominal pain, diarrhea, dyspepsia and nausea were the most frequent events reported in 18 studies(39-47, 49-52, 54-58). NSAIDs responsible for the highest incidence of these events were diclofenac(42, 43, 55) and naproxen(40, 41, 44-46, 50, 52, 57) at any dose.

Hypertension(40, 44, 46) and headache(40, 42, 46, 51, 56, 57) were commonly reported adverse events. No study reported serious adverse events leading to death or

hospitalization. Early discontinuation due to treatment failure or to adverse events did not differ statistically between the groups and was not associated with any specific NSAID.

Figure 6 - Comparative adverse events between drugs using network meta-analysis. Comparisons should be read from left to right. Odds ratio for comparisons are located in the common cell between the column-defining and row-defining treatment. Numbers on highlighted background are statistically significant.



Placebo	3.03 (0.10;93.40)	1.86 (0.12;29.94)	2.54 (0.13;51.62)	1.16 (0.52;2.62)	0.92 (0.18;4.72)	2.79 (0.29;26.70)	1.39 (0.21;9.34)	1.79 (0.27;12.06)	2.01 (0.39;10.36)	0.98 (0.13;7.11)	3.12 (0.10;96.58)	4.43 (1.22;16.08)	1.90 (0.24;15.35)	1.61 (0.20;13.12)	1.99 (0.25;16.04)	1.77 (0.26;11.91)	4.83 (0.51;46.06)	1.01 (0.16;6.33)	1.35 (0.22;8.25)	0.72 (0.15;3.52)	6.00 (0.71;50.64)	6.79 (0.33;139.53)	1.71 (0.11;27.01)
	Tenoxicam 20mg	0.61 (0.01;34.17)	0.84 (0.01;63.81)	0.38 (0.01;12.80)	0.30 (0.01;13.36)	0.92 (0.02;43.16)	0.46 (0.01;14.80)	0.59 (0.02;19.10)	0.66 (0.02;20.45)	0.32 (0.01;16.92)	1.03 (0.06;18.29)	1.46 (0.04;56.43)	0.63 (0.01;34.74)	0.53 (0.01;29.58)	0.66 (0.01;36.28)	0.59 (0.03;10.12)	1.59 (0.03;74.53)	0.33 (0.01;15.41)	0.45 (0.01;20.37)	0.24 (0.01;8.96)	1.98 (0.03;112.11)	2.24 (0.03;171.91)	0.56 (0.07;4.29)
		Naproxen 750mg	1.37 (0.03;63.56)	0.63 (0.04;11.10)	0.50 (0.02;12.24)	1.50 (0.06;40.00)	0.75 (0.10;5.66)	0.97 (0.06;16.45)	1.08 (0.07;17.43)	0.53 (0.02;15.98)	1.68 (0.03;93.86)	2.38 (0.11;50.50)	1.02 (0.03;33.08)	0.87 (0.03;28.19)	1.07 (0.03;34.56)	0.95 (0.06;16.25)	2.60 (0.10;69.06)	0.54 (0.02;14.25)	0.73 (0.03;18.80)	0.39 (0.02;7.97)	3.23 (0.10;107.17)	3.65 (0.08;171.41)	0.92 (0.03;29.49)
			Naproxen 500mg	0.46 (0.02;9.83)	0.36 (0.01;10.64)	1.10 (0.15;8.06)	0.55 (0.02;14.31)	0.71 (0.03;18.47)	0.79 (0.05;12.62)	0.38 (0.01;14.17)	1.23 (0.02;93.85)	1.74 (0.07;44.97)	0.75 (0.02;29.24)	0.64 (0.02;24.91)	0.78 (0.02;30.54)	0.70 (0.03;18.24)	1.90 (0.11;32.06)	0.40 (0.01;11.28)	0.53 (0.02;14.89)	0.28 (0.02;5.01)	2.36 (0.06;94.58)	2.67 (0.16;45.28)	0.67 (0.01;30.87)
				Naproxen 1000mg	0.79 (0.19;3.27)	2.40 (0.23;24.71)	1.20 (0.15;9.24)	1.54 (0.20;11.92)	1.73 (0.30;10.15)	0.84 (0.10;7.17)	2.68 (0.08;89.91)	3.80 (1.04;13.86)	1.64 (0.17;15.37)	1.39 (0.15;13.13)	1.71 (0.18;16.06)	1.53 (0.20;11.78)	4.15 (0.40;42.62)	0.87 (0.14;5.52)	1.16 (0.19;7.21)	0.62 (0.12;3.19)	5.16 (0.53;50.55)	5.84 (0.27;126.78)	1.47 (0.08;25.62)
					Nabumetone 2000mg	3.03 (0.20;46.28)	1.51 (0.13;18.12)	1.95 (0.16;23.39)	2.18 (0.23;21.03)	1.06 (0.08;13.83)	3.38 (0.08;149.13)	4.80 (0.71;32.61)	2.06 (0.15;29.19)	1.75 (0.12;24.91)	2.15 (0.15;30.50)	1.92 (0.16;23.10)	5.23 (0.34;79.87)	1.09 (0.11;11.24)	1.46 (0.15;14.75)	0.78 (0.09;6.82)	6.50 (0.44;95.38)	7.36 (0.25;217.87)	1.85 (0.08;44.97)
						Nabumetone 1000mg	0.50 (0.04;6.61)	0.64 (0.05;8.53)	0.72 (0.11;4.93)	0.35 (0.02;7.08)	1.12 (0.02;52.62)	1.59 (0.12;20.70)	0.68 (0.03;14.77)	0.58 (0.03;12.59)	0.71 (0.03;15.43)	0.64 (0.05;8.42)	1.73 (0.23;12.83)	0.36 (0.02;5.32)	0.48 (0.03;7.00)	0.26 (0.03;2.04)	2.15 (0.10;48.01)	2.43 (0.33;18.15)	0.61 (0.02;16.06)
							Meloxicam 7.5mg	1.29 (0.18;9.40)	1.45 (0.22;9.71)	0.70 (0.04;10.99)	2.24 (0.07;72.69)	3.18 (0.32;31.36)	1.37 (0.08;23.08)	1.16 (0.07;19.69)	1.43 (0.08;24.11)	1.28 (0.18;9.28)	3.47 (0.26;45.90)	0.73 (0.06;9.44)	0.97 (0.08;12.41)	0.52 (0.06;4.89)	4.31 (0.25;75.25)	4.88 (0.18;128.91)	4.88 (0.18;128.91)
								Meloxicam 22.5mg	1.12 (0.17;7.54)	0.54 (0.03;8.52)	1.74 (0.05;56.38)	2.47 (0.25;24.33)	1.06 (0.06;17.90)	0.90 (0.05;15.27)	1.11 (0.07;18.70)	0.99 (0.14;7.20)	2.69 (0.20;35.60)	0.56 (0.04;7.32)	0.75 (0.06;9.62)	0.40 (0.04;3.79)	3.34 (0.19;58.37)	3.78 (0.14;99.98)	3.78 (0.14;99.98)
									Meloxicam 15mg	0.49 (0.04;6.36)	1.55 (0.05;47.98)	2.20 (0.28;17.23)	0.95 (0.07;13.43)	0.80 (0.06;11.46)	0.99 (0.07;14.03)	0.88 (0.13;5.92)	2.40 (0.35;16.33)	0.50 (0.05;4.94)	0.67 (0.07;6.48)	0.36 (0.06;2.01)	2.98 (0.20;43.88)	3.37 (0.21;54.39)	0.85 (0.05;13.42)
										Ketoprofen 20mg	3.19 (0.06;168.04)	4.52 (0.42;48.22)	1.95 (0.11;34.65)	1.65 (0.09;29.56)	2.03 (0.11;36.20)	1.81 (0.12;28.35)	4.94 (0.24;99.51)	1.03 (0.07;15.39)	1.38 (0.09;20.24)	0.74 (0.06;9.35)	6.13 (0.33;112.91)	6.94 (0.19;258.04)	1.75 (0.06;52.29)
											Indomethacin 100mg	1.42 (0.04;55.25)	0.61 (0.01;33.99)	0.52 (0.01;28.94)	0.64 (0.01;35.50)	0.57 (0.03;9.93)	1.55 (0.03;72.94)	0.32 (0.01;15.08)	0.43 (0.01;19.94)	0.23 (0.01;8.77)	1.93 (0.03;109.70)	2.18 (0.03;168.14)	0.55 (0.07;4.22)
												Etoricoxib 90mg	0.43 (0.04;5.00)	0.36 (0.03;4.27)	0.45 (0.04;5.23)	0.40 (0.04;3.95)	1.09 (0.08;14.21)	0.23 (0.03;2.01)	0.31 (0.04;2.63)	0.16 (0.02;1.19)	1.36 (0.11;16.40)	1.53 (0.06;40.04)	0.39 (0.02;8.06)
													Etodolac 50mg	0.85 (0.11;6.84)	1.04 (0.13;8.36)	0.93 (0.06;15.70)	2.54 (0.12;54.76)	0.53 (0.03;8.53)	0.71 (0.04;11.23)	0.38 (0.03;5.21)	3.15 (0.38;26.39)	3.57 (0.09;140.36)	0.90 (0.03;28.54)
														Etodolac 200mg	1.23 (0.15;9.94)	1.10 (0.06;18.63)	2.99 (0.14;64.95)	0.62 (0.04;10.13)	0.84 (0.05;13.33)	0.45 (0.03;6.18)	3.72 (0.44;31.39)	4.21 (0.11;166.34)	1.06 (0.03;33.84)
															Etodolac 100mg	0.89 (0.05;15.06)	2.43 (0.11;52.53)	0.51 (0.03;8.19)	0.68 (0.04;10.77)	0.36 (0.03;5.00)	3.02 (0.36;25.34)	3.42 (0.09;134.64)	0.86 (0.03;27.38)
																Diclofenac 150mg	2.72 (0.21;35.99)	0.57 (0.04;7.40)	0.76 (0.06;9.73)	0.41 (0.04;3.83)	3.38 (0.19;59.01)	3.83 (0.14;101.10)	0.96 (0.13;7.12)
																	Diclofenac 100mg	0.21 (0.01;3.07)	0.28 (0.02;4.04)	0.15 (0.02;1.17)	1.24 (0.06;27.70)	1.41 (0.08;24.01)	0.35 (0.01;9.26)
																		Celecoxib 800mg	1.34 (0.17;10.76)	0.72 (0.10;5.34)	5.95 (0.36;99.26)	6.73 (0.23;193.34)	1.69 (0.07;43.82)
																			Celecoxib 400mg	0.54 (0.07;3.89)	4.44 (0.27;72.90)	5.03 (0.18;142.39)	1.26 (0.05;32.25)
																				Celecoxib 200mg	8.29 (0.58;117.86)	9.38 (0.53;166.94)	2.36 (0.12;47.48)
																					Aspirin 3900mg	1.13 (0.03;45.76)	0.28 (0.01;9.32)
																						Aspirin 3600mg	0.25 (0.01;11.65)
																							Aceclofenac 200mg

Ranking of treatments and outcomes

Table 2 shows the mean values of SUCRA providing the hierarchy of 24 treatments on the outcomes assessed based on absolute rank probabilities. Tenoxicam 20, nabumetone 2,000 and aceclofenac 200 were most effective at reducing pain (4.3%, 4.6% and 4.8%, respectively).

As for improvement of physical function, naproxen 1,000 (2.6%), meloxicam 22.5 (2.7%) and meloxicam 15 (3.0%) showed the best results.

Regarding number of tender/painful joints and swollen joints, etoricoxib 90 (2.1%) and naproxen 750 (1.1%) had the highest improvement rates, respectively.

As for patient's global assessment and physician's global assessment, etoricoxib 90 was considered the best intervention for both variables (2.0% and 1.2%, respectively). Celecoxib 200, placebo and nabumetone 2,000 were associated with a smaller number of adverse events and had the best safety profile, with rates of 6.0%, 7.8% and 7.9%, respectively.

Table 2 - Ranking of treatments for the outcomes assessed. Bold numbers on highlighted background are first in ranking. For the safety outcome, the highlight represents the safest. For effectiveness outcomes, the highlight represents the most effective.

	Safety		Improvement of pain		Improvement of physical function		Number of tender/painful joints		Number of swollen joints		Patient's Global Assessment		Physician's Global Assessment	
Interventions	SUCRA	Mean Rank	SUCRA	Mean Rank	SUCRA	Mean Rank	SUCRA	Mean Rank	SUCRA	Mean Rank	SUCRA	Mean Rank	SUCRA	Mean Rank
Celecoxib 200 mg	78.1	**6.0**	-	-	-	-	-	-	-	-	-	-	-	-
Placebo	70.4	7.8	10.7	9.9	10.7	6.4	12.9	8	13.0	8.0	4.0	7.7	2.3	7.8
Nabumetone 2.0g	69.9	7.9	63.9	4.6	-	-	-	-	-	-	-	-	-	-
Ketoprofen 20 mg	66.9	8.6	-	-	-	-	-	-	-	-	-	-	-	-
Celecoxib 800 mg	66.1	8.8	-	-	-	-	-	-	-	-	-	-	-	-
Naproxen 1.0g	64.3	9.2	-	-	73.2	**2.6**	65.9	3.7	-	-	63.9	3.5	52.8	4.3
Meloxicam 7.5 mg	60.1	10.2	35.9	7.4	37.0	4.8	36.2	6.1	55.2	4.6	31.0	5.8	44.3	4.9
Celecoxib 400 mg	59.3	10.4	45.2	6.5	45.6	4.3	55.1	4.6	42.1	5.6	57.7	4.0	30.0	5.9
Etodolac 200 mg	52.9	11.8	-	-	-	-	-	-	-	-	-	-	-	-
Aceclofenac 200g	52.3	12.0	62.4	4.8	-	-	-	-	-	-	-	-	-	-
Naproxen 750 mg	51.2	12.2	55.2	5.5	-	-	79.6	2.6	99.2	**1.1**	-	-	-	-
Diclofenac 150 mg	51.0	12.3	55.0	5.5	43.9	4.4	50.0	5.0	32.4	6.4	58.3	3.9	57.9	3.9
Meloxicam 22.5 mg	50.4	12.4	49.5	6.0	72.2	2.7	37.8	6.0	52.8	4.8	52.4	4.3	58.7	3.9
Etodolac 100 mg	49.0	12.7	-	-	-	-	-	-	-	-	-	-	-	-
Meloxicam 15 mg	49.3	12.7	53.9	5.6	67.4	3.0	26.6	6.9	18.7	7.5	47.7	4.7	57.4	4.0
Etodolac 50 mg	48.7	12.8	-	-	-	-	-	-	-	-	-	-	-	-
Naproxen 500 mg	43.8	13.9	-	-	-	-	-	-	-	-	-	-	-	-
Nabumetone 1.0g	40.8	14.6	51.4	5.9	-	-	-	-	54.8	4.6	-	-	-	-
Indomethacin 100mg	38.6	15.1	-	-	-	-	-	-	-	-	-	-	-	-
Tenoxicam 20 mg	38.9	15.1	67.1	**4.3**	-	-	-	-	-	-	-	-	-	-
Diclofenac 100 mg	26.8	17.8	-	-	-	-	-	-	-	-	-	-	-	-
Etoricoxib 90 mg	25.8	18.1	-	-	-	-	86.1	**2.1**	81.9	2.4	85.0	**2.0**	96.6	**1.2**
Aspirin 3.600 mg	24.1	18.5	-	-	-	-	-	-	-	-	-	-	-	-
Aspirin 3.900 mg	21.5	19.1	-	-	-	-	-	-	-	-	-	-	-	-

Notes. SUCRA: surface under the cumulative ranking curve. Ranking: ordering of treatments according to their relative effectiveness. The first ranked treatment is most likely to be the most effective treatment regarding a particular outcome compared to other treatments in the network. Numbers on highlighted background are statistically significant.

Steroidal anti-inflammatories for rheumatoid arthritis

Description of studies

Five trials involving 1,544 patients were included. The mean age of the participants ranged from 39.9 to 58 years. These studies investigated the drugs prednisone 5, 7.5, 10 and 15 and prednisolone 7.5, administered orally. Patient follow-up ranged from 12 to 104 weeks (table 3).

Table 3 - Characteristics of the 5 studies on steroidal anti-inflammatories included

Study	Interventions	Outcomes reported	Sample size (N)	Lost follow-up (%)	Duration (weeks)	Mean age (years)	Woman (%)
Bakker et al., 2012[15]	**methotrexate* and prednisone 10, methotrexate* and placebo**	**1,2,5**	**236**	**27.9**	**52**	**53.5**	**60.1**
Buttgereit et al., 2013[63]	prednisone 5, placebo	2,5	350	7.7	12	57.3	84
Choy et al., 2008[14]	methotrexate alone**, methotrexate** and ciclosporin***, methotrexate** and prednisolone, methotrexate**, ciclosporin*** and prednisolone[$]	1,2,3,4,5	467	18.8	52	54	69.5
Ding et al., 2012[64]	prednisone 7.5, prednisone 15, placebo[$$]	5	266	5.6	12	43	85.3
Hafstrom et al., 2014[65]	prednisolone 7.5, placebo	1	225	46.2	104	54.5	64

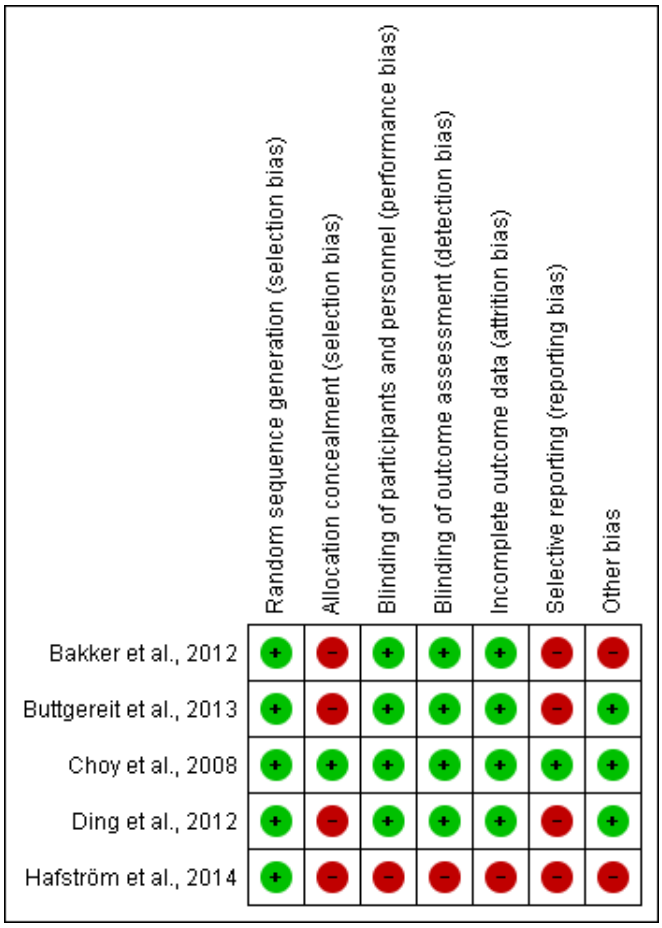
Notes. *dose increased by 5 mg/week until remission; **starting at 7.5 mg/week, increasing incrementally up to target dose of 15 mg/week; ***ciclosporin started 3 months after methotrexate (initial dose 100 mg/day, increased gradually up to target dose of 3 mg/kg daily); [$]60 mg/day initially, reduced to 7.5 mg daily from 6 to 28 weeks, stopped by week 34; [$$]all groups received leflunomide 20 mg/day and methotrexate 10 mg/day; Outcomes reported: 1. Progression of the disease assessed by radiological imaging of joints; 2. Disease activity; 3. Function; 4. Quality of life; 5. Adverse events.

Risk of bias of eligible studies (Figure 7)

All of the assessed trials considered eligible were at high risk of bias, except for the trial of Choy et al. (2008)(60) which was at minimum risk of bias. Allocation concealment was insufficiently described in four studies(15, 61-63). One study did not describe the blinding of patients and healthcare professionals and failed to report whether there were patients lost at follow-up(63).

The studies of Bakker et al. (2012)(15), Buttegereit et al. (2013)(61), Ding et al. (2012)(62) and Hafstrom et al. (2014)(63) did not describe other important outcomes, such as reduction of pain, swelling and duration of morning stiffness or the main adverse events reported by patients, leading to reporting bias. Two clinical trials did not cite diagnostic criteria used for participants inclusion(15, 63).

Figure 7 - Risk of bias for studies on steroidal anti-inflammatories (n=5)



Effect of interventions

One placebo-controlled randomized controlled trial of 2 years investigated whether adding prednisone 10 to the therapy increased effectiveness of methotrexate (dose was increased by 5 mg/week until remission) for treatment of early rheumatoid arthritis. Erosive joint damage was significantly lower for the methotrexate and prednisone group ($p<0.022$), which was also more effective at reducing disease activity ($p<0.001$) compared to the control group (methotrexate and placebo). Adverse events were similar for both groups, with the most frequent gastrointestinal-related events being nausea, diarrhea and stomachache, whereas central nervous system events included headache, dizziness and blurred vision. The number of serious adverse events also did not differ between groups(15).

In another randomized controlled trial, 350 patients were randomized and received prednisone 5 or placebo. The authors showed that prednisone significantly increased the

proportion of patients achieving low disease activity (p=0.0109) and that the incidence of adverse events was similar for both groups (7.8% vs 8.4%). In both groups, the most frequent adverse events were related to worsening of the disease and to arthralgia and occurred statistically more frequently in the placebo group (p=0.0141). The most reported events after arthralgia were nasopharyngitis, headache, hypertension and diarrhea(61).

Choy et al. (2008)(60) randomized patients into four groups: methotrexate (starting at 7.5 mg/week, increasing incrementally up to target dose of 15 mg/week); prednisolone (starting at 60 mg/day, reduced to 7.5 mg at the 6th week, 7.5 mg daily from the 6th to the 28th week, stopped at the 34th week); cyclosporin (started 3 months after methotrexate treatment at initial dose of 100 mg/day, increased gradually up to target dose of 3 mg/kg daily); and triple therapy (methotrexate, prednisolone and cyclosporin). Erosions were reduced due to the use of prednisolone (p=0.03) and cyclosporin (p=0.01). There was an improvement in quality of life for all assessed treatments for 6 months. A great number of patients on triple therapy left the study due to adverse events.

One randomized controlled trial assessed outcome safety in 266 patients randomized in three groups: placebo, prednisone 7.5 and prednisone 15. All groups used concomitantly leflunomide 20 and methotrexate 10. The combination therapy with prednisone 7.5, leflunomide 20 and methotrexate 10 showed that the incidence of adverse events, such as skin rash, liver dysfunction and oral ulcers decreased. The authors concluded that this therapy could be a useful option for initial treatment of early rheumatoid arthritis (62).

One randomized controlled trial assessed the predictors of radiographic progression in 225 patients suffering from rheumatoid arthritis treated with or without prednisolone. The study showed that the frequency of patients with radiographic progression after 2 years was smaller (26%) for the prednisolone group 7.5 in comparison to the placebo group (39%) (p=0.033)(63).

DISCUSSION

Summary of evidence and comparison of findings with previous studies

This systematic review assessed the available evidence on effectiveness and safety of NSAIDs and corticoids for the treatment of rheumatoid arthritis. Twenty-one included randomized controlled trials assessed the use of NSAIDs, mainly via oral administration. The main methodological flaws were absence of allocation concealment and high dropout rates; it was also often unclear how analyses were performed or how the studies dealt with missing data.

In general, it was observed that naproxen 1,000 improved physical function and reduced overall pain and number of painful and swollen joints, providing benefits according to the patient's and physician's global assessment compared to placebo. Also, naproxen 750 was better than most of the NSAIDs at reducing the number of swollen joints (including naproxen 1,000), except in comparation to etoricoxib 90. However, the quality of evidence was very low overall. It can be observed that naproxen did not exhibit a dose-dependent behaviour as the 750 dose was more effective than the 1,000 dose for the number of swollen joints outcome.

Etoricoxib 90 was also reported to reduce the number of painful and swollen joints and provided better results according to the patient's global assessment compared to placebo. In addition, it was better than both celecoxib 400 and naproxen 1,000, according to physician's global assessment. Likewise, the quality of evidence was very low.

No study using NSAIDs reported the primary outcome "progression of disease as assessed by radiological imaging of joints". Also, it was not possible to perform meta-analysis for the outcomes morning stiffness, average grip strength and improvement of quality of life.

In another review, celecoxib 200 showed significant pain reduction compared to placebo (11% absolute improvement; 95% CI 8% to 14%),[66] which was not evidenced in our review. However, this study also related low quality of the evidence, mainly due to risk of bias and inconsistency among randomized controlled trials.

Etoricoxib 90 improved overall outcomes when compared to placebo, but did not have a good safety profile according to the ranking hierarchy of 24 treatments. Celecoxib 200, nabumetone 2,000 and placebo were associated with a smaller number of adverse events. The most common side effects reported by patients using NSAIDs were gastrointestinal events and no serious adverse events were documented.

Findings from safety data showed that piroxicam or etodolac did not lead to clinically significant adverse events and that mild adverse events were evidenced by the use of celecoxib or etoricoxib such as nausea, vomiting and headaches. However, the quality of the evidence did not allow confirmation as to which NSAID is safest(9).

Evidence of moderate to low quality reported fewer withdrawals among patients which had received celecoxib compared to those receiving placebo. Celecoxib 200 was associated with a smaller number of adverse events but it was observed that patients developed more ulcers and severe short-term symptoms. (64).

We summarized dates of 5 studies that assessed the use of corticoids (prednisolone 7.5 and prednisone 5.0, 7.5 and 10) for treatment of rheumatoid arthritis. It was observed benefits due to use of these drugs in reduction of joint erosion (15, 60, 63) and of disease activity(15, 61). Due to different interventions employed in these clinical trials, it was not possible to perform meta-analysis. Besides that, issues regarding risk of bias decreased reliability of such findings.

Regarding safety of corticoids, gastrointestinal adverse events were the issues most often reported by patients using these drugs. In the described studies, corticoids are usually used in association with methotrexate, and thus attention should be focused on the adverse effects of combined therapy.

The effects of prednisone or similar corticoid preparations administered alongside standard therapy (doses ranging from 270mg to 5,800mg, over the first year) reduced progression of joint erosion in rheumatoid arthritis, according to a systematic review published in 2007(25). Only one clinical trial included in this review(14) was also selected for our study due to differences in eligibility criteria. In our findings, two studies used prednisone at doses of 5-10 demonstrating benefit of using this medication for this outcome (62, 63).

A systematic review showed that prednisolone administrated orally at low doses (maximum of 15 mg/day) was more effective than placebo and NSAIDs at decreasing joint tenderness and pain, but the quality of the evidence was not assessed by the authors(26). According to older evidences, after six months, the effects of prednisolone (maximum 15 mg/day) were significantly better compared to placebo for number of painful joints, number of swollen joints, pain and physical function(24). However, small sample size, high risk of bias and the fact that quality of evidence was not assessed compromise such findings.

Strengths and limitations of this study

The methodology employed in this review includes explicit eligibility criteria, comprehensive and extensive database searches and independent and paired evaluation to select studies. Meticulous search and selection processes were carried out, and we are confident that all trials meeting the inclusion criteria were included in the review. Robust statistical techniques were used to assess risk of bias of the included studies.

The decision to provide network analysis is relevant as it provides information in situations where primary evidence is scarce or nonexistent and allows for more accurate

estimates of effects[68]. Even though a broad search strategy was carried out and that we did not exclude any studies due to language barriers or to date of publication, some bias cannot be considered inexistent. It was possible analyse publicatio bias just for safety outcomes, due to the small number of studies reporting the same outcome in effectiveness.

Some studies did not record the concomitant use of other analgesic agents and/or the dose used, which can mislead outcomes for pain measurement, for example.

For some studies that did not provide variance measures necessary for meta-analysis, we estimated missing data with approximate values derived graphically from the studies themselves. This could have created some bias, but the overall impact on the estimation of statistically significant differences between groups is probably small.

The quality of the primary studies included in this review was a limiting factor for proper analysis to be carried out. Besides that, the diversity of drugs and doses used and the poor manner how outcomes were reported could have decreased the quality of our findings.

Implications for clinical practice and research

According to our findings, even though etoricoxib 90 and naproxen 1,000 appear to be effective NSAIDs and that celecoxib 200 seems to be the safest option, the low quality of the evidence suggests that futures randomized controlled trials can demonstrate different results.

Prednisone and prednisolone are the corticoids used for treatment of rheumatoid arthritis and they seem to be effective and generate only mild adverse events when used at lower doses. However, due to not being possible to perform the meta-analysis of the studies involving these drugs, the evidence of such findings could not be confirmed.

We observed that the clinical trials suffered from methodological limitations, differences regarding the anti-inflammatories studied and their doses, concurrent use of other medications and differents outcomes, which contributed to limiting the conclusions based on our findings. Future randomized controlled trials should consider these limitations and therefore obtain long-term data. Also, adequate follow-up and larger sample sizes are required for future research.

Conclusion

Naproxen, prednisolone and prednisone were considered the most effective drugs and celecoxib showed fewer adverse events. However, the low quality of the evidence observed for

the outcomes of NSAIDs, the absence of meta-analyses to assess the outcomes of corticoids and the risk of bias observed in the trials indicate that future randomized controlled trials are needed to confirm such findings.

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Competing interests None.

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Appendix A. PRISMA Checklist incorporating Network Meta-analyses

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review incorporating a network meta-analysis (or related form of meta-analysis).	42
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and synthesis methods, such as network meta-analysis. Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity. Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	42
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, including mention of why a network meta-analysis has been conducted.	43
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	44
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	44
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. Clearly describe eligible treatments included in the treatment network and note whether any have been clustered or merged into the same node (with justification).	44

Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	46
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	46
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	46
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	46
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	47
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were com piled and used to describe the evidence base to readers.	47
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	47
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (5UCRA) values, as well as modified approaches used to present summary findings from meta-analyses.	48
Planned methods of analysis	14	Describe the methods of handling data and com bining results of studies for each network meta-analysis. This should include, but not be limited to: handling of multigroup trials; selection of variance structure; selection of prior distributions in Bayesian analyses; and assessment of model fit.	48
Assessment of inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	48
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	48
Addition al analyses	16	Describe methods of additional analyses if done, indicating which were prespecified. This may include, but not be limited to, the following: Sensitivity or subgroup analyses; Meta-regression analyses; Alternative formulations of the treatment network; and use of alternative prior distributions for Bayesian analyses (if applicable).	48

Section/topic	#	Checklist item	Reported on page #
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	50
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	56
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	56
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	52
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	53
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. Modified approaches may be needed to deal with information from larger networks.	55
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. In larger networks, authors may focus on comparisons versus a particular comparator (e.g., placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.	56
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, P values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	56

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	56
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth).	63
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	67
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).	69
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	70
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	71

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix B. Terms used for search strategies.

MESH TERMS	ENTRY TERMS
"Arthritis, Rheumatoid"	Arthritis, Rheumatoid
"Anti Inflammatory Agents, Non teroidal"	Anti Inflammatory Agents, Non Steroidal OR Antiinflammatory Agents, Non Steroidal OR Antiinflammatory Agents, Nonsteroidal OR Nonsteroidal Anti-Inflammatory Agents OR Nonsteroidal Anti Inflammatory Agents OR NSAIDs OR Anti Inflammatory Agents, Nonsteroidal OR Non-Steroidal Anti-Inflammatory Agents OR Non Steroidal Anti Inflammatory Agents OR Aspirin-Like Agents OR Aspirin Like Agents OR Analgesics, Anti-Inflammatory OR Analgesics, Anti Inflammatory OR Anti-Rheumatic Agents, Non-Steroidal OR Agents, Non-Steroidal Anti-Rheumatic OR Anti Rheumatic Agents, Non Steroidal OR Antirheumatic Agents, Non-Steroidal OR Agents, Non-Steroidal Antirheumatic OR Antirheumatic Agents, Non Steroidal OR Non-Steroidal Antirheumatic Agents OR nsaid
"Glucocorticoid"	Glucocorticoid OR Glucocorticoid Effect OR Effect, Glucocorticoid OR Glucorticoid Effects OR Effects, Glucorticoid
Other terms combined	Aceclofenac OR aspirin OR Acetaminophen OR Ampyrone OR Amynopirin OR Antipyrine OR Apazone OR Bufexamac OR Clofazimine OR Clonixin OR Curcumin OR Diclofenac OR Diflunisal OR Epirizole OR Etodolac OR Fenbufen OR Fenclofenac OR Fenoprofen OR Floctafenine OR Flurbiprofen OR Ibuprofen OR Indomethacin OR Ketoprofen OR Ketorolac OR Lederfen OR Meclofenamic Acid OR Mefenamic Acid OR Mesalamine OR Nabumeton OR Naproxen OR Niflumic Acid OR Oxaprozin OR Oxyphenbutazone OR Antipyrine OR Phenylbutazone OR Piroxicam OR pirazolac OR pirprofen OR Mefenamic Acid OR Feprazone OR Sulfasalazine OR Sulindac OR Suprofen OR Tenoxicam OR Tiaprofenic acid OR tolfenamic acid OR Tolmetin OR ximoprofen OR beclomethasone OR betamethasone OR budesonide OR cortisone OR dexamethasone OR flunisolide OR fluticasone OR fludrocortisone OR hydrocortisone OR methylprednisolone OR mometasone Furoate OR prednisolone OR prednisone OR triamcinolone

Appendix C. Search strategies for different databases.

COCHRANE

(Arthritis, Rheumatoid) AND (Anti Inflammatory Agents, Non Steroidal OR Glucocorticoid) AND (randomized controlled trial)

MEDLINE (Via Ovid)

((Arthritis, Rheumatoid)) AND ((Anti Inflammatory Agents, Non Steroidal OR Analgesics, Anti-Inflammatory OR Glucocorticoid OR corticoids OR corticosteroids)) AND ((randomized controlled trial) OR randomization OR (control group) AND limit to human.

EMBASE (Via Ovid)

((Arthritis, Rheumatoid)) AND ((Anti Inflammatory Agents, Non Steroidal OR Analgesics, Anti-Inflammatory OR Glucocorticoid OR corticoids OR corticosteroids)) AND ((randomized controlled trial) OR randomization OR (control group) AND limit to human.

CINAHAL (Via Ovid)

((Arthritis, Rheumatoid)) AND ((Anti Inflammatory Agents, Non Steroidal OR Analgesics, Anti-Inflammatory OR Glucocorticoid OR corticoids OR corticosteroids)) AND ((randomized controlled trial) OR randomization OR (control group)

Web of science

((Arthritis, Rheumatoid)) AND ((Anti Inflammatory Agents, Non Steroidal OR Analgesics, Anti-Inflammatory OR Glucocorticoid OR corticoids OR corticosteroids)) AND ((randomized controlled trial) OR randomization OR (control group)

Clinical trial.gov

(Arthritis, Rheumatoid) AND (Anti Inflammatory Agents, Non Steroidal OR Glucocorticoid)

BVS

(Arthritis, Rheumatoid) AND (Anti Inflammatory Agents, Non Steroidal OR Analgesics, Anti-Inflammatory OR Glucocorticoid OR corticoids OR corticosteroids) AND (randomized

controlled trial OR randomization OR control group)

WHO

(Arthritis, Rheumatoid) AND (Anti Inflammatory Agents, Non Steroidal OR Glucocorticoid) AND (randomized controlled trial)

Appendix D. Main outcomes found in the articles not included in the meta-analysis

Study	Sample size (N)	Interventions mg/day (N)	Pain	Physical function	N of painful joints	N of swollen joints	Morning stiffness	Grip strength	Quality of life	Patients' global assessment	Physicians' global assessment
Bernhard et al., 1987[43]	234	nabumetone 1,000, aspirin 900	-	-	-	-	improvement in relation to baseline levels in both groups	improvement in relation to baseline levels in both groups	-	improvement in relation to baseline levels in both groups	-
Collantes et al., 2002[45]	687	placebo, etoricoxib 90, naproxen 1,000	naproxen 1,000 was superior to placebo	etoricoxib 90 and naproxen 1,000 were more effective than placebo	-	-	-	-	-	-	-
Emery et al., 1992[46]	284	nabumetone 2,000, naproxen 1,000	-	-	-	-	improvement in relation to baseline levels in both groups	-	-	-	-
Emery et al., 1999[47]	497	celecoxib 400, diclofenac 150	-				improvement in relation to baseline levels in both groups				
Geusens et al., 2002[49]	1023	placebo, naproxen 1,000	-	naproxen 1,000 was superior to placebo	-	-	naproxen 1,000 was superior to placebo	-	-	-	Naproxen 1,000 was superior to placebo
Geusens et al., 2004[50]	726	naproxen 500, placebo	-								
Gibofsky et al., 2007[51]	340	naproxen 1,000, placebo	-	-	-	-	naproxen 1,000 superior to placebo		Naproxen 1,000 was superior to placebo	-	-

Jacob et al., 1986[52]	264	placebo, etodolac 50, 100, 200, aspirin 3,900	etodolac 100 and 200 were superior to placebo and etodolac 50	etodolac 200 and aspirin 3,900 were superior to placebo	etodolac 200 and aspirin 3,900 were superior to placebo	etodolac 200 and aspirin 3,900 were superior to placebo	etodolac 200 and aspirin 3.900 were superior to placebo and etodolac 50	etodolac 200 and aspirin 3,900 were not superior to placebo	-	etodolac 200 or aspirin 3,900 were superior to etodolac 50	etodolac 200 was superior to placebo and aspirin 3,900 was superior to etodolac 50
Kawai et al., 2010[42]	652	placebo, ketoprofen 20	ketoprofen 20 was not superior to placebo	-	-	-	-	-	-	-	-
Kornasoff et al., 1996[53]	219	aceclofenac 200, indomethacin 100	-	improvement in relation to baseline levels in both groups	improvement in relation to baseline levels in both groups	improvement in relation to baseline levels in both groups	improvement in relation to baseline levels in both groups	-	-	improvement in relation to baseline levels in both groups	improvement in relation to baseline levels in both groups
Krug et al., 2000[54]	344	nabumetone 2,000, naproxen 1,000	-	-	improvement in relation to baseline levels in both groups	improvement in relation to baseline levels in both groups	-	-	-	improvement in relation to baseline levels in both groups	improvement in relation to baseline levels in both groups
Lightfoot, 1997[55]	361	etodolac 400, 600, piroxicam 20	-	-	improvement in relation to baseline levels in all groups	improvement in relation to baseline levels in all groups	improvement in relation to baseline levels in all groups	improvement in relation to baseline levels in both groups	-	-	-
Matsumoto et al., 2002[56]	448	placebo, etoricoxib 90, naproxen 1,000	etoricoxib 90 and naproxen 1,000 was superior to placebo; etoricoxib 90 was superior to naproxen 1,000	etoricoxib 90 was superior to placebo and naproxen 1,000	-	-	-	-	-	-	-
Pasero et al., 1995[57]	327	aceclofenac 200, diclofenac 150	-	-	-	-	improvement in relation to baseline levels in both groups	improvement in relation to baseline levels in both groups	-	-	-

Perez ruiz; Alonso ruiz; Ansoleaga, 1996[58]	237	aceclofenac 200, tenoxicam 20	-	-	-	-	improvement in relation to baseline levels in both groups	improvement in relation to baseline levels in both groups	-	-	-
Vasey et al., 1987[44]	318	nabumetone 1,000, naproxen 500	-	-	-	-	improvement in relation to baseline levels in both groups	improvement in relation to baseline levels in both groups	-	improvement in relation to baseline levels in both groups	improvement in relation to baseline levels in both groups
Williams et al., 2006[60]	1093	placebo, naproxen 500	-	-	-	-	-	-	-	naproxen (1,000 mg/day) was superior to placebo (p<0.001	naproxen (1,000 mg/day) was superior to placebo (p<0.001
Wojtulewski et al., 1996[61]	306	meloxicam 7.5, naproxen 750	-	-	-	-	improvement in relation to baseline levels in all groups	showed no statistically significant changes for variables from baseline and final	-	improvement in relation to baseline levels in both groups	improvement in relation to baseline levels in both groups
Zhao et al., 2000[62]	688	placebo, celecoxib 100, 200, 400, naproxen 1,000	-	Celecoxib 200 and 400 and naproxen 1,000 were better than placebo; celecoxib 200 was superior to naproxen 1,000.	-	-	-	-	-	-	-

Notes. Outcomes reported: 1: pain; 2: functional disability score; 3: swollen joint count; 4. tender joint count; 5: morning stiffness; 6: grip strength; 7: physician assessment; 8: patient assessment; 9: quality of life scale; 10: adverse events. NR: not reported.

Appendix E. GRADE for effectiveness and safety outcomes

CHA 1: Quality of evidence for pain outcome, according to GRADE

Comparison	Direct evidence			Indirect evidence			Network meta-analysis		
	SMD	**95% confidence interval**	**Quality of evidence**	**SMD**	**95% confidence interval**	**Quality of evidence**	**SMD**	**95% confidence interval**	**Quality of evidence**
Placebo *v* tenoxicam 20 mg	-	-	-	-15.9	(-41.5; 9.7)	Very Low**,‡,¶	-15.9	(-41.5; 9.7)	Very Low
Placebo *v* naproxen 750 mg	-	-	-	-11.0	(-20.4; -0.2)	Very Low**,‡,¶	-11.0	(-20.4; -0.2)	Very Low
Placebo *v* naproxen 1,000 mg	10.3	(5.8; 14.8)	Very Low**,†	-2.0	(-58.7; 54.8)	Very Low**,‡,†,¶	-10.3	(-20.4; -0.2)	**Very Low**
Placebo *v* nabumetone 2,000 mg	-	-	-	-14.2	(-32.0; 3.6)	Very Low**,‡,¶	-14.2	(-32.0; 3.6)	Very Low
Placebo *v* meloxicam 7,5 mg	6.8	(7.3; 12.1)	Moderate†	-9.9	(-63.0; 43.2)	Very Low‡,†,¶	-6.6	(-20.6; 7.2)	Moderate
Placebo *v* meloxicam 22,5 mg	9.9	(7.3; 15.2)	Moderate†	-14.7	(-75.6; 46.2)	Very Low‡,†,¶	-9.8	(-23.7; 4.1)	Moderate
Placebo *v* meloxicam 15 mg	10.7	(7.3; 16.0)	Moderate†	-13.9	(-74.8; 47.0)	Very Low‡,†,¶	-10.6	(-24.5; 3.3)	Moderate
Placebo *v* diclofenac 150 mg	11.0	(7.3; 16.3)	Moderate†	-2.7	(-48.1; 42.6)	Very Low‡,†,¶	-10.8	(-24.6; 3.0)	Moderate
Placebo *v* celecoxib 400 mg	-	-	-	-8.7	(-28.7; 11.1)	Very Low*,‡,¶	-8.7	(-28.7; 11.1)	Very Low
Placebo *v* aceclofenac 200 mg	-	-	-	-13.9	(-35.1; 7.2)	Very Low**,‡,¶	-13.9	(-35.1; 7.2)	Very Low
Tenoxicam 20 mg *v* naproxen 750 mg	-	-	-	4.9	(-24.9; 34.8)	Very Low**,‡,¶	4.9	(-24.9; 34.8)	Very Low
Tenoxicam 20 mg *v* naproxen 1,000 mg	-	-	-	5.6	(-21.9; 33.1)	Very Low**,‡,¶	5.6	(-21.9; 33.1)	Very Low
Tenoxicam 20 mg *v* nabumetone 2,000 mg	-	-	-	1.7	(-29.5; 32.9)	Very Low**,‡,¶	1.7	(-29.5; 32.9)	Very Low
Tenoxicam 20 mg *v* meloxicam 7,5 mg	-	-	-	9.2	(-16.7; 35.2)	Very Low**,‡,¶	9.2	(-16.7; 35.2)	Very Low
Tenoxicam 20 mg *v* meloxicam 22,5 mg	-	-	-	6.1	(-19.8; 32.1)	Very Low**,‡,¶	6.1	(-19.8; 32.1)	Very Low
Tenoxicam 20 mg *v* meloxicam 15 mg	-	-	-	5.3	(-20.7; 31.3)	Very Low**,‡,¶	5.3	(-20.7; 31.3)	Very Low
Tenoxicam 20 mg *v* diclofenac 150 mg	-	-	-	5.1	(-16.5; 26.7)	Very Low**,‡,¶	5.1	(-16.5; 26.7)	Very Low
Tenoxicam 20 mg *v* celecoxib 400 mg	-	-	-	7.1	(-18.8; 33.1)	Very Low**,‡,¶	7.1	(-18.8; 33.1)	Very Low
Tenoxicam 20 mg *v* aceclofenac 200 mg	-2.0	(-7.4; 3.4)	Very Low**,‡,†	28.6	(-47.7;104)	Very Low**,‡,†,¶	1.9	(-12.4; 16.4)	Very Low
Naproxen 750 mg *v* naproxen 1,000 mg	-	-	-	0.7	(-21.9; 23.3)	Very Low**,‡,¶	0.7	(-21.9; 23.3)	Very Low
Naproxen 750 mg *v* nabumetone 2,000 mg	-	-	-	-3.2	(-30.2; 23.7)	Very Low**,‡,¶	-3.2	(-30.2; 23.7)	Very Low
Naproxen 750 mg *v* meloxicam 7,5 mg	-4.3	(-9.7; 1.1)	Very Low**,‡,†	13.4	(-73.4; 100)	Very Low**,‡,†,¶	4.2	(-10.4; 19.0)	Very Low
Naproxen 750 mg *v* meloxicam 22,5 mg	-	-	-	1.2	(-19.5; 21.8)	Very Low**,‡,¶	1.2	(-19.5; 21.8)	Very Low

Naproxen 750 mg *v* meloxicam 15 mg	-	-	-	0.4	(-10.3; 21.0)	Very Low**,‡,¶	0.4	(-10.3; 21.0)	Very Low
Naproxen 750 mg *v* diclofenac 150 mg	-	-	-	0.2	(-20.5; 20.9)	Very Low**,‡,¶	0.2	(-20.5; 20.9)	Very Low
Naproxen 750 mg *v* celecoxib 400 mg	-	-	-	2.2	(-22.9; 27.3)	Very Low**,‡,¶	2.2	(-22.9; 27.3)	Very Low
Naproxen 750 mg *v* aceclofenac 200 mg	-	-	-	-2.9	(-29.1; 23.2)	Very Low**,‡,¶	-2.9	(-29.1; 23.2)	Very Low
Naproxen 1,000 mg *v* nabumetone 2,000 mg	4.0	(-1.4; 9.4)	Very Low**,‡,†	-20.5	(-100; 59.7)	Very Low**,‡,†,¶	-3.9	(-18.6; 10.7)	Low
Naproxen 1,000 mg *v* meloxicam 7,5 mg	-	-	-	3.6	(-13.6; 20.8)	Very Low**,‡,¶	3.6	(-13.6; 20.8)	Very Low
Naproxen 1,000 mg *v* meloxicam 22,5 mg	-	-	-	0.5	(-16.7; 17.7)	Very Low**,‡,¶	0.5	(-16.7; 17.7)	Very Low
Naproxen 1,000 mg *v* meloxicam 15 mg	-	-	-	-0.3	(-17.5; 16.7)	Very Low**,‡,¶	-0.3	(-17.5; 16.7)	Very Low
Naproxen 1,000 mg *v* diclofenac 150 mg	-	-	-	-0.5	(-17.7; 16.6)	Very Low**,‡,¶	-0.5	(-17.7; 16.6)	Very Low
Naproxen 1,000 mg *v* celecoxib 400 mg	-	-	-	1.5	(-10.8; 23.8)	Very Low**,‡,¶	1.5	(-10.8; 23.8)	Very Low
Naproxen 1,000 mg *v* aceclofenac 200 mg	-	-	-	-3.6	(-27.1; 19.8)	Very Low**,‡,¶	-3.6	(-27.1; 19.8)	Very Low
Nabumetone 2,000 mg *v* meloxicam 7,5 mg	-	-	-	7.5	(-15.0; 30.1)	Very Low**,‡,¶	7.5	(-15.0; 30.1)	Very Low
Nabumetone 2,000 mg *v* meloxicam 22,5 mg	-	-	-	4.4	(-18.2; 27.0)	Very Low**,‡,¶	4.4	(-18.2; 27.0)	Very Low
Nabumetone 2,000 mg *v* meloxicam 15 mg	-	-	-	3.6	(-19.0; 26.2)	Very Low**,‡,¶	3.6	(-19.0; 26.2)	Very Low
Nabumetone 2,000 mg *v* diclofenac 150 mg	-	-	-	3.4	(-19.1; 26.0)	Very Low**,‡,¶	3.4	(-19.1; 26.0)	Very Low
abumetone 2,000 mg *v* celecoxib 400 mg	-	-	-	5.4	(-21.3; 32.2)	Very Low**,‡,¶	5.4	(-21.3; 32.2)	Very Low
Nabumetone 2,000 mg *v* aceclofenac 200mg	-	-	-	0.3	(-27.4; 28.0)	Very Low**,‡,¶	0.3	(-27.4; 28.0)	Very Low
Meloxicam 7,5 mg *v* meloxicam 22,5 mg	3.1	(2.3; 8.5)	High	20.8	(-66; 107.5)	Low‡,¶	-3.1	(-17.6; 11.4)	High
Meloxicam 7,5 mg *v* meloxicam 15 mg	3.9	(-1.5; 9.3)	Moderate‡	21.5	(-65.1; 108)	Low‡,¶	-3.9	(-18.4; 10.6)	Moderate
Meloxicam 7,5 mg *v* diclofenac 150 mg	4.2	(-1.2; 9.6)	Low‡,†	-11.8	(-72.7; 49.2)	Very Low‡,†,¶	-4.1	(-18.6; 10.4)	Low
Meloxicam 7,5 mg *v* celecoxib 400 mg	-	-	-	-2.1	(-22.5; 18.3)	Very Low*,‡,¶	-2.1	(-22.5; 18.3)	Very Low
Meloxicam 7,5 mg *v* aceclofenac 200 mg	-	-	-	-7.2	(-28.9; 14.4)	Very Low**,‡,¶	-7.2	(-28.9; 14.4)	Very Low
Meloxicam 22,5 mg *v* meloxicam 15 mg	-	-	-	-0.8	(-15.3; 13.7)	Low‡,¶	-0.8	(-15.3; 13.7)	Low
Meloxicam 22,5 mg *v* diclofenac 150 mg	0.3	(-5.1; 5.7)	Moderate‡	26.5	(-38.9; 91.9)	Low‡,¶	-1.0	(-15.5; 13.5)	Moderate
Meloxicam 22,5 mg *v* celecoxib 400 mg	-	-	-	1.0	(-19.3; 21.4)	Very Low*,‡,¶	1.0	(-19.3; 21.4)	Very Low
Meloxicam 22,5 mg *v* aceclofenac 200 mg	-	-	-	-4.1	(-25.8; 17.5)	Very Low**,‡,¶	-4.1	(-25.8; 17.5)	Very Low
Meloxicam 15 mg *v* diclofenac 150 mg	1.1	(-4.3; 6,5)	Low‡,†	-25.7	(-91.1; 39.6)	Very Low‡,†,¶	-0.2	(-14.7; 14.3)	Low
Meloxicam 15 mg *v* celecoxib 400 mg	-	-	-	1.8	(-18.5; 22.2)	Very Low*,‡,¶	1.8	(-18.5; 22.2)	Very Low
Meloxicam 15 mg *v* aceclofenac 200 mg	-	-	-	-3.3	(-25.0; 18.3)	Very Low**,‡,¶	-3.3	(-25.0; 18.3)	Very Low
Diclofenac 150 mg *v* celecoxib 400 mg	-2.0	(-7.4; 3.4)	Low*,‡	-22.0	(-114; 70.5)	Very Low*,‡,¶	2.0	(-12.3; 16.4)	Low
Diclofenac 150 mg *v* aceclofenac 200 mg	3.3	(-2.4; 9.0)	Very Low**,‡,†	-12.9	(65.6; 39.8)	Very Low**,†,¶	-3.1	(-19.3; 13.0)	Very Low

Celecoxib 400 mg *v* aceclofenac 200 mg	-	-	-	-5.1	(-26.8; 16.4)	Very Low**,‡,¶	-5.1	(-26.8; 16.4)	Very Low

*risk of bias moderate. ** risk of bias High. ‡Imprecision. †Inconsistency. ¶ Indirectness because of questionable comparability of trial populations

CHART 2: Quality of evidence for physical function outcome, according to GRADE

Comparison	Direct evidence			Indirect evidence			Network meta-analysis		
	SMD	95% confidence interval	Quality of evidence	SMD	95% confidence interval	Quality of evidence	SMD	95% confidence interval	Quality of evidence
Placebo *v* naproxen 1,000 mg	-	-	-	-0.1	(-0.2; -0.0)	Very Low**,¶	-0.1	(-0.2; -0.0)	**Very Low**
Placebo *v* meloxicam 7.5 mg	-	-	-	-0.0	(-0.2; 0.1)	Low‡,¶	-0.0	(-0.2; 0.1)	Low
Placebo *v* meloxicam 22.5 mg	0.1	(-0.4; 0.7)	Low‡,†	-0.0	(-15.1; 15.1)	Very Low ‡,†,¶	-0.1	(-0.3; 0.0)	Low
Placebo *v* meloxicam 15 mg	0.1	(-0.4; 0.6)	Low‡,†	-0.0	(-15.2; 15.1)	Very Low‡,†,¶	-0.1	(-0.3; 0.0)	Low
Placebo *v* diclofenac 150 mg	0.1	(-0.4; 0.6)	Low‡,†	-0.0	(-10.7; 10.7)	Very Low‡,†,¶	-0.1	(-0.2; 0.0)	Low
Placebo *v* celecoxib 400 mg	-	-	-	-0.1	(-0.3; 0.1)	Very Low*,‡,¶	-0.1	(-0.3; 0.1)	Very Low
Naproxen 1,000 mg *v* meloxicam 7.5 mg	-	-	-	0.1	(-0.1; 0.2)	Very Low**,‡,¶	0.1	(-0.1; 0.2)	Very Low
Naproxen 1,000 mg *v* meloxicam 22.5 mg	-	-	-	0.0	(-0.2; 0.2)	Very Low**,‡,¶	0.0	(-0.2; 0.2)	Very Low
Naproxen 1,000 mg *v* meloxicam 15 mg	-	-	-	0.0	(-0.1; 0.2)	Very Low**,‡,¶	0.0	(-0.1; 0.2)	Very Low
Naproxen 1,000 mg *v* diclofenac 150 mg	-	-	-	0.0	(-0.1; 0.2)	Very Low**,‡,¶	0.0	(-0.1; 0.2)	Very Low
Naproxen 1,000 mg *v* celecoxib 400 mg	-	-	-	0.0	(-0.2; 0.3)	Very Low**,‡,¶	0.0	(-0.2; 0.3)	Very Low
Meloxicam 7.5 mg *v* meloxicam 22.5 mg	-	-	-	-0.1	(-0.2; 0.1)	Low‡,¶	-0.1	(-0.2; 0.1)	Low
Meloxicam 7.5 mg *v* meloxicam 15 mg	-	-	-	-0.0	(-0.2; 0.1)	Low‡,¶	-0.0	(-0.2; 0.1)	Low
Meloxicam 7.5 mg *v* diclofenac 150 mg	0.0	(-0.5; 0.5)	Low‡,†	-0.1	(-15.3; 15.0)	Very Low‡,†,¶	-0.0	(-0.1; 0.1)	Low
Meloxicam 7.5 mg *v* celecoxib 400 mg	-	-	-	-0.0	(-0.2; 0.2)	Very Low*,‡,¶	-0.0	(-0.2; 0.2)	Very Low
Meloxicam 22.5 mg *v* meloxicam 15 mg	-	-	-	0.0	(-0.1; 0.1)	Low*,‡,¶	0.0	(-0.1; 0.1)	Low
Meloxicam 22.5 mg *v* diclofenac 150 mg	-0.0	(-0.6; 0.4)	Moderate‡	-0.2	(-15.4; 15.0)	Very Low‡,†,¶	0.0	(-0.0; 0.2)	Moderate
Meloxicam 22.5 mg *v* celecoxib 400 mg	-	-	-	0.0	(-0.2; 0.3)	Very Low*,‡,¶	0.0	(-0.2; 0.3)	Very Low
Diclofenac 150 mg *v* celecoxib 400 mg	0.1	(-0.5; 0.6)	Low*,‡	0.1	(-15.0; 15.3)	Very Low*,‡,¶	0.0	(-0.2; 0.1)	Low
Meloxicam 15 mg *v* diclofenac 150 mg	-0.0	(-0.6; 0.5)	Moderate‡	-0.2	(-15.4; 15.0)	Low‡,¶	0.0	(-0.1; 0.2)	Moderate
Meloxicam 15 mg *v* celecoxib 400 mg	-	-	-	0.0	(-0.2; 0.3)	Very Low*,‡,¶	0.0	(-0.2; 0.3)	Very Low

*risk of bias moderate. ** risk of bias High. ‡Imprecision. †Inconsistency. ¶ Indirectness because of questionable comparability of trial populations

CHART 3: Quality of evidence for number of tender/painful joints outcome, according to GRADE

Comparison	Direct evidence			Indirect evidence			Network meta-analysis		
	SMD	**95% confidence interval**	**Quality of evidence**	**SMD**	**95% confidence interval**	**Quality of evidence**	**SMD**	**95% confidence interval**	**Quality of evidence**
Placebo *v* naproxen 750 mg	-	-	-	-5.3	(-12.2; 1.5)	Very Low**,‡,¶	-5.3	(-12.2; 1.5)	Very Low
Placebo *v* naproxen 1,000 mg	-	-	-	-3.5	(-5.1; -1.9)	Very Low**,¶	-3.5	(-5.1; -1.9)	**Very Low**
Placebo *v* meloxicam 7.5 mg	1.6	(-1.0; 4.2)	Low‡,†	-0.7	(-19.3; 17.7)	Very Low‡,,†,¶	-1.6	(-5.1; 1.9)	Low
Placebo *v* meloxicam 22.5 mg	1.6	(-1.0; 4.2)	Low‡,†	-3.0	(-26.1; 20.5)	Very Low‡,,†,¶	-1.6	(-5.1; 1,9)	Low
Placebo *v* meloxicam 15 mg	0.9	(-1.7; 3.5)	Low‡,†	-3.0	(-26.8; 19.8)	Very Low‡,,†,¶	-0.9	(-4.4; 2.6)	Low
Placebo *v* etoricoxib 90 mg	5.0	(2.5; 6.9)	Very Low**,‡	7.0	(3.5; 10.5)	Very Low**,¶	-4.9	(-7.1; -2.8)	**Very Low**
Placebo *v* diclofenac 150 mg	2.3	(-0.3; 4.9)	-	-1.0	(-6.3; 5.1)	Very Low‡,†,¶	-2.3	(-5.8; 1.2)	Very Low
Placebo *v* celecoxib 400 mg	-	-	-	-2.8	(-8.4; 2.8)	Very Low*,‡,¶	-2.8	(-8.4; 2.8)	Very Low
Naproxen 750 mg *v* naproxen 1,000 mg	-	-	-	1.8	(-5.2; 8.8)	Very Low**,‡,¶	1.8	(-5.2; 8.8)	Very Low
Naproxen 750 mg *v* meloxicam 7.5 mg	-3.7	(-7.1; -0.3)	Low**	-0.5	(-28.3; 27.2)	Very Low**,‡,¶	3.7	(-2.1; 9.6)	Low
Naproxen 750 mg *v* meloxicam 15 mg	-	-	-	4.4	(-2.4; 11.3)	Very Low**,‡,¶	4.4	(-2.4; 11.3)	Very Low
Naproxen 750 mg *v* meloxicam 22.5 mg	-	-	-	3.7	(-3.1; 10.6)	Very Low**,‡,¶	3.7	(-3.1; 10.6)	Very Low
Naproxen 750 mg *v* etoricoxib 90 mg	-	-	-	0.3	(-6.8; 7.5)	Very Low**,‡,¶	0.3	(-6.8; 7.5)	Very Low
Naproxen 750 mg *v* diclofenac 150 mg	-	-	-	3.0	(-3.8; 9.9)	Very Low**,‡,¶	3.0	(-3.8; 9.9)	Very Low
Naproxen 750 mg *v* celecoxib 400 mg	-	-	-	2.5	(-5.6; 10.7)	Very Low**,‡,¶	2.5	(-5.6; 10.7)	Very Low
Naproxen 1,000 mg *v* meloxicam 7.5 mg	-	-	-	1.9	(-1.9; 5.8)	Very Low**,‡,¶	1.9	(-1.9; 5.8)	Very Low
Naproxen 1,000 mg *v* meloxicam 22.5 mg	-	-	-	1.9	(-1.9; 5.8)	Very Low**,‡,¶	1.9	(-1.9; 5.8)	Very Low
Naproxen 1,000 mg *v* meloxicam 15 mg	-	-	-	2.6	(-1.2; 6.5)	Very Low**,‡,¶	2.6	(-1.2; 6.5)	Very Low
Naproxen 1,000 mg *v* etoricoxib 90 mg	2.0	(-0.5; 4.0)	Very Low**,‡,†	-0.5	(-4.1; 3.0)	Very Low**,‡,†,¶	-1.4	(-3.6; 0.7)	Very Low
Naproxen 1,000 mg *v* diclofenac 150 mg	-	-	-	1.2	(-2.6; 5.1)	Very Low**,‡,¶	1.2	(-2.6; 5.1)	Very Low
Naproxen 1,000 mg *v* celecoxib 400 mg	-	-	-	0.7	(-5.1; 6.6)	Very Low**,‡,¶	0.7	(-5.1; 6.6)	Very Low

Meloxicam 7.5 mg *v* meloxicam 22.5 mg	2.6	(0.0; 5.2)	High	0	(-3.5; 3.5)	Low‡,¶	0	(-3.5; 3.5)	
Meloxicam 7.5 mg *v* meloxicam 15 mg	-0.7	(-3.3; 1.9)	Low‡,†	2.0	(-25.2; 30.2)	Very Low‡,†,¶	0.7	(-2.8; 4.2)	Low
Meloxicam 7.5 mg *v* etoricoxib 90 mg	-	-	-	3.3	(-7.5; 0.7)	Very Low**,‡,¶	3.3	(-7.5; 0.7)	Very Low
Meloxicam 7.5 mg *v* diclofenac 150 mg	0.7	(-1.9; 3.3)	Low‡,†	-0.4	(-23.8; 22.8)	Very Low‡,†,¶	-0.7	(-4.2; 2.8)	Low
Meloxicam 7.5 mg *v* celecoxib 400 mg	-	-	-	-1.2	(-6.8; 4.4)	Very Low*,‡,¶	-1.2	(-6.8; 4.4)	Very Low
Meloxicam 22.5 mg *v* meloxicam 15 mg	-	-	-	0.7	(-2.8; 4.2)	Low‡,¶	0.7	(-2.8; 4.2)	Low
Meloxicam 22.5 mg *v* etoricoxib 90 mg	-	-	-	-3.3	(-7.5; 0.7)	Very Low**,‡,¶	-3.3	(-7.5; 0.7)	Very Low
Meloxicam 22.5 mg *v* diclofenac 150 mg	0.7	(-1.9; 3.3)	Low‡,†	-5.0	(-32.6; 22.8)	Very Low‡,†,¶	-0.7	(-4.2; 2.8)	Low
Meloxicam 22.5 mg *v* celecoxib 400 mg	-	-	-	-1.2	(-6.8; 4.4)	Very Low*,‡,¶	-1.2	(-6.8; 4.4)	Very Low
Meloxicam 15 mg *v* etoricoxib 90 mg	-	-	-	-4.0	(-8.2; 0.0)	Very Low**,‡,¶	-4.0	(-8.2; 0.0)	Very Low
Meloxicam 15 mg *v* diclofenac 150 mg	1.4	(-1.2; 4.0)	Low‡,†	-4.0	(-31.9; 23.5)	Very Low‡,†,¶	-1.4	(-4.9; 2.1)	Low
Meloxicam 15 mg *v* celecoxib 400 mg	-	-	-	-1.9	(-7.5; 3.7)	Very Low*,‡,¶	-1.9	(-7.5; 3.7)	Very Low
Etoricoxib 90 mg *v* diclofenac 150 mg	-	-	-	2.7	(-1.4; 6.8)	Very Low**,‡,¶	2.7	(-1.4; 6.8)	Very Low
Etoricoxib 90 mg *v* celecoxib 400 mg	-	-	-	2.1	(-3.9; 8.2)	Very Low**,‡,¶	2.1	(-3.9; 8.2)	Very Low
Diclofenac 150 mg *v* celecoxib 400mg	0.5	(-2.4; 3.4)	Very Low*,‡,†	-5.0	(-32.8; 22.6)	Very Low*,‡,†,¶	-0.5	(-4.9; 3.9)	Very Low

*risk of bias moderate. ** risk of bias High. ‡Imprecision. †Inconsistency. ¶ Indirectness because of questionable comparability of trial populations

CHART 4: Quality of evidence for number of swollen joints outcome, according to GRADE

Comparison	Direct evidence			Indirect evidence			Network meta-analysis		
	SMD	95% confidence interval	Quality of evidence	SMD	95% confidence interval	Quality of evidence	SMD	95% confidence interval	Quality of evidence
Placebo *v* naproxen 750 mg				-6.7	(-11.0; -2.4)	Very Low**,¶	-6.7	(-11.0; -2.4)	**Very Low**
Placebo *v* naproxen 1,000 mg				-1.5	(-2.3; -0.7)	Very Low**,¶	-1.5	(-2.3; -0.7)	**Very Low**
Placebo *v* meloxicam 7.5 mg	1.5	(-0.4; 3.4)	Low‡,†	-0.1	(-18.6; 18.4)	Very Low‡,†,¶	-1.5	(-3.3; 0.3)	Low
Placebo *v* meloxicam 22.5 mg	1.4	(-0.5; 3.3)	Low‡,†	-1.1	(-24.4; 22.2)	Very Low‡,†,¶	-1.4	(-3.2; 0.4)	Low
Placebo *v* meloxicam 15 mg	0.2	(-1.7; 2.1)	Low‡,†	-2.3	(-25.6; 21.0)	Low†,¶	-0.2	(-2.0; 1.64)	Low
Placebo *v* etoricoxib 90 mg	2.5	(1.1; 3.9)	Low**	3.5	(1.0; 6.0)	Very Low**,¶	-2.6	(-3.2; -1.7)	**Low**
Placebo *v* diclofenac 150 mg	0.7	(-1.2; 2.6)	Low‡,†	-0.7	(-19.2; 17.8)	Very Low‡,†,¶	-0.7	(-2.5; 1.4)	Low
Placebo *v* celecoxib 400 mg				-1	(-4.1; 2.1)	Low*,¶	-1	(-4.1; 2.1)	Low
Naproxen 750 mg *v* naproxen 1.000 mg				5.2	(0.8; 9.6)	Very Low**,¶	5.2	(0.8; 9.6)	**Very Low**
Naproxen 750 mg *v* meloxicam 7.5 mg	-5.2	(-8.0; -2.4)	Low**	-2.2	(-29.9; 25.5)	Very Low**‡,¶	5.2	(1.4; 9.1)	**Low**
Naproxen 750 mg *v* meloxicam 22.5 mg				5.3	(1.0; 9.3)	Very Low**,¶	5.3	(1.0; 9.3)	**Very Low**
Naproxen 750 mg *v* meloxicam 15 mg				6.4	(2.2; 10.8)	Very Low**,¶	6.4	(2.2; 10.8)	**Very Low**
Naproxen 750 mg *v* etoricoxib 90 mg				4.1	(-0.3; 8.5)	Very Low**,‡,¶	4.1	(-0.3; 8.5)	Very Low
Naproxen 750 mg *v* diclofenac 150 mg				6	(1.7; 10.3)	Very Low**,¶	6	(1.7; 10.3)	**Very Low**
Naproxen 750 mg *v* celecoxib 400 mg				5.7	(0.8; 10.7)	Very Low**‡,¶	5.7	(0.8; 10.7)	**Very Low**
Naproxen 1,000 mg *v* meloxicam 7.5 mg				0	(-1.9; 2.0)	Very Low**,¶	0	(-1.9; 2.0)	Very Low
Naproxen 1,000 mg *v* meloxicam 22.5 mg				0.1	(-1.9; 2.1)	Very Low**,¶	0.1	(-1.9; 2.1)	Very Low
Naproxen 1,000 mg *v* meloxicam 15 mg				1.3	(0.7; 3.3)	Very Low**,¶	1.3	(0.7; 3.3)	Very Low
Naproxen 1,000 mg *v* etoricoxib 90 mg	1.2	(-0.2; 2.6)	Very Low**,‡	0.2	(-2.3; 2.7)	Very Low**,¶	-1.1	(-2.0; -0.1)	**Very Low**
Naproxen 1,000 mg *v* diclofenac 150 mg				0.8	(-1.9; 2.8)	Very Low**,¶	0.8	(-1.9; 2.8)	Very Low
Naproxen 1,000 mg *v* celecoxib 400 mg				0.5	(-2.7; 3.7)	Very Low**,¶	0.5	(-2.7; 3.7)	Very Low

Meloxicam 7.5 mg *v* meloxicam 22.5 mg	-0.1	(-2.0; 1.8)	Low[‡,†]	2.9	(-24.8; 30.6)	Low[†,¶]	0.1	(-1.7; 1.9)	Low
Meloxicam 7.5 mg *v* meloxicam 15 mg	-1.3	(-3.2; 0.6)	Low[‡,†]	1.7	(-26.0; 29.4)	Low[†,¶]	1.3	(-0.5; 3.1)	Low
Meloxicam 7.5 mg *v* etoricoxib 90 mg				-1.1	(-3.1; 0.9)	Very Low[**,¶]	-1.1	(-3.1; 0.9)	Very Low
Meloxicam 7.5 mg *v* diclofenac 150 mg	-0.8	(-2.7; 1.1)	Moderate[‡]	-0.3	(-23.7; 23.1)	Moderate[,¶]	0.8	(1.0; 2.6)	Moderate
Meloxicam 7.5 mg *v* celecoxib 400 mg				0.5	(-2.6; 3.6)	Low[*,¶]	0.5	(-2.6; 3.6)	Low
Meloxicam 22.5 mg *v* meloxicam 15 mg				1.2	(-6.4; 3.0)	Moderate[,¶]	1.2	(-6.4; 3.0)	Moderate
Meloxicam 22.5 mg *v* etoricoxib 90 mg				-1.2	(-3.2; 0.8)	Very Low[**,¶]	-1.2	(-3.2; 0.8)	Very Low
Meloxicam 22.5 mg *v* diclofenac 150 mg	-0.7	(-2.6; 1.2)	Moderate[‡]	-2.7	(-30.4; 25.0)	Moderate[,¶]	0.7	(-1.1; 2.5)	Moderate
Meloxicam 22.5 mg *v* celecoxib 400 mg				0.4	(-2.7; 3.5)	Low[*,¶]	0.4	(-2.7; 3.5)	Low
Meloxicam 15 mg *v* etoricoxib 90 mg				-2.4	(-4.5; 0.4)	Very Low[**,¶]	-2.4	(-4.5; 0.4)	**Very Low**
Meloxicam 15 mg *v* diclofenac 150 mg	0.5	(-1.4; 2.4)	Low[‡,†]	-1.5	(-29.2; 26.2)	Low[,¶]	-0.5	(-2.3; 1.3)	Low
Meloxicam 15 mg *v* celecoxib 400 mg				-0.8	(-3.9; 2.3)	Low[*,¶]	-0.8	(-3.9; 2.3)	Low
Etoricoxib 90 mg *v* diclofenac 150 mg				1.9	(-0.1; 4.0)	Very Low[**,†]	1.9	(-0.1; 4.0)	Very Low
Etoricoxib 90 mg *v* celecoxib 400 mg				1.6	(-1.6; 4.9)	Very Low[**,¶]	1.6	(-1.6; 4.9)	Very Low
Diclofenac 150 mg *v* celecoxib 400mg	0.3	(-1.9; 2.5)	Very Low[*,‡,†]	-1.7	(-29.4; 26.0)	Very Low[*,†,¶]	-0.3	(-2.8; 2.2)	Very Low

*risk of bias moderate. ** risk of bias High. ‡Imprecision. †Inconsistency. ¶ Indirectness because of questionable comparability of trial populations

CHART 5: Quality of evidence for patients' global assessment outcome, according to GRADE

Comparison	Direct evidence			Indirect evidence			Network meta-analysis		
	SMD	95% confidence interval	Quality of evidence	SMD	95% confidence interval	Quality of evidence	SMD	95% confidence interval	Quality of evidence
Placebo x naproxen 1,000 mg	-	-	-	-11.1	(-15.7; -6.5)	Very Low**,¶	-11.1	(-15.7; -6.5)	Very Low
Placebo x meloxicam 7.5 mg	6.2	(1.9; 10.5)	Moderate†	-14.0	(-41.7; 13.7)	Very Low‡,†,¶	-6.2	(-15.6; 3.2)	Moderate
Placebo x meloxicam 22.5 mg	9.1	(4.8; 13.3)	Moderate†	-11.1	(-38.8; 16.6)	Very Low‡,†,¶	-9.1	(-18.5; 0.3)	Moderate
Placebo x meloxicam 15 mg	8.7	(4.4; 12.9)	Moderate†	-11.5	(-39.2; 16.2)	Very Low‡,†,¶	-8.7	(-18.1; 0.7)	Moderate
Placebo x etoricoxib 90 mg	14.4	(10.6; 18.1)	Low**	14.0	(7.6; 19.9)	Very Low**,¶	14.3	(-20.2; -8.4)	Low
Placebo x diclofenac 150 mg	10.1	(5.8; 14.3)	High	4.0	(-15.6; 23.6)	Low‡,¶	-10.0	(-19.5; -0.6)	High
Placebo x celecoxib 400 mg	-	-	-	-10.0	(-22.7; 2.6)	Very Low*,‡,¶	-10.0	(-22.7; 2.6)	Very Low
Naproxen 1,000 mg x meloxicam 7.5 mg	-	-	-	4.9	(-5.6; 15.4)	Very Low**,‡,¶	4.9	(-5.6; 15.4)	Very Low
Naproxen 1,000 mg x meloxicam 22.5 mg	-	-	-	2.0	(-8.5; 12.5)	Very Low**,‡,¶	2.0	(-8.5; 12.5)	Very Low
Naproxen 1,000 mg x meloxicam 15 mg	-	-	-	2.4	(-8.1; 12.9)	Very Low**,‡,¶	2.4	(-8.1; 12.9)	Very Low
Naproxen 1,000 mg x etoricoxib 90 mg	3.1	(-0.6; 6.8)	Very Low**,‡,†	3.6	(-2.6; 9.7)	Very Low**,‡,¶	-3.2	(-8.9; 2.5)	Very Low
Naproxen 1,000 mg x diclofenac 150 mg	-	-	-	1.0	(-9.4; 11.5)	Very Low**,‡,¶	1.0	(-9.4; 11.5)	Very Low
Naproxen 1,000 mg x celecoxib 400 mg	-	-	-	1.0	(-12.5; 14.5)	Very Low**,‡,¶	1.0	(-12.5; 14.5)	Very Low
Meloxicam 7.5 mg x meloxicam 22.5 mg	-	-	-	-2.9	(-12.3; 6.5)	Low‡,¶	-2.9	(-12.3; 6.5)	Low
Meloxicam 7.5 mg x meloxicam 15 mg	-	-	-	-2.5	(-11.9; 6.9)	Low‡,¶	-2.5	(-11.9; 6.9)	Low
Meloxicam 7.5 mg x etoricoxib 90 mg	-	-	-	-8.1	(-19.3; 3.0)	Very Low**,‡,¶	-8.1	(-19.3; 3.0)	Very Low
Meloxicam 7.5 mg x diclofenac 150 mg	3.9	(-0.4; 8.1)	Low‡,†	-16.3	(-44.0; 11.4)	Very Low‡,†,¶	-3.9	(-13.3; 5.5)	Low
Meloxicam 7.5 mg x celecoxib 400 mg	-	-	-	-3.8	(-16.6; 8.8)	Very Low*,‡,¶	-3.8	(-16.6; 8.8)	Very Low
Meloxicam 22.5 mg x meloxicam 15 mg	-	-	-	0.4	(-9.0; 9.8)	Low‡,¶	0.4	(-9.0; 9.8)	Low
Meloxicam 22.5 mg x etoricoxib 90 mg	-	-	-	-5.2	(-16.4; 5.9)	Very Low**,‡,¶	-5.2	(-16.4; 5.9)	Very Low

Meloxicam 22.5 mg x diclofenac 150 mg	1.0	(-3.3; 5.3)	Low‡,†	-19.2	(-46.9; 8.5)	Very Low‡,†,¶	-1.0	(-10.4; 8.4)	Low
Meloxicam 22.5 mg x celecoxib 400 mg	-	-	-	-1.0	(-13.7; 11.7)	Very Low*,‡,¶	-1.0	(-13.7; 11.7)	Very Low
Meloxicam 15 mg x etoricoxib 90 mg	-	-	-	-5.6	(-16.8; 5.5)	Very Low**,‡,¶	-5.6	(-16.8; 5.5)	Very Low
Meloxicam 15 mg x diclofenac 150 mg	1.4	(-2.9; 5.7)	Moderate‡,†	-18.8	(-46.5; 8.9)	Very Low‡,†,¶	-1.3	(-10.8; 8.0)	Moderate
Meloxicam 15 mg x celecoxib 400 mg	-	-	-	-1.0	(-14.0; 11.3)	Very Low*,‡,¶	-1.0	(-14.0; 11.3)	Very Low
Etoricoxib 90 mg x diclofenac 150 mg	-	-	-	4.0	(-6.9; 15.4)	Very Low**,‡,¶	4.0	(-6.9; 15.4)	Very Low
Etoricoxib 90 mg x celecoxib 400 mg	-	-	-	4.0	(-9.7; 18.3)	Very Low**,‡,¶	4.0	(-9.7; 18.3)	Very Low
Diclofenac 150 mg x celecoxib 400mg	2.4	(-1.6; 6.5)	Very Low*,‡,†	-20.0	(-47.9; 7.5)	Very Low*,‡,¶	0.0	(-8.5; 8.5)	Very Low

*risk of bias moderate. ** risk of bias High. ‡Imprecision. †Inconsistency. ¶ Indirectness because of questionable comparability of trial populations

CHART 6: Quality of evidence for physicians' global assessment outcome, according to GRADE

Comparison	Direct evidence			Indirect evidence			Network meta-analysis		
	SMD	**95% confidence interval**	**Quality of evidence**	**SMD**	**95% confidence interval**	**Quality of evidence**	**SMD**	**95% confidence interval**	**Quality of evidence**
Placebo *v* naproxen 1,000 mg	-	-	-	-5.6	(-7.4; -3.8)	Very Low**,¶	-5.6	(-7.4; -3.8)	**Very Low**
Placebo *v* meloxicam 7.5 mg	5.0	(1.9; 8.0)	Moderate†	-2.5	(-30.2; 25.2)	Very Low‡,†,¶	-5.0	(-9.8; -0.1)	**Moderate**
Placebo *v* meloxicam 22.5 mg	6.0	(2.9; 9.0)	Moderate†	-1.5	(-29.2; 26.2)	Very Low‡,†,¶	-6.0	(-10.8; -1.1)	**Moderate**
Placebo *v* meloxicam 15 mg	5.7	(2.6; 8.7)	Moderate†	-2.0	(-29.4; 26.0)	Very Low‡,†,¶	-6.0	(-10.6; -0.9)	**Moderate**
Placebo *v* etoricoxib 90 mg	9.8	(7.7; 11.8)	Low**	12.0	(8.2; 15.6)	Very Low**,‡,¶	-10.0	(-12.1; -7.9)	**Low**
Placebo *v* diclofenac 150 mg	6.0	(2.6; 8.8)	High	2.0	(-17.6; 21.6)	Low‡,¶	-6.0	(-10.6; -0.9)	**High**
Placebo *v* celecoxib 400 mg	-	-	-	-4.0	(-9.6; 2.1)	Very Low*,‡,¶	-4.0	(-9.6; 2.1)	Very Low
Naproxen 1,000 mg *v* meloxicam 7.5 mg	-	-	-	1.0	(-4.6; 5.8)	Very Low**,‡,¶	1.0	(-4.6; 5.8)	Very Low
Naproxen 1,000 mg *v* meloxicam 22.5 mg	-	-	-	-4.0	(-5.6; 4.8)	Very Low**,‡,¶	-4.0	(-5.6; 4.8)	Very Low
Naproxen 1,000 mg *v* meloxicam 15 mg	-	-	-	0.0	(-5.3; 5.0)	Very Low**,‡,¶	0.0	(-5.3; 5.0)	Very Low
Naproxen 1,000 mg *v* etoricoxib 90 mg	4.9	(2.5; 7.3)	Low**	2.8	(-0.6; 6.2)	Very Low**,‡,¶	-4.0	(-6.8; -2.0)	**Low**
Naproxen 1,000 mg *v* diclofenac 150 mg	-	-	-	0.0	(-5.3; 5.0)	Very Low**,‡,¶	0.0	(-5.3; 5.0)	Very Low
Naproxen 1,000 mg *v* celecoxib 400 mg	-	-	-	2.0	(-4.3; 8.0)	Very Low**,‡,¶	2.0	(-4.3; 8.0)	Very Low
Meloxicam 7.5 mg *v* meloxicam 22.5 mg	-	-	-	-1.0	(-5.8; 3.8)	Low‡,¶	-1.0	(-5.8; 3.8)	Low
Meloxicam 7.5 mg *v* meloxicam 15 mg	-	-	-	-1.0	(-5.6; 4.1)	Low‡,¶	-1.0	(-5.6; 4.1)	Low
Meloxicam 7.5 mg *v* etoricoxib 90 mg	-	-	-	-5.0	(-10.3; 0.3)	Very Low**,‡,¶	-5.0	(-10.3; 0.3)	Very Low
Meloxicam 7.5 mg *v* diclofenac 150 mg	0.7	(-2.3; 3.7)	Low‡,†	-6.7	(-34.4; 21.0)	Very Low‡,†,¶	-1.0	(-5.6; 4.1)	Low
Meloxicam 7.5 mg *v* celecoxib 400 mg	-	-	-	1.0	(-4.6; 7.1)	Very Low*,‡,¶	1.0	(-4.6; 7.1)	Very Low
Meloxicam 22.5 mg *v* meloxicam 15 mg	-	-	-	0.0	(-4.6; 5.1)	Low‡,¶	0.0	(-4.6; 5.1)	Low
Meloxicam 22.5 mg *v* etoricoxib 90 mg	-	-	-	-4.0	(9.3; 1.3)	Very Low**,‡,¶	-4.0	(9.3; 1.3)	Very Low

Meloxicam 22.5 mg *v* diclofenac 150 mg	0.2	(-3.3; 2.9)	Moderate‡	-7.7	(-35.4; 10.0)	Low‡,¶	0.0	(-4.6; 5.1)	Moderate
Meloxicam 22.5 mg *v* celecoxib 400 mg	-	-	-	2.0	(-3.6; 8.1)	Very Low*,‡,¶	2.0	(-3.6; 8.1)	Very Low
Meloxicam 15 mg *v* etoricoxib 90 mg	-	-	-	-4.3	(-9.6; 1.0)	Very Low**,‡,¶	-4.3	(-9.6; 1.0)	Very Low
Meloxicam 15 mg x diclofenac 150 mg	1.2	(-4.3; 1.9)	Moderate‡	-7.5	(-27.1; 12.1)	Low‡,¶	0.0	(-4.8; 4.8)	Moderate
Meloxicam 15 mg x celecoxib 400 mg	-	-	-	2.0	(-3.9; 7.9)	Very Low*,‡,¶	2.0	(-3.9; 7.9)	Very Low
Etoricoxib 90 mg x diclofenac 150 mg	-	-	-	4.0	(-1.0; 9.6)	Very Low**,‡,¶	4.0	(-1.0; 9.6)	Very Low
Etoricoxib 90 mg x celecoxib 400 mg	-	-	-	6.0	(0.0; 12.5)	Very Low**,‡,¶	6.0	(0.0; 12.5)	**Very Low**
Diclofenac 150 mg x celecoxib 400mg	-2	(4.5; 0.5)	Moderate*	-9.4	(-37.1; 18.3)	Very Low*,¶	2.0	(-1.4; 5.4)	Moderate

*risk of bias moderate. ** risk of bias High. ‡Imprecision. †Inconsistency. ¶ Indirectness because of questionable comparability of trial populations

CHART 7: Quality of evidence for **safety** outcome, according to GRADE

Comparison	Direct evidence			Indirect evidence			Network meta-analysis		
	RR	**95% confidence interval**	**Quality of evidence**	**RR**	**95% confidence interval**	**Quality of evidence**	**RR**	**95% confidence interval**	**Quality of evidence**
Placebo *v* tenoxicam 20 mg	-	-	-	-	-	-	3.0	0.2; 93.4	-
Placebo *v* naproxen 750 mg	-	-	-	-	-	-	1.8	0.1; 29.9	-
Placebo *v* naproxen 1,000 mg	0.4	-1; 0.6	Very Low**,‡,†	-4.0	-1;1	Very Low**,‡,†,¶	2.5	0.2; 51.6	Very Low
Placebo *v* naproxen 500 mg	-	-	-	-	-	-	1.1	0.5; 2.6	-
Placebo *v* nabumetone 2,000 mg	-	-	-	-	-	-	0.9	0.1; 4.7	-
Placebo *v* nabumetone 1,000 mg	-	-	-	-	-	-	2.8	0.3; 26.7	-
Placebo *v* meloxicam 7.5mg	1.0	-2; 2	Low‡,†	-10.0	-10; 3	Very Low‡,†,¶	1.4	0.2; 9.3	Low
Placebo *v* meloxicam 22.5mg	1.0	-2; 2	Low‡,†	-10.5	-10.5; 2.9	Very Low‡,†,¶	1.8	0.2; 12.0	Low
Placebo *v* meloxicam 15mg	1.0	-2.1; 1.8	Low‡,†	-4.8	-4.8; 1	Very Low‡,†,¶	2.0	0.4; 10.3	Low
Placebo *v* ketoprofen 20 mg	-	-	-	-	-	-	0.9	0.1; 7.1	-
Placebo *v* indomethacin 100 mg	-	-	-	-	-	-	3.1	0.1; 96.6	-
Placebo *v* etoricoxib 90 mg	0.7	-2.9; 0.1	Very Low**,‡,†	-5.3	-5.3; 1.4	Very Low**,‡,†,¶	4.4	1.2; 16.0	**Very Low**
Placebo *v* etodolac 50 mg	-	-	-	-	-	-	1.9	0.2; 15.3	-
Placebo *v* etodolac 200 mg	-	-	-	-	-	-	1.6	0.2; 13.1	-
Placebo *v* etodolac 100 mg	-	-	-	-	-	-	1.9	0.2; 16.0	-
Placebo *v* diclofenac 150 mg	1.0	-2.2; 1.7	Low‡,†	-5.5	-5.5; 1.4	Very Low‡,†,¶	1.7	0.2; 11.9	Very Low
Placebo *v* diclofenac 100 mg	0	-	-	-	-	-	4.8	0.5; 46.0	-
Placebo *v* celecoxib 800 mg	1.1	-2; 2	Very Low**,‡,†	-2.1	-2.1; 2.4	Very Low**,‡,†,¶	1.0	0.1; 6.3	Very Low
Placebo *v* celecoxib 400 mg	1.1	-2.6; 1.7	Very Low**,‡,†	-2.3	-2.4; 2.0	Very Low**,‡,†,¶	1.3	0.2; 8.2	Very Low
Placebo *v* celecoxib 200 mg	1.0	-1.9; 2.2	Very Low**,‡,†	-1.4	-1.4; 2.3	Very Low**,‡,†,¶	0.7	0.1; 3.5	Very Low

Placebo *v* aspirin 3,900 mg	-	-	-	-	-	-	6.0	0.7; 50.6	-
Placebo*v* aspirin 3,600 mg	-	-	-	-	-	-	6.7	0.3; 139.5	-
Placebo *v* aceclofenac 200 mg	-	-	-	-	-	-	1.7	0.1; 27.0	-
Tenoxicam 20 mg *v* naproxen 750 mg	-	-	-	-	-	-	0.6	0.0; 34.1	-
Tenoxicam 20 mg *v* naproxen 1,000 mg	-	-	-	-	-	-	0.3	0.0; 12.8	-
Tenoxicam 20 mg *v* naproxen 500 mg	-	-	-	-	-	-	0.8	0.0; 63.8	-
Tenoxicam 20 mg *v* nabumetone 2,000 mg	-	-	-	-	-	-	0.3	0.0; 13.3	-
Tenoxicam 20 mg *v* nabumetone 1,000 mg	-	-	-	-	-	-	0.9	0.0; 43.1	-
Tenoxicam 20 mg *v* meloxicam 7.5mg	-	-	-	-	-	-	0.4	0.0; 14.8	-
Tenoxicam 20 mg *v* meloxicam 22.5mg	-	-	-	-	-	-	0.5	0.0; 19.1	-
Tenoxicam 20 mg *v* meloxicam 15mg	-	-	-	-	-	-	0.6	0.0; 20.4	-
Tenoxicam 20 mg *v* ketoprofen 20 mg	-	-	-	-	-	-	0.3	0.0; 16.9	-
Tenoxicam 20 mg *v* indomethacin 100 mg	-	-	-	-	-	-	1.0	0.0; 18.2	-
Tenoxicam 20 mg *v* etoricoxib 90 mg	-	-	-	-	-	-	1.4	0.0; 56.4	-
Tenoxicam 20 mg *v* etodolac 50 mg	-	-	-	-	-	-	0.6	0.0; 34.7	-
Tenoxicam 20 mg *v* etodolac 200 mg	-	-	-	-	-	-	0.5	0.0; 29.5	-
Tenoxicam 20 mg *v* etodolac 100 mg	-	-	-	-	-	-	0.6	0.0; 36.2	-
Tenoxicam 20 mg *v* diclofenac 150 mg	-	-	-	-	-	-	0.5	0.0; 10.1	-
Tenoxicam 20 mg *v* diclofenac 100 mg	-	-	-	-	-	-	1.5	0.0; 74.5	-
Tenoxicam 20 mg *v* celecoxib 800 mg	-	-	-	-	-	-	0.3	0.0; 15.4	-
Tenoxicam 20 mg *v* celecoxib 400 mg	-	-	-	-	-	-	0.4	0.0; 20.3	-
Tenoxicam 20 mg *v* celecoxib 200 mg	-	-	-	-	-	-	0.2	0.0; 8.9	-
Tenoxicam 20 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	1.9	0.0; 112.1	-
Tenoxicam 20 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	2.2	0.0; 171.9	-
Tenoxicam 20 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	0.5	0.0; 4.2	-
Naproxen 750 mg *v* naproxen 1,000 mg	-	-	-	-	-	-	1.3	0.0; 63.5	-
Naproxen 750 mg *v* naproxen 500 mg	-	-	-	-	-	-	0.6	0.0; 11.1	-
Naproxen 750 mg *v* nabumetone 2,000 mg	-	-	-	-	-	-	0.5	0.0; 12.2	-

Naproxen 750 mg *v* nabumetone 1,000 mg	-	-	-	-	-	-	1.5	0.0; 40.0	-
Naproxen 750 mg *v* meloxicam 7.5 mg	-	-	-	-	-	-	0.7	0.1; 5.6	-
Naproxen 750 mg *v* meloxicam 22.5 mg	-	-	-	-	-	-	0.9	0.0; 16.4	-
Naproxen 750 mg *v* meloxicam 15 mg	-	-	-	-	-	-	1.0	0.0; 17.4	-
Naproxen 750 mg *v* ketoprofen 20 mg	-	-	-	-	-	-	0.5	0.0; 15.9	-
Naproxen 750 mg *v* indomethacin 100 mg	-	-	-	-	-	-	1.6	0.0; 93.8	-
Naproxen 750 mg *v* etoricoxib 90 mg	-	-	-	-	-	-	2.3	0.1; 50.5	-
Naproxen 750 mg *v* etodolac 50 mg	-	-	-	-	-	-	1.0	0.0; 33.0	-
Naproxen 750 mg *v* etodolac 200 mg	-	-	-	-	-	-	0.8	0.0; 28.1	-
Naproxen 750 mg *v* etodolac 100 mg	-	-	-	-	-	-	1.0	0.0; 34.5	-
Naproxen 750 mg *v* diclofenac 150 mg	-	-	-	-	-	-	0.9	0.0; 16.2	-
Naproxen 750 mg *v* diclofenac 100 mg	-	-	-	-	-	-	2.6	0.1; 69.0	-
Naproxen 750 mg *v* celecoxib 800 mg	-	-	-	-	-	-	0.5	0.0; 14.2	-
Naproxen 750 mg *v* celecoxib 400 mg	-	-	-	-	-	-	0.7	0.0; 18.8	-
Naproxen 750 mg *v* celecoxib 200 mg	-	-	-	-	-	-	0.3	0.0; 7.9	-
Naproxen 750 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	3.2	0.1; 107.1	-
Naproxen 750 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	3.6	0.0; 171.4	-
Naproxen 750 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	0.9	0.0; 29.4	-
Naproxen 500 mg *v* naproxen 1,000 mg	-	-	-	-	-	-	0.4	0.0; 9.8	-
Naproxen 500 mg *v* nabumetone 2,000 mg	-	-	-	-	-	-	0.3	0.0; 10.6	-
Naproxen 500 mg *v* nabumetone 1,000 mg	-	-	-	-	-	-	1.1	0.1; 8.0	-
Naproxen 500 mg *v* meloxicam 7.5 mg	-	-	-	-	-	-	0.5	0.0; 14.3	-
Naproxen 500 mg *v* meloxicam 22.5 mg	-	-	-	-	-	-	0.7	0.0; 18.4	-
Naproxen 500 mg *v* meloxicam 15mg	-	-	-	-	-	-	0.7	0.0; 12.6	-
Naproxen 500 mg *v* ketoprofen 20 mg	-	-	-	-	-	-	0.3	0.0; 14.1	-
Naproxen 500 mg *v* indomethacin 100 mg	-	-	-	-	-	-	1.2	0.0; 93.8	-
Naproxen 500 mg *v* etoricoxib 90 mg	-	-	-	-	-	-	1.7	0.0; 44.9	-
Naproxen 500 mg *v* etodolac 50 mg	-	-	-	-	-	-	0.7	0.0; 29.2	-

Naproxen 500 mg *v* etodolac 200 mg	-	-	-	-	-	-	0.6	0.0; 24.9	-
Naproxen 500 mg *v* etodolac 100 mg	-	-	-	-	-	-	0.7	0.0; 30.5	-
Naproxen 500 mg *v* diclofenac 150 mg	-	-	-	-	-	-	0.7	0.0; 18.2	-
Naproxen 500 mg *v* diclofenac 100 mg	-	-	-	-	-	-	1.9	0.1; 32.0	-
Naproxen 500 mg *v* celecoxib 800 mg	-	-	-	-	-	-	0.4	0.0; 11.2	-
Naproxen 500 mg *v* celecoxib 400 mg	-	-	-	-	-	-	0.5	0.0; 14.8	-
Naproxen 500 mg *v* celecoxib 200 mg	-	-	-	-	-	-	0.2	0.0; 5.0	-
Naproxen 500 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	2.3	0.0; 94.5	-
Naproxen 500 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	2.6	0.1; 45.2	-
Naproxen 500 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	0.6	0.0; 30.8	-
Naproxen 1,000 mg *v* nabumetone 2,000 mg	0.7	-1.2; 0.6	Very Low**,‡,†	-97.3	-97.2; 97.8	Very Low**,‡,†,¶	0.7	0.2; 3.2	Very Low
Naproxen 1,000 mg *v* nabumetone 1,000 mg	-	-	-	-	-	-	2.4	0.2; 24.7	-
Naproxen 1,000 mg *v* meloxicam 7.5 mg	-	-	-	-	-	-	1.2	0.1; 9.2	-
Naproxen 1,000 mg *v* meloxicam 22.5 mg	-	-	-	-	-	-	1.5	0.2; 11.9	-
Naproxen 1,000 mg *v* meloxicam 15mg	-	-	-	-	-	-	1.7	0.3; 10.1	-
Naproxen 1,000 mg *v* ketoprofen 20 mg	-	-	-	-	-	-	0.8	0.1; 7.1	-
Naproxen 1,000 mg *v* indomethacin 100 mg	-	-	-	-	-	-	2.6	0.0; 89.9	-
Naproxen 1,000 mg *v* etoricoxib 90 mg	0.7	-2.9; 0.7	Very Low**,‡,†	-2.9	-2.9; 0.7	Very Low**,‡,†,¶	3.8	1.0; 13.8	Very Low
Naproxen 1,000 mg *v* etodolac 50 mg	-	-	-	-	-	-	1.6	0.1; 15.3	-
Naproxen 1,000 mg *v* etodolac 200 mg	-	-	-	-	-	-	1.3	0.1; 13.1	-
Naproxen 1,000 mg *v* etodolac 100 mg	-	-	-	-	-	-	1.7	0.1; 16.0	-
Naproxen 1,000 mg *v* diclofenac 150 mg	-	-	-	-	-	-	1.5	0.2; 11.7	-
Naproxen 1,000 mg *v* diclofenac 100 mg	-	-	-	-	-	-	4.1	0.4; 42.6	-
Naproxen 1,000 mg *v* celecoxib 800 mg	1.1	-2.2; 2.2	Very Low**,‡,†	-1.9	-1.9; 2.7	Very Low**,‡,†,¶	0.8	0.1; 5.5	Very Low
Naproxen 1,000 mg *v* celecoxib 400 mg	1.1	-2.5; 1.8	Very Low**,‡,†	-2.2	-2.2; 2.3	Very Low**,‡,†,¶	1.1	0.2; 7.2	Very Low
Naproxen 1,000 mg *v* celecoxib 200 mg	1.0	-1.8; 2.3	Very Low**,‡,†	-1.3	-1.3; 2.7	Very Low**,‡,†,¶	0.6	0.1; 3.1	Very Low
Naproxen 1,000 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	5.1	0.5; 50.5	-
Naproxen 1,000 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	5.8	0.3; 126.7	-

Naproxen 1,000 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	1.4	0.2; 25.6	
Nabumetone 2,000 mg *v* nabumetone 1,000 mg	-	-	-	-	-	-	3.0	0.2; 46.2	-
Nabumetone 2,000 mg *v* meloxicam 7.5 mg	-	-	-	-	-	-	1.5	0.1; 18.1	-
Nabumetone 2,000 mg *v* meloxicam 22.5 mg	-	-	-	-	-	-	1.9	0.1; 23.3	-
Nabumetone 2,000 mg *v* meloxicam 15 mg	-	-	-	-	-	-	2.1	0.2; 21.0	-
Nabumetone 2,000 mg *v* ketoprofen 20 mg	-	-	-	-	-	-	1.0	0.2; 13.8	-
Nabumetone 2,000 mg *v* indomethacin 100 mg	-	-	-	-	-	-	3.3	0.2; 149.1	-
Nabumetone 2,000 mg *v* etoricoxib 90 mg	-	-	-	-	-	-	4.8	0.7; 32.6	-
Nabumetone 2,000 mg *v* etodolac 50 mg	-	-	-	-	-	-	2.0	0.1; 29.1	-
Nabumetone 2,000 mg *v* etodolac 200 mg	-	-	-	-	-	-	1.7	0.1; 24.9	-
Nabumetone 2,000 mg *v* etodolac 100 mg	-	-	-	-	-	-	2.1	0.1; 30.5	-
Nabumetone 2,000 mg *v* diclofenac 150 mg	-	-	-	-	-	-	1.9	0.1; 23.1	-
Nabumetone 2,000 mg *v* diclofenac 100 mg	-	-	-	-	-	-	5.2	0.3; 79.8	-
Nabumetone 2,000 mg *v* celecoxib 800 mg	-	-	-	-	-	-	1.0	0.1; 11.2	-
Nabumetone 2,000 mg *v* celecoxib 400 mg	-	-	-	-	-	-	1.4	0.1; 14.7	-
Nabumetone 2,000 mg *v* celecoxib 200 mg	-	-	-	-	-	-	0.7	0.0; 6.8	-
Nabumetone 2,000 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	6.5	0.4; 95.3	-
Nabumetone 2,000 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	7.3	0.2; 217.8	-
Nabumetone 2,000 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	1.8	0.0; 44.9	-
Nabumetone 1,000 mg *v* meloxicam 7.5 mg	-	-	-	-	-	-	0.5	0.0; 6.6	-
Nabumetone 1,000 mg *v* meloxicam 22.5 mg	-	-	-	-	-	-	0.6	0.0; 8.5	-
Nabumetone 1,000 mg *v* meloxicam 15 mg	0.9	-1.5; 2.2	Very Low**,‡,†	-91.9	-91.9; 90.2	Very Low**,‡,†,¶	0.7	0.1; 4.9	Very Low
Nabumetone 1,000 mg *v* ketoprofen 20 mg	-	-	-	-	-	-	0.3	0.0; 7.0	-
Nabumetone 1,000 mg *v* indomethacin 100 mg	-	-	-	-	-	-	1.1	0.0; 52.6	-
Nabumetone 1,000 mg *v* etoricoxib 90 mg	-	-	-	-	-	-	1.5	0.1; 20.7	-
Nabumetone 1,000 mg *v* etodolac 50 mg	-	-	-	-	-	-	0.6	0.0; 14.7	-
Nabumetone 1,000 mg *v* etodolac 200 mg	-	-	-	-	-	-	0.5	0.0; 12.5	-
Nabumetone 1,000 mg *v* etodolac 100 mg	-	-	-	-	-	-	0.7	0.0; 15.4	-

Nabumetone 1,000 mg *v* diclofenac 150 mg	-	-	-	-	-	-	0.6	0.0; 8.4	-
Nabumetone 1,000 mg *v* diclofenac 100 mg	1.0	-2.5; 1.4	Very Low**,‡,†	-92.8	-92.3; 89.3	Very Low**,‡,†,¶	1.7	0.2; 12.8	Very Low
Nabumetone 1,000 mg *v* celecoxib 800 mg	-	-	-	-	-	-	0.3	0.0; 5.3	-
Nabumetone 1,000 mg *v* celecoxib 400 mg	-	-	-	-	-	-	0.4	0.0; 7.0	-
Nabumetone 1,000 mg *v* celecoxib 200 mg	1.0	-0.7; 3.4	Very Low**,‡,†	-90.9	-90.9; 91.2	Very Low**,‡,†,¶	0.2	0.0; 2.0	Very Low
Nabumetone 1,000 mg *v* aspirin 3,900 mg		-	-	-	-	-	2.1	0.1; 48.0	-
Nabumetone 1,000 mg *v* aspirin 3,600 mg	1.0	-2.9; 1.1	Very Low**,‡,†	-128.7	-128.7; 129.8	Very Low**,‡,†,¶	2.4	0.3; 18.1	Very Low
Nabumetone 1,000 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	0.6	0.0; 16.0	-
Meloxicam 7.5 mg *v* meloxicam 22.5mg	1.0	-2.2; 1.7	Low‡,†	-178.0	-178; 176.6	Very Low‡,†,¶	1.2	0.1; 9.4	Low
Meloxicam 7.5 mg *v* meloxicam 15 mg	0.9	-2.2; 1.5	Low‡,†	-178.2	-178.1; 176.4	Very Low‡,†,¶	1.4	0.2; 9.7	Low
Meloxicam 7.5 mg *v* ketoprofen 20 mg	-	-	-	-	-	-	0.7	0.0; 10.9	-
Meloxicam 7.5 mg *v* indomethacin 100 mg	-	-	-	-	-	-	2.2	0.0; 72.6	-
Meloxicam 7.5 mg *v* etoricoxib 90 mg	-	-	-	-	-	-	3.1	0.3; 31.3	-
Meloxicam 7.5 mg *v* etodolac 50 mg	-	-	-	-	-	-	1.3	0.0; 23.0	-
Meloxicam 7.5 mg *v* etodolac 200 mg	-	-	-	-	-	-	1.1	0.0; 19.6	-
Meloxicam 7.5 mg *v* etodolac 100 mg	-	-	-	-	-	-	1.4	0.0; 24.1	-
Meloxicam 7.5 mg *v* diclofenac 150 mg	1.0	-2.2; 1.7	Low‡,†	-178	-178; 176.6	Very Low‡,†,¶	1.2	0.1; 9.2	Low
Meloxicam 7.5 mg *v* diclofenac 100 mg	-	-	-	-	-	-	3.4	0.2; 45.9	-
Meloxicam 7.5 mg *v* celecoxib 800 mg	-	-	-	-	-	-	0.7	0.0; 9.4	-
Meloxicam 7.5mg *v* celecoxib 400 mg	-	-	-	-	-	-	0.9	0.0; 12.4	-
Meloxicam 7.5 mg *v* celecoxib 200 mg	-	-	-	-	-	-	0.5	0.0; 4.8	-
Meloxicam 7.5 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	4.3	0.2; 75.2	-
Meloxicam 7.5 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	4.8	0.1; 128.9	-
Meloxicam 7.5 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	4.8	0.1; 128.9	-
Meloxicam 22.5 mg *v* meloxicam 15 mg	1.0	-1.8; 2.1	Low‡,†	-10.1	-10.1; 3.4	Very Low‡,†,¶	1.1	0.1; 7.5	Low
Meloxicam 22.5 mg *v* ketoprofen 20 mg	-	-	-	-	-	-	0.5	0.0; 8.5	-
Meloxicam 22.5 mg *v* indomethacin 100 mg	-	-	-	-	-	-	1.7	0.0; 56.3	-

Meloxicam 22.5 mg *v* etoricoxib 90 mg	-	-	-	-	-	-	2.4	0.2; 24.3	-
Meloxicam 22.5 mg *v* etodolac 50 mg	-	-	-	-	-	-	1.0	0.0; 17.9	-
Meloxicam 22.5 mg *v* etodolac 200 mg	-	-	-	-	-	-	0.9	0.0; 15.2	-
Meloxicam 22.5 mg *v* etodolac 100 mg	-	-	-	-	-	-	1.1	0.0; 18.7	-
Meloxicam 22.5 mg *v* diclofenac 150 mg	-	-	-	-	-	-	0.9	0.1; 7.2	-
Meloxicam 22.5 mg *v* diclofenac 100 mg	-	-	-	-	-	-	2.6	0.2; 35.6	-
Meloxicam 22.5 mg *v* celecoxib 800 mg	-	-	-	-	-	-	0.5	0.0; 7.3	-
Meloxicam 22.5mg *v* celecoxib 400 mg	-	-	-	-	-	-	0.7	0.0; 9.6	-
Meloxicam 22.5 mg *v* celecoxib 200 mg	-	-	-	-	-	-	0.4	0.0; 3.7	-
Meloxicam 22.5 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	3.3	0.2; 58.3	-
Meloxicam 22.5 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	3.7	0.1; 99.9	-
Meloxicam 22.5 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	0.9	0.0; 15.9	-
Meloxicam 15 mg *v* ketoprofen 20 mg	-	-	-	-	-	-	0.4	0.0; 6.3	-
Meloxicam 15 mg *v* indomethacin 100 mg	-	-	-	-	-	-	1.5	0.0; 47.9	-
Meloxicam 15 mg *v* etoricoxib 90 mg	-	-	-	-	-	-	2.2	0.3; 17.2	-
Meloxicam 15 mg *v* etodolac 50 mg	-	-	-	-	-	-	0.9	0.0; 13.4	-
Meloxicam 15 mg *v* etodolac 200 mg	-	-	-	-	-	-	0.8	0.0; 11.4	-
Meloxicam 15 mg *v* etodolac 100 mg	-	-	-	-	-	-	0.9	0.0; 14.0	-
Meloxicam 15 mg *v* diclofenac 150 mg	1.0	-2.1; 1.8	Low[‡,†]	-1.9	-1.9; 5.1	Very Low[‡,†,¶]	0.8	0.1; 5.9	Low
Meloxicam 15 mg *v* diclofenac 100 mg	1.0	-2.6; 1.4	Very Low**[,‡,†]	-5.8	-5.9; 1.1	Very Low**[,‡,†,¶]	2.4	0.3; 16.3	
Meloxicam 15 mg *v* celecoxib 800 mg	-	-	-				0.5	0.0; 4.9	
Meloxicam 15mg *v* celecoxib 400 mg	1.1	-0.5; 3.9	Very Low**[,‡,†]	-2.7	-2.7; 2.7	Very Low**[,‡,†,¶]	0.6	0.0; 6.4	Very Low
Meloxicam 15 mg *v* celecoxib 200 mg	-	-	-	-	-	-	0.3	0.0; 2.0	-
Meloxicam 15 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	2.9	0.2; 43.8	-
Meloxicam 15 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	3.3	0.2; 54.3	-
Meloxicam 15 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	0.8	0.0; 13.4	-
Ketoprofen 20 mg *v* indomethacin 100 mg	-	-	-	-	-	-	3.1	0.0; 168.0	-
Ketoprofen 20 mg *v* etoricoxib 90 mg	-	-	-	-	-	-	4.5	0.4; 48.2	-

Ketoprofen 20 mg *v* etodolac 50 mg	-	-	-	-	-	-	1.9	0.1; 34.6	
Ketoprofen 20 mg *v* etodolac 200 mg	-	-	-	-	-	-	1.6	0.0; 29.5	-
Ketoprofen 20 mg *v* etodolac 100 mg	-	-	-	-	-	-	2.0	0.1; 36.2	-
Ketoprofen 20 mg *v* diclofenac 150 mg	-	-	-	-	-	-	1.8	0.1; 28.3	-
Ketoprofen 20 mg *v* diclofenac 100 mg	-	-	-	-	-	-	4.9	0.2; 99.5	-
Ketoprofen 20 mg *v* celecoxib 800 mg	-	-	-	-	-	-	1.0	0.0; 15.3	-
Ketoprofen 20 mg *v* celecoxib 400 mg	-	-	-	-	-	-	1.3	0.0; 20.2	-
Ketoprofen 20 mg *v* celecoxib 200 mg	-	-	-	-	-	-	0.7	0.0; 9.3	-
Ketoprofen 20 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	6.1	0.3; 112.9	-
Ketoprofen 20 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	6.9	0.1; 258.0	-
Ketoprofen 20 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	1.7	0.0; 52.2	-
Indomethacin 100 mg *v* etoricoxib 90 mg	-	-	-	-	-	-	1.4	0.0; 55.2	-
Indomethacin 100 mg *v* etodolac 50 mg	-	-	-	-	-	-	0.6	0.0; 33.9	-
Indomethacin 100 mg *v* etodolac 200 mg	-	-	-	-	-	-	0.5	0.0; 28.9	-
Indomethacin 100 mg *v* etodolac 100 mg	-	-	-	-	-	-	0.6	0.0; 35.5	-
Indomethacin 100 mg *v* diclofenac 150 mg	-	-	-	-	-	-	0.5	0.0; 9.9	-
Indomethacin 100 mg *v* diclofenac 100 mg	-	-	-	-	-	-	1.5	0.0; 72.9	-
Indomethacin 100 mg *v* celecoxib 800 mg	-	-	-	-	-	-	0.3	0.0; 15.0	-
Indomethacin 100 mg *v* celecoxib 400 mg	-	-	-	-	-	-	0.4	0.0; 19.9	-
Indomethacin 100 mg *v* celecoxib 200 mg	-	-	-	-	-	-	0.2	0.0; 8.7	-
Indomethacin 100 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	1.9	0.0; 109.7	-
Indomethacin 100 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	2.1	0.0; 168.1	-
Indomethacin 100 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	0.5	0.0; 4.2	-
Etoricoxib 90 mg *v* etodolac 50 mg	-	-	-	-	-	-	0.4	0.0; 5.0	-
Etoricoxib 90 mg *v* etodolac 200 mg	-	-	-	-	-	-	0.3	0.0; 4.2	-
Etoricoxib 90 mg *v* etodolac 100 mg	-	-	-	-	-	-	0.4	0.0; 5.2	-
Etoricoxib 90 mg *v* diclofenac 150 mg	-	-	-	-	-	-	0.4	0.0; 3.9	-
Etoricoxib 90 mg *v* diclofenac 100 mg	-	-	-	-	-	-	1.0	0.0; 14.2	-

Etoricoxib 90 mg *v* celecoxib 800 mg	-	-	-	-	-	-	0.2	0.0; 2.0	-
Etoricoxib 90 mg *v* celecoxib 400 mg	-	-	-	-	-	-	0.3	0.0; 2.6	-
Etoricoxib 90 mg *v* celecoxib 200 mg	-	-	-	-	-	-	0.1	0.0; 1.1	-
Etoricoxib 90 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	1.3	0.1; 16.4	-
Etoricoxib 90 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	1.5	0.0; 40.0	-
Etoricoxib 90 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	0.3	0.0; 8.0	-
Etodolac 50 mg *v* etodolac 200 mg	-	-	-	-	-	-	0.8	0.1; 6.8	-
Etodolac 50 mg *v* etodolac 100 mg	-	-	-	-	-	-	1.0	0.1; 8.3	-
Etodolac 50 mg *v* diclofenac 150 mg	-	-	-	-	-	-	0.9	0.0; 15.7	-
Etodolac 50 mg *v* diclofenac 100 mg	-	-	-	-	-	-	2.5	0.1; 54.7	-
Etodolac 50 mg *v* celecoxib 800 mg	-	-	-	-	-	-	0.5	0.0; 8.5	-
Etodolac 50 mg *v* celecoxib 400 mg	-	-	-	-	-	-	0.7	0.0; 11.2	-
Etodolac 50 mg *v* celecoxib 200 mg	-	-	-	-	-	-	0.3	0.0; 5.2	-
Etodolac 50 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	3.1	0.3; 26.3	-
Etodolac 50 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	3.5	0.0; 140.3	-
Etodolac 50 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	0.9	0.0; 28.5	-
Etodolac 200 mg *v* etodolac 100 mg	-	-	-	-	-	-	1.2	0.1; 9.9	-
Etodolac 200 mg *v* diclofenac 150 mg	-	-	-	-	-	-	1.1	0.0; 18.6	-
Etodolac 200 mg *v* diclofenac 100 mg	-	-	-	-	-	-	2.9	0.1; 64.9	-
Etodolac 200 mg *v* celecoxib 800 mg	-	-	-	-	-	-	0.6	0.0; 10.1	-
Etodolac 200 mg *v* celecoxib 400 mg	-	-	-	-	-	-	0.8	0.0; 13.3	-
Etodolac 200 mg *v* celecoxib 200 mg	-	-	-	-	-	-	0.4	0.0; 6.1	-
Etodolac 200 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	3.7	0.4; 31.3	-
Etodolac 200 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	4.2	0.1; 166.3	-
Etodolac 200 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	1.0	0.0; 33.8	-
Etodolac 100 mg *v* diclofenac 150 mg	-	-	-	-	-	-	0.8	0.0; 15.0	-
Etodolac 100 mg *v* diclofenac 100 mg	-	-	-	-	-	-	2.4	0.1; 52.5	-
Etodolac 100 mg *v* celecoxib 800 mg	-	-	-	-	-	-	0.5	0.0; 8.1	-

Etodolac 100 mg *v* celecoxib 400 mg	-	-	-	-	-	-	0.6	0.0; 10.7	-
Etodolac 100 mg *v* celecoxib 200 mg	-	-	-	-	-	-	0.3	0.0; 5.0	-
Etodolac 100 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	3.0	0.3; 25.3	-
Etodolac 100 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	3.4	0.0; 134.6	-
Etodolac 100 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	0.8	0.0; 27.3	-
Diclofenac 150 mg *v* diclofenac 100 mg	-	-	-	-	-	-	2.7	0.2; 35.9	-
Diclofenac 150 mg *v* celecoxib 800 mg	-	-	-	-	-	-	0.5	0.0; 7.4	-
Diclofenac 150 mg *v* celecoxib 400 mg	-	-	-	-	-	-	0.7	0.0; 9.7	-
Diclofenac 150 mg *v* celecoxib 200 mg	-	-	-	-	-	-	0.4	0.0; 3.8	-
Diclofenac 150 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	3.3	0.1; 59.0	-
Diclofenac 150 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	3.8	0.1;101.1	-
Diclofenac 150 mg *v* aceclofenac 200 mg	1.0	-1.9; 2.0	Very Low**,‡,†	-84.5	-84.6; 86.1	Very Low**,‡,†,¶	0.9	0.1; 7.1	Very Low
Diclofenac 100 mg *v* celecoxib 800 mg	-	-	-	-	-	-	0.2	0.0; 3.0	-
Diclofenac 100 mg *v* celecoxib 400 mg	-	-	-	-	-	-	0.2	0.0; 4.0	-
Diclofenac 100 mg *v* celecoxib 200 mg	-	-	-	-	-	-	0.1	0.0; 1.1	-
Diclofenac 100 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	1.2	0.0; 27.7	-
Diclofenac 100 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	1.4	0.0; 24.0	-
Diclofenac 100 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	0.3	0.0; 9.2	-
Celecoxib 800 mg *v* celecoxib 400 mg	-	-	-	-	-	-	1.3	0.1; 10.7	-
Celecoxib 800 mg *v* celecoxib 200 mg	-	-	-	-	-	-	0.7	0.1; 5.3	-
Celecoxib 800 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	5.9	0.3; 99.2	-
Celecoxib 800 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	6.7	0.2; 193.3	-
Celecoxib 800 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	1.6	0.0; 43.8	-
Celecoxib 400 mg *v* celecoxib 200 mg	-	-	-	-	-	-	0.5	0.0; 3.8	-
Celecoxib 400 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	4.4	0.2; 72.9	-
Celecoxib 400 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	5.0	0.1; 142.3	-
Celecoxib 400 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	1.2	0.0; 32.2	-
Celecoxib 200 mg *v* aspirin 3,900 mg	-	-	-	-	-	-	8.2	0.5; 117.8	-

Celecoxib 200 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	9.3	0.5; 166.9	-
Celecoxib 200 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	2.3	0.1; 47.4	-
Aspirin 3,900 mg *v* aspirin 3,600 mg	-	-	-	-	-	-	1.1	0.0; 45.7	-
Aspirin 3,900 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	0.2	0.0; 9.3	-
Aspirin 3,600 mg *v* aceclofenac 200 mg	-	-	-	-	-	-	0.2	0.0; 11.6	-

Note: date for indirect meta-analysis could not be calculated by the statistical program..

*risk of bias moderate. ** risk of bias High. ‡Imprecision. †Inconsistency. ¶ Indirectness because of questionable comparability of trial populations

Appendix F. Reason for exclusion of studies

Study	Reason for exclusion
Adler, S. "Early rheumatoid arthritis: Less joint erosion with methotrexate, prednisolone and/or cyclosporine." 33 (2008): 190-192.	Not found abstract or full text
Ammitzbøll, F. "Fenbufen and indomethacin in the treatment of rheumatoid arthritis. A comparative double-blind, crossover study." Scandinavian journal of rheumatology. Supplement 23 (1979): 5-10.	Not found abstract or full text
Ardia, A., et al. "Comparative Studies with Tolfenamic Acid in Rheumatic Disorders." Pharmacology & toxicology 75 (1994): 66-71.	Not found abstract or full text
Auteri, A., et al. "Effect of a long-term treatment with two different corticosteroids on patients suffering from rheumatoid arthritis: clinical and immunological study." International journal of immunotherapy 10.2 (1994): 67-75.	Not found abstract or full text
Azuma, T., et al. "Long-term comparative studies on gold, D-penicillamine, and NSAIDs for the treatment of early rheumatoid arthritis. 1. Evaluation of one year's treatment." Ryumachi.[Rheumatism] 26.3 (1986): 200-209.	Not found abstract or full text
Bickham, Kara, et al. "Evaluation of two doses of etoricoxib, a COX-2 selective non-steroidal anti-inflammatory drug (NSAID), in the treatment of Rheumatoid Arthritis in a double-blind, randomized controlled trial." BMC musculoskeletal disorders17.1 (2016): 331.	Wrong intervention
Blackburn Jr, Warren D., et al. "Tenidap in rheumatoid arthritis a 24-week double-blind comparison with hydroxychloroquine-plus-piroxicam, and piroxicam alone." Arthritis & Rheumatism38.10 (1995): 1447-1456.	Wrong intervention
Bensen, W., et al. "Efficacy and safety of valdecoxib in treating the signs and symptoms of *rheumatoid arthritis: a randomized*, controlled comparison with placebo and naproxen." Rheumatology 41.9 (2002): 1008-1016.	Non-commercially drug
Blechman, W. J., and B. L. Lechner. "Clinical comparative evaluation of choline magnesium trisalicylate and acetylsalicylic acid in rheumatoid arthritis." Rheumatology 18.2 (1979): 119-124.	Wrong intervention
Boers, M., et al. "What is the relationship between morning symptoms and measures of disease activity in patients with rheumatoid arthritis?." Arthritis care & research 67.9 (2015): 1202-1209.	wrong type of study
Bombardier, C., P. M. Peloso, and C. H. Goldsmith. "Salsalate, a nonacetylated salicylate, is as efficacious as diclofenac in patients with rheumatoid arthritis. Salsalate-Diclofenac Study Group." The Journal of rheumatology 22.4 (1995): 617-624.	Not found abstract or full text
Briancon, D. "International experience with etodolac therapy for rheumatoid arthritis: an interim report of comparative efficacy." Clinical rheumatology 8.1 (1989): 63-72.	wrong population of study
Buttgereit, Frank, et al. "Targeting pathophysiological rhythms: prednisone chronotherapy shows sustained efficacy in rheumatoid arthritis." Annals of the rheumatic diseases 69.7 (2010): 1275-1280.	Wrong intervention
Buttgereit, Frank, et al. "Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial." The Lancet 371.9608 (2008): 205-214.	Wrong intervention
Cardoe, N., and F. Dudley Hart. "Double-blind multicentre UK hospital studies of isoxicam vs naproxen." British journal of clinical pharmacology 22.S2 (1986): 167S-172S.	Wrong intervention

Caruso, I., et al. "Lornoxicam versus diclofenac in rheumatoid-arthritis: a double-blind, multicenter study." Advances in Therapy 11.3 (1994): 132-138.	Not found abstract or full text
Ciompi, M. L., et al. "Etodolac versus diclofenac: double-blind cross-over study in rheumatoid arthritis." International journal of clinical pharmacology research 9.3 (1989): 217-222.	Wrong type of study
De, I. Salcedo. "Fenbufen--a new nonsteroidal anti-inflammatory agent: comparison with phenylbutazone in rheumatoid arthritis." Current therapeutic research, clinical and experimental 18.2 (1975): 295-302.	Not found abstract or full text
Eichler, H-G., et al. "Association between health-related quality of life and clinical efficacy endpoints in rheumatoid arthritis patients after four weeks treatment with anti-inflammatory agents." International Journal of Clinical Pharmacology & Therapeutics 43.5 (2005).	Not found abstract or full text
Emery, P., et al. "Nabumetone compared with naproxen in the treatment of rheumatoid arthritis: a multicenter, double blind, randomized, parallel group trial in hospital outpatients." The Journal of rheumatology. Supplement 36 (1992): 41-47.	Not found abstract or full text
Furst, Daniel E., et al. "A controlled study of concurrent therapy with a nonacetylated salicylate and naproxen in rheumatoid arthritis." Arthritis & Rheumatism: Official Journal of the American College of Rheumatology 30.2 (1987): 146-154.	Wrong type of study
Goekoop-Ruiterman, YPM D., et al. "Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial." Arthritis & Rheumatism 52.11 (2005): 3381-3390.	Wrong intervention
Goekoop-Ruiterman, Yvonne PM, et al. "Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial." Annals of internal medicine 146.6 (2007): 406-415.	Wrong intervention
Havranek, H. "Double-blind study of tenoxicam 20 mg versus piroxicam 20 mg in rheumatoid arthritis." European journal of rheumatology and inflammation 9.2 (1987): 105.	Not found abstract or full text
Hill, J., et al. "A double-blind crossover study to compare lysine acetyl salicylate (aspergesic) with ibuprofen in the treatment of rheumatoid arthritis." Journal of clinical pharmacy and therapeutics 15.3 (1990): 205-211.	Wrong type of study
Imbimbo, B., et al. "Clinical equivalence of a new glucocorticoid, deflazacort and prednisone in rheumatoid arthritis and SLE patients." Advances in experimental medicine and biology 171 (1984): 241.	Not found abstract or full text
Jonderko, G., et al. "Evaluation of the efficacy and tolerability of nabumetone and piroxicam in patients with reumatoid arthritis." REUMATOLOGIA-WARSAW- 36 (1998): 49-55.	Not found abstract or full text
Kahabbazi, A., et al. "Comparing control of rheumatoid arthritis flare up in pulse therapy with dexamethasone and methylprednisolone: 703274." International Journal of Rheumatic Diseases 15 (2012).	Not found abstract or full text
Kellner, Herbert L., Chunming Li, and Margaret N. Essex. "Efficacy and safety of celecoxib versus diclofenac and omeprazole in elderly arthritis patients: a subgroup analysis of the CONDOR trial." Current medical research and opinion 28.9 (2012): 1537-1545.	Wrong population of study
Kellner, Herbert L., Chunming Li, and Margaret N. Essex. "Celecoxib and diclofenac plus omeprazole are similarly effective in the treatment of arthritis in patients at high GI risk in the CONDOR trial." The open rheumatology journal 7 (2013): 96.	Wrong population of study

Kessler, S., et al. "The Role of Intraarticular Glucocorticoid Injections for the Outcome after 3 Months in Polyarticular Active Rheumatoid Arthritis." Aktuelle Rheumatologie 34.06 (2009): 356-362.	Not found abstract or full text
Kessler, S., et al. "The Role of Intraarticular Glucocorticoid Injections for the Outcome after 3 Months in Polyarticular Active Rheumatoid Arthritis." Aktuelle Rheumatologie 34.06 (2009): 356-362.	Not found abstract or full text
Laine, L., et al. "Risk factors for NSAID-associated upper GI clinical events in a long-term prospective study of 34 701 arthritis patients." Alimentary pharmacology & therapeutics32.10 (2010): 1240-1248.	Wrong outcome
Lemmel, E. M., et al. "Efficacy and safety of meloxicam in patients with rheumatoid arthritis." The Journal of rheumatology 24.2 (1997): 282-290.	Not found abstract or full text
Lisse, Jeffrey R. "Clinical efficacy and safety of Naprelan versus Naprosyn in the treatment of rheumatoid arthritis." American journal of orthopedics (Belle Mead, NJ) 25.9 Suppl (1996): 21-29.	Not found abstract or full text
Lipsky, P. E., and P. C. Isakson. "Outcome of specific COX-2 inhibition in rheumatoid arthritis." The Journal of rheumatology. Supplement 49 (1997): 9-14.	Not found abstract or full text
Lucca, F., M. G. Souto, and J. R. Silva. "Comparative study of 2 corticosteroids, in a test of double anonymity, in the treatment of the rheumatoid arthritis." Hospital (Rio de Janeiro, Brazil) 70.4 (1966): 981-990.	Not found abstract or full text
Malaia, L. T., M. M. Liashenko, and VIa Brigidina. "Dynamics of the joint pains at night in rheumatoid arthritis and arthroses treated with Rengasil and piroxicam." Farmakologiia i toksikologiia 49.6 (1986): 83-87.	Not found abstract or full text
Marcos, F. Sánchez, et al. "Proglumetacin in the treatment of rheumatoid arthritis." Anales de medicina interna (Madrid, Spain: 1984). Vol. 6. No. 4. 1989.	Not found abstract or full text
Markusse, Iris M., et al. "Long-term outcomes of patients with recent-onset rheumatoid arthritis after 10 years of tight controlled treatment: a randomized trial." Annals of internal medicine 164.8 (2016): 523-531.	Wrong intervention
Masi, A. T., and R. T. Chatterton. "Glucocorticoid-like anti-inflammatory versus immunosuppressive effects of CPH 82 as a single drug therapy of moderately active rheumatoid arthritis patients." Scandinavian journal of rheumatology 29.2 (2000): 85-88.	Not found abstract or full text
Neustadt, David H. "Double blind evaluation of the long-term effects of etodolac versus ibuprofen in patients with rheumatoid arthritis." The Journal of rheumatology. Supplement 47 (1997): 17-22.	Not found abstract or full text
Orozco-Alcalá, J. J., and E. F. Barrera-Tenorio. "Long-term treatment with tenoxicam in rheumatoid arthritis." European journal of rheumatology and inflammation 9.2 (1987): 118-121.	Not found abstract or full text
Palmer, M., J. Highton, and D. G. Palmer. "A double blind comparison of tiaprofenic acid with placebo." The New Zealand medical journal 101.845 (1988): 240-241.	Not found abstract or full text
Paulus, Harold E., et al. "Patient retention and hand-wrist radiograph progression of rheumatoid arthritis during a 3-year prospective study that prohibited disease modifying antirheumatic drugs." The Journal of rheumatology 31.3 (2004): 470-481.	Not found abstract or full text
Pavelka, K., D. Kanková, and O. Vojtíšěk. "Comparison of 3 therapeutic regimes using non-steroidal antirheumatic agents in rheumatoid arthritis." Fysiatricky a reumatologicky vestnik59.5 (1981): 250.	Not found abstract or full text

Pavelka, K. and Stolfa, Jirí. "Coxibs in the treatment of osteoarthrosis and rheumatoid arthritis." 5 (2002): 89-96.	Not found abstract or full text
Perepel'chenko, A. I., et al. "Use of flugalin and profenid in patients with rheumatoid arthritis." Vrachebnoe delo 6 (1988): 38-40.	Not found abstract or full text
Prupas, H. M., et al. "Tenidap in Patients with Rheumatoid Arthritis." Scandinavian journal of rheumatology 25.6 (1996): 345-351.	Not found abstract or full text
Safy, Mary, et al. "Long-term outcome is better when a methotrexate-based treatment strategy is combined with 10 mg prednisone daily: follow-up after the second Computer-Assisted Management in Early Rheumatoid Arthritis trial." Annals of the rheumatic diseases 76.8 (2017): 1432-1435.	Wrong outcome
Schnitzer, Thomas J., et al. "The safety profile, tolerability, and effective dose range of rofecoxib in the treatment of rheumatoid arthritis." Clinical therapeutics 21.10 (1999): 1688-1702.	Wrong intervention
Shichikawa, K., I. Nagaya, and N. Ogawa. "Double-blind clinical trial of pirprofen in patients with rheumatoid arthritis." Ryumachi.[Rheumatism] 24.5 (1984): 407-414.	Not found abstract or full text
Soldati, R., G. Sorbilli, and P. Di Benedetto. "Long-term comparative study of fenbufen and aspirin in patients with rheumatoid arthritis." La Clinica terapeutica 92.4 (1980): 417.	Not found abstract or full text
Solomon, Daniel H., et al. "Differences in safety of nonsteroidal antiinflammatory drugs in patients with osteoarthritis and patients with rheumatoid arthritis: a randomized clinical trial." Arthritis & Rheumatology 70.4 (2018): 537-546.	Wrong population of study
ten Wolde, Saskia, et al. "Randomised placebo-controlled study of stopping second-line drugs in rheumatoid arthritis." The Lancet 347.8998 (1996): 347-352.	Wrong type of study
Van Jaarsveld, C. H. M., et al. "Toxicity of anti-rheumatic drugs in a randomized clinical trial of early rheumatoid arthritis." Rheumatology 39.12 (2000): 1374-1382.	Wrong intervention
Verschueren, P., et al. "Methotrexate in combination with other DMARDs is not superior to methotrexate alone for remission induction with moderate-to-high-dose glucocorticoid bridging in early rheumatoid arthritis after 16 weeks of treatment: the CareRA trial." Annals of the rheumatic diseases 74.1 (2015): 27-34.	Wrong intervention
Verstappen, Suzan MM, et al. "Five-year followup of rheumatoid arthritis patients after early treatment with disease-modifying antirheumatic drugs versus treatment according to the pyramid approach in the first year." Arthritis & Rheumatism: Official Journal of the American College of Rheumatology 48.7 (2003): 1797-1807.	Wrong intervention
Wankya, B. M. "Tolfenamic acid and ibuprofen in rheumatoid arthritis: a double-blind cross over study." East Afr Med J 58.8 (1981): 622-625.	Not found abstract or full text
Wylie, Graham, et al. "A comparative study of tenidap, a cytokine-modulating anti-rheumatic drug, and diclofenac in rheumatoid arthritis: a 24-week analysis of a 1-year clinical trial." Rheumatology 34.6 (1995): 554-563.	Wrong intervention

Appendix G. Studies included in the review.

Nonsteroidal anti-inflammatories

BERNHARD, G. C. et al. Long-term treatment of rheumatoid arthritis comparing nabumetone with aspirin. **The American journal of medicine,** v. 83, n. 4, p. 44-49, 1987. ISSN 0002-9343.

COLLANTES, E. et al. A multinational randomized, controlled, clinical trial of etoricoxib in the treatment of rheumatoid arthritis [ISRCTN25142273]. **BMC Family Practice,** v. 3, n. 1, p. 10, 2002. ISSN 1471-2296.

EMERY, P. et al. Nabumetone compared with naproxen in the treatment of rheumatoid arthritis: a multicenter, double blind, randomized, parallel group trial in hospital outpatients. **The Journal of rheumatology. Supplement,** v. 36, p. 41-47, 1992. ISSN 0380-0903.

EMERY, P. et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. **The Lancet,** v. 354, n. 9196, p. 2106-2111, 1999. ISSN 0140-6736.

FURST, D. E. et al. Dose response and safety study of meloxicam up to 22.5 mg daily in rheumatoid arthritis: a 12 week multicenter, double blind, dose response study versus placebo and diclofenac. **The Journal of rheumatology,** v. 29, n. 3, p. 436-446, 2002. ISSN 0315-162X.

GEUSENS, P. et al. Efficacy, safety and tolerability of lumiracoxib in patients with rheumatoid arthritis. **International journal of clinical practice,** v. 58, n. 11, p. 1033-1041, 2004. ISSN 1368-5031.

GEUSENS, P. et al. A placebo and active comparator-controlled trial of rofecoxib for the treatment of rheumatoid arthritis. **Scandinavian journal of rheumatology,** v. 31, n. 4, p. 230-238, 2002. ISSN 0300-9742.

GIBOFSKY, A. et al. Efficacy and tolerability of valdecoxib in treating the signs and symptoms of severe rheumatoid arthritis: a 12-week, multicenter, randomized, double-blind, placebo-controlled study. **Clinical therapeutics,** v. 29, n. 6, p. 1071-1085, 2007. ISSN 0149-2918.

JACOB, G. et al. Minimum effective dose of etodolac for the treatment of rheumatoid arthritis. **The Journal of Clinical Pharmacology,** v. 26, n. 3, p. 195-202, 1986. ISSN 0091-2700.

KAWAI, S. et al. Efficacy and Safety of Ketoprofen Patch in Patients With Rheumatoid Arthritis: A Randomized, Double-Blind, Placebo-Controlled Study. **The Journal of Clinical Pharmacology,** v. 50, n. 10, p. 1171-1179, 2010. ISSN 0091-2700.

KORNASOFF, D. et al. The efficacy and tolerability of aceclofenac compared to indomethacin in patients with rheumatoid arthritis. **Rheumatology international,** v. 15, n. 6, p. 225-230, 1996. ISSN 0172-8172.

KRUG, H. et al. Tolerability and efficacy of nabumetone and naproxen in the treatment of rheumatoid arthritis. **Clinical therapeutics,** v. 22, n. 1, p. 40-52, 2000. ISSN 0149-2918.

LIGHTFOOT, R. Comparison of the efficacy and safety of etodolac and piroxicam in patients with rheumatoid arthritis. Etodolac Study 326 Rheumatoid Arthritis Investigators Group. **The Journal of rheumatology. Supplement,** v. 47, p. 10-16, 1997. ISSN 0380-0903.

MATSUMOTO, A. K. et al. A randomized, controlled, clinical trial of etoricoxib in the treatment of rheumatoid arthritis. **The Journal of rheumatology,** v. 29, n. 8, p. 1623-1630, 2002. ISSN 0315-162X.

PASERO, G. et al. A multi-centre, double-blind comparative study of the efficacy and safety of aceclofenac and diclofenar in the treatment of rheumatoid arthritis. **Current medical research and opinion,** v. 13, n. 6, p. 305-315, 1995. ISSN 0300-7995.

PEREZ-RUIZ, F.; ALONSO-RUIZ, A.; ANSOLEAGA, J. Comparative study of the efficacy and safety of aceclofenac and tenoxicam in rheumatoid arthritis. **Clinical rheumatology,** v. 15, n. 5, p. 473-477, 1996. ISSN 0770-3198.

SHI, W. et al. Safety and efficacy of oral nonsteroidal anti-inflammatory drugs in patients with rheumatoid arthritis. **Clinical drug investigation,** v. 24, n. 2, p. 89-101, 2004. ISSN 1173-2563.

VASEY, F. B. et al. Controlled evaluation of nabumetone in the treatment of active adult rheumatoid arthritis: nabumetone versus naproxen double-blind parallel study. **The American journal of medicine,** v. 83, n. 4, p. 55-59, 1987. ISSN 0002-9343.

WILLIAMS, G. W. et al. A comparison of valdecoxib and naproxen in the treatment of rheumatoid arthritis symptoms. **Clinical therapeutics,** v. 28, n. 2, p. 204-221, 2006. ISSN 0149-2918.

WOJTULEWSKI, J. et al. A six-month double-blind trial to compare the efficacy and safety of meloxicam 7.5 mg daily and naproxen 750 mg daily in patients with rheumatoid arthritis. **Rheumatology,** v. 35, n. suppl_1, p. 22-28, 1996. ISSN 1462-0332.

ZHAO, S. Z. et al. Evaluation of health-related quality of life of rheumatoid arthritis patients treated with celecoxib. **Arthritis Care & Research,** v. 13, n. 2, p. 112-121, 2000. ISSN 0004-3591.

Steroidal anti-inflammatories

BAKKER, M. F. et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. **Ann Intern Med,** v. 156, n. 5, p. 329-39, Mar 6 2012. ISSN 0003-4819.

BUTTGEREIT, F. et al. Low-dose prednisone chronotherapy for rheumatoid arthritis: a randomised clinical trial (CAPRA-2). **Ann Rheum Dis,** v. 72, n. 2, p. 204-10, Feb 2013. ISSN 0003-4967.

CHOY, E. H. et al. Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. **Ann Rheum Dis,** v. 67, n. 5, p. 656-63, May 2008. ISSN 0003-4967.

DING, C. Z. et al. Clinical analysis of chinese patients with rheumatoid arthritis treated with leflunomide and methotrexate combined with different dosages of glucocorticoid. **Curr Ther Res Clin Exp,** v. 73, n. 4-5, p. 123-33, Sep 2012. ISSN 0011-393X (Print) 0011-393x.

HAFSTROM, I. et al. Rheumatoid factor and anti-CCP do not predict progressive joint damage in patients with early rheumatoid arthritis treated with prednisolone: a randomised study. **BMJ Open,** v. 4, n. 7, p. e005246, Jul 30 2014. ISSN 2044-6055 (Print) 2044-6055.

Appendix H. Characteristics of included studies.

Characteristics of included studies- nonsteroidal anti-inflammatories

Bernhard et al., 1987

Methods	Multi-centre, randomized, double-blind, placebo-controlled, 2 parallel groups, washout 2 14 days, duration 24 weeks.
Participants	Randomised n= 257. Completed n= 234. Mean age 50.7 yrs, M:F 58:176. Inclusion criteria: Adults, RA, for at least 6 months, active class II or Ill.
Interventions	Nabumetone 1.000 mg (n=126), aspirin 900 mg (n=131).
Outcomes	Articular index, morning stiffness, grip strength, walking time, and physician s' and patient s assessment, adverse events.
Notes	Concluded that nabumetone was an effective anti-inflammatory drug in the treatment of rheumatoid arthritis with less toxicity than aspirin.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised of sequence using the next number of the randomization schedule.
Allocation concealment (selection bias)	Low risk	Author confirms information.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals >10%, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	High risk	Criteria for diagnosis of RA not specified.

Collantes et al., 2002

Methods	Multi-centre, randomized, double-blind, placebo-controlled, 3 parallel groups, not report washout, duration 12 weeks.
Participants	Randomised n= 891, Completed n= 687. Mean age 52.3 yrs. Inclusion criteria: Adults, RA, according to American Rheumatism Association criteria, for at least 6 months, > 6 tender joints, > 3 swollen joints, and at least a 20% increase in the number of tender and swollen joints compared with screening visit assessments, 1) morning stiffness for > 45 minutes plus increased duration of morning stiffness by at least 15 minutes since screening visit evaluation, or 2) a score of >40 mm on patient global assessment of pain (a 100-mm visual analog scale [VAS]) and at least a 10-mm increase in patient assessment of pain over that reported at screening visit evaluation.
Interventions	Placebo (n= 242), etoricoxib 90 mg (n= 294) once daily, or naproxen 1.000 mg (n= 151).
Outcomes	Tender joint count, swollen joint count, patient global assessment of disease activity, investigator global assessment of disease activity, Stanford Health Assessment Questionnaire (HAQ) of disability (an assessment of the patient's mobility and ability to carry out activities of daily living), patient global assessment of pain, C-reactive protein level, adverse events.
Notes	In this study, etoricoxib 90 mg once daily was more effective than placebo and similar in efficacy to naproxen 500 mg twice daily for treating patients with RA over 12 weeks. Etoricoxib 90 mg was generally well tolerated in RA patients.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals >10%, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ARA criteria.

Emery et al., 1992

Methods	Randomized, double-blind, 2 parallel groups, duration 12 weeks.
Participants	Randomised n= 298, Completed n= 284. Mean age 53.2 yrs. Inclusion criteria: Adults, RA, according to American Rheumatism Association criteria (ARA), functional class I, II or III, least a 10-mm increase in patient assessment of pain over that reported at screening visit evaluation.
Interventions	Nabumetone 2.000 mg (n= 149), naproxen 1.000 mg (n= 149).
Outcomes	Improvement in pain, ritchie articular index, duration morning stiffines, adverse events.
Notes	Nabumetone was tolerated than naproxen because fewer patients withdrew for advense events or experienced severe adverse events, and significatly fewer patients required treatment for advense events.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	Low risk	Reported withdrawals <10%, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ARA criteria.

Emery et al., 1999

Methods	Multi-centre, randomized, double-blind, placebo-controlled, 2 parallel groups, not required to undergo washout, duration 24 weeks.
Participants	Randomised n= 655, Completed n= 497. Mean age 55.2 yrs, M:F 174:481. Inclusion criteria: Adults, RA, according to American rheumatism Association criteria, for at least 6 months, functional capacity classification of III or les.
Interventions	Celecoxib 200 mg (n= 326) twice daily or diclofenac SR 75 mg (n= 329) twice daily.
Outcomes	Physician s and patient s assessments of arthritis, number of tender or painful joints, and number of swollen joints, tenderness and swelling, functional disability score with the modified health assessment questionnaire, duration of morning stiffness, pain visual analogue scale, C-reactive protein concentrations, withdrawals because of treatment failure, gastrointestinal endoscopic, adverse events.
Notes	Celecoxib showed sustained anti-inflammatory and analgesic activity similar to diclofenac, with a lower frequency of upper gastrointestinal ulceration or gastrointestinal adverse events, and tolerability was better.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised of number was generated by computerized method.
Allocation concealment (selection bias)	Low risk	Author confirms information.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals >10%, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ARA criteria.

Furst et al., 2002

Methods	Multi-centre, randomized, double-blind, placebo-controlled, 5 parallel groups, not required to undergo washout, duration 12 weeks.
Participants	Randomised n= 894, Completed n= 888. Mean age 55.4 yrs. Inclusion criteria: Adults, RA, least 6 or more tender joints; at least 3 swollen joints; patient s assessment of pain at least 20 mm on a 100 mm visual analog scale (VAS); morning stiffness lasting at least 45 minutes; erythrocyte sedimentation rate (ESR) > 28 mm or C-reactive protein (CRP) > 1.2 mg/dl, worsening of at least one grade from screening on the investigator s global assessment of disease activity; worsening 10 mm from screening on the 100 mm VAS patient global assessment of disease activity; worsening 10 mm from screening on the 100 mm VAS patient assessment of pain; at least 20% increase compared with screening visit in the number of painful or more tender joints; and at least 20% increase compared with screening visit in the number of swollen joints.
Interventions	Meloxicam 7.5 mg (n= 175), meloxicam 15 mg (n= 184), meloxicam 22.5 mg (n= 177), diclofenac 150 mg (n= 181), placebo (n= 177).
Outcomes	Swollen joint count, tender joint count, patient pain, patient, physician global, modified Health Assessment Questionnaire, ACR20, use of rescue medication, GI events.
Notes	This trial demonstrated a dose response relationship for meloxicam 7.5, 15, and 22.5 mg using AUC measurement of response for the treatment of RA. All 3 doses of meloxicam, and positive control, were effective in the treatment of RA. The overall incidence rate of GI events did not differ significantly from placebo in either the meloxicam treatment groups or the positive control.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised of sequence using computer generated algorithm.
Allocation concealment (selection bias)	Low risk	Author confirms information.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	Low risk	Reported withdrawals <10%, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria.

Geusens et al., 2002

Methods	Multi-centre, randomized, double-blind, placebo-controlled, 4 parallel groups, washout of 3 to 16 days, duration 12 weeks.
Participants	Randomised n= 1023, not reported withdrawals. Mean age 53.6 yrs, M:F 176:847. Inclusion criteria: Adults, RA, defined by ACR criteria, for at least 6 months, functional capacity classification of III or les, these were as follows: a score performed 40mm on the patient global assessment of disease activity (with an increase of 15 mm from screening value); 9 tender joints (with an increase in number 20% from screening value); and 6 swollen joints.
Interventions	Placebo (n = 289), rofecoxib 25 mg (n = 306), 50 mg (n = 286), naproxen 1.000 mg (n = 142).
Outcomes	Tender joint count, swollen joint count, patient global assessment of disease activity, investigator global assessment of disease activity, the modifited HAQ, C-reactive protein levels, the percentage of patients discontinued due to lack of efficacy, the duration of morning stiffiness, use of rescue medication were also assessed. Adverse events.
Notes	Rofecoxib 25 mg once daily had similar efficacy to naproxen 1.000 mg (a standard dose). No additional benefit was seen with 50 mg rofecoxib.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	High risk	Not reported withdrawals.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria.

Geusens et al., 2004

Methods	Multi-centre, randomized, double-blind, placebo-controlled, 4 parallel groups, washout of 3 to 14 days, duration 26 weeks.
Participants	Randomised n= 1124,Completed n= 726. Mean age 53.5 yrs, M:F 235:889. Inclusion criteria: Adults, RA, defined by ACR criteria, functional capacity classification I, II or III ,with symptoms for > 3 months and receiving regular NSAID therapy, a minimum of three swollen joints and an increase of 2 or 20% in the number of swollen jointssince screening (whichever was greater) and a minimum of six tender joints and an increase of 2 or 20% in the number of tender joints since screening (whichever was greater) were eligible to enter the treatment phase. Additionally, patients were required to have pain intensity >40mm on a 100mm visual analogue scale (VAS) during the 24 h prior to baseline and an increase in pain intensity of either 20% or 10mm since screening (whichever was greater).
Interventions	Lumiracoxib 200 mg (n= 280), lumiracoxib 400 mg (n= 281), naproxen 500 mg (n= 279), placebo (n=284).
Outcomes	ACR20 criteria, pain intensity, patient s global assessment of disease activity, physician s global assessment of disease activity, swollen 66-joint count, tender 68-joint count, C-reactive protein (CRP) level and Health Assessment Questionnaire (HAQ) score], rescue medication use, adverse events.
Notes	Significantly more patients receiving lumiracoxib than placebo were responders according to ACR20 criteria at week 13 (41.1 and 42.7% for lumiracoxib 200 and 400 mg o.d., respectively; 32.4% for placebo; both $p<0.05$). The proportion responding to naproxen (39.1%) was not significantly different from placebo. Prespecified gastrointestinal adverse events were more frequent with naproxen than with either lumiracoxib dose or placebo. Lumiracoxib is therefore an effective and well-tolerated therapy for RA.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals >10%, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria.

Gibofsky et al., 2007

Methods	Multi-centre, randomized, double-blind, placebo-controlled, 3 parallel groups, washout of 2 to 14 days, duration 12 weeks.
Participants	Randomised n= 508, Completed n= 340. Mean age 55.9 yrs, M:F 107:233. Inclusion criteria: Adults, RA, defined by ACR criteria, for at least 6 months, Functional Capacity Classification between II and III, severe RA: physician s and patient s global assessment of disease activity of fair, poor, or very poor at baseline; □ 6 tender or painful joints; □ 3 swollen joints; □ 45 minutes of morning stiffness; a visual analog scale pain rating of □ 40 mm; or increases since baseline in these measures.
Interventions	Valdecoxib 10 mg QD (n= 170) ou naproxen 500 mg BID (n= 167) com placebo (n= 171).
Outcomes	Percentage of patients achieving an ACR Responder Index 20% (ACR-20) at week 12, VAS score, patient s global assessment of disease activity, physician s global assessment of disease activity, Health Assessment Questionnaire (HAQ),22 and C-reactive protein (CRP), patient s assessment of arthritis pain, patient s and physician s global assessment of disease activity, tender or painful joint count and score, swollen joint count and score, duration of morning stiffness, HAQ Disability Index, Medical Outcomes Study 36-Item Short Form (SF-36) Acute Health Survey, patient Treatment Satisfaction Scale (PTSS), adverse events.
Notes	Valdecoxib 10 mg QD administered over 12 weeks was significantly better than placebo and similar to naproxen 500 mg BID in treating the signs and symptoms of severe RA in these patients.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals >10%, included intention-to-treat.
Selective reporting (reporting bias)	High risk	The study protocol was not recorded. Although it reports adverse events, it does not portray other important outcomes.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria.

Jacob et al., 1986

Methods	Multi-centre, randomized, double-blind, placebo-controlled, 5 parallel groups, washout period of up to two weeks, duration 6 weeks.
Participants	Randomised n= 264, Completed n= 152. Mean age 52.9 yrs, M:F 105:159. Inclusion criteria: Adults, RA, defined by American Rheumatism Association (ARA) diagnostic criteria, of more than three months, functional class 1, 2, or 3 and in stage II or III of the Steinbrocker Progression Scale.
Interventions	Etodolac at 50 (n= 56), 100 (n= 55), or 200 mg/d (n= 50); aspirin at 3.900 mg/d (n= 52); or placebo (n= 51).
Outcomes	Number of painful joints, number of swollen joints, duration of morning stiffness, grip strength, 50-ft walking time, pain intensity, articular index, erythrocyte sedimentation rate, investigator s global evaluation, and patient s global evaluation, adverse events.
Notes	Although the 100-mg/d dose was effective in many of the efficacy parameters measured, the 200-mg/d dose, which is comparably efficacious to aspirin 3.9 g/d, was suggested as the minimum effective dose for the relief of the signs and symptoms of active rheumatoid arthritis.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals >10%, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ARA criteria.

Kawai et al., 2010

Methods	Multi-centre, randomized, 2 parallel groups, duration 2 weeks
Participants	Randomised n= 676, Completed n= 652. Mean age 58.7 yrs, M:F 116:560. Inclusion criteria: Adults with RA, defined by ACR criteria.
Interventions	Ketoprofen 20 mg patch; placebo patch
Outcomes	Scored the intensity of pain in the study wrist joint by using the VAS, adverse events.
Notes	The actual difference of the mean pain intensity scale between the 2 groups was small at the end of treatment. The frequency of adverse events was similar in both groups. The ketoprofen patch was more effective than placebo for relieving persistent local joint pain in patients with rheumatoid arthritis. The patch was also safe and well tolerated during the 2-week treatment period.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	Low risk	Reported withdrawals <10%, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria.

Kornasoff et al., 1996

Methods	Multi-centre, randomized, double-blind, parallel groups, washout period of up to two weeks, duration 12 weeks.
Participants	Randomised n= 219, Completed n= 180. Mean age 56 yrs, M:F 64:155. Inclusion criteria: Adults, RA, defined by American Rheumatism Association (ARA) diagnostic criteria.
Interventions	Aceclofenac 200 mg/day (n= 109); Indomethacin 100 mg/day (n= 110).
Outcomes	Number of painful and swollen joints, the duration of morning stiffness, grip strength, ARA functional class and the investigator's and the patient's global evaluation of the disease, C-reactive protein levels and adverse events.
Notes	Patients in both treatment groups showed a notable and significant improvement during the study.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals >10%.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ARA criteria.

Krug et al., 2000

Methods	Multi-centre, randomized, double-blind, placebo-controlled, parallel group, washout period of up to two weeks, duration 12 weeks.
Participants	Randomised n= 346, Completed n= 344. Mean age 54 yrs, M:F 102:244. Inclusion criteria: Adults, RA, defined by American College of Rheumatology (ACR) diagnostic criteria, functional class 1, 2 or 3.
Interventions	Nabumetone 2.000 mg/day; naproxen 1.000 mg/day.
Outcomes	The physician s glqbal assessmen, the patient s globaļ assessmen, number of painful/tender joints (possible total of 68) and number of swollen joints (possible total of 66), arthritis Impact Measurement Scale 2 (AIMS2), ls Rapid Assessment of Disease Activity in Rheumatology (RADAR), acetaminophen consumption during the first 14 days of treatment, adverse events.
Notes	Nabumetone was as effective as naproxen in relieving the signs and symptoms of RA. In this study, no serious GI adverse events were observed with either NSAID, but nabumetone was associated with a higher incidence of diarrhea.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	Low risk	Reported withdrawals <10%, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria.

Lightfoot, R.1997

Methods	Multi-centre, randomized, double-blind,parallel, washout period of up to two weeks, duration 12 weeks.
Participants	Randomised n= 426, Completed n=361. Mean age 57 yrs, M:F 105:304. Inclusion criteria: Adults, RA, defined by American Rheumatism Association (ARA) diagnostic criteria, of more than six months.
Interventions	Etodolac 400 mg/d (n= 140), 600 mg/d (n= 147); piroxicam 20 mg/d (n= 139).
Outcomes	Number of paintful joints, number of swollen joints, westergren erythrocyte sedimentation rate (ESR), duration of morning stiffness, adverse events.
Notes	No significant differences accurred between the etodolac 600 mg/d and piroxicam in change from baseline for the primary efficacy variables. All treatments produced significant ($p<0.01$) improvement from baseline in ESR. No significant differences accured in the incidence of any specific adverse event.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals >10%, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ARA criteria.

Matsumoto et al., 2002

Methods	Multi-centre, randomized, double-blind, placebo and active comparator controlled, 3 parallel groups, not report period of washout, duration 12 weeks.
Participants	Randomised n= 816, Completed n= 448. Mean age 55.6 yrs, Inclusion criteria: Adults, RA, diagnostic criteria for RA as specified by the 1987 revised criteria of the American Rheumatism Association, least 6 months duration, a history of a clinical response to NSAID therapy, and to have been taking NSAID therapy on a regular basis (at least 25 of the past 30 days), □ 6 tender joints, □ 3 swollen joints, and at least a 20% increase in the number of tender and swollen joints compared with initial assessments, morning stiffness for □ 45 min plus increased duration of morning stiffness by at least 15 min since, a score of > 40 mm on patient global assessment of pain [100 mm visual analog scale (VAS)] and at least a 10 mm increase in patient assessment of pain over that reported at initial evalution.
Interventions	Etoricoxib 90 mg once daily (n= 323), naproxen 1.000 mg, (n= 170), placebo (n= 323).
Outcomes	Patient and investigator global assessments of disease activity and direct assessment of arthritis by counts of tender and swollen joints, patient global assessment of pain, the HAQ, and the percentage of patients both completing the study and meeting the ACR20 criteria, adverse events.
Notes	Etoricoxib 90 mg once daily was more effective than either placebo or naproxen 500 mg twice daily for treating patients with RA over 12 weeks. Etoricoxib 90 mg was generally well tolerated in patients with RA.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals >10%, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ARA criteria

Pasero et al., 1995

Methods	Multi-centre, randomized, double-blind, duration 24 weeks.
Participants	Randomised n= 342, Completed n= 327. Mean age 50,7 yrs, M:F 61:266. Inclusion criteria: Adults, RA, defined by American Rheumatism Association (ARA) diagnostic criteria.
Interventions	Aceclofenac 200 mg (n= 170), diclofenac 150 mg, (n= 173).
Outcomes	assessment of pain; assessment of joint inflammation; duration of morning stiffness; hand grip strength measured by dynamometer; adverse events.
Notes	this study supports a therapeutic role for aceclofenac in the treatment of rheumatoid arthritis, and suggests it is an effective and safe NSAID for the treatment of this disease.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	Low risk	Reported withdrawals <10%, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ARA criteria

Perez ruiz; Alonso ruiz; Ansoleaga, 1996

Methods	Multi-centre, randomized, double-blind, 2 parallel groups, washout of 7 days duration 12 weeks.
Participants	Randomised n= 292, Completed n= 237. Mean age 56.6 yrs, M:F 58:234. Inclusion criteria: Adults, RA, defined by American Rheumatism Association (ARA) diagnostic criteria, pain which was greater than 40 mm on a 100mm visual analogue pain scale.
Interventions	Aceclofenac 200 mg (n= 145), tenoxicam 20 mg (n= 147).
Outcomes	Ritchie Index, visual analogue pain scale, grip strength of the right hand (GSR) and of the left hand (GSL), pontaneous morning pain (MP), spontaneous nocturnal pain (NP) and pain on movement (PMO), Morning stiffness, Adverse effects.
Notes	Both treatment groups showed amelioration of clinical parameters monitored at 15 days, and this improvement continued until the end of the trial, no statistically significant differences.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals >10%.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ARA criteria.

Shi et al., 2004

Methods	Multi-centre, randomized, 4 parallel groups, washout of 30 days duration 24 weeks.
Participants	Randomised n= 461, Completed n= 407. Mean age 46.9 yrs, M:F 148:313. Inclusion criteria: Adults, diagnosis of RA met the 1987 American College of Rheumatology (ACR), functional class 1, 2, 3 or 4.
Interventions	Diclofenac 75 100 mg (n= 131), meloxicam 15 mg (n= 144), nabumetone 1000 mg (n= 131) or celecoxib 200 mg (n= 52).
Outcomes	ACR 20%, ACR 50%, rheumatoid factor (RF) and adverse events.
Notes	Among the investigated NSAIDs, celecoxib did not prove to be superior to diclofenac, nabumetone or meloxicam with respect to its efficacy in the treatment of rheumatoid arthritis; however, it did show good patient compliance and safety profiles.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	High risk	Open trial. Patients had to pay for the use of the study drugs themselves.
Blinding of outcome assessment (detection bias)	High risk	Open trial. Patients had to pay for the use of the study drugs themselves.
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals >10%, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria.

Vasey et al., 1987

Methods	Multi-centre, randomized, double-blind, 2 parallel groups, washout of 14 days duration 24 weeks.
Participants	Randomised n= 367, Completed n= 194. Mean age 55 yrs, M:F 152:506. Inclusion criteria: Adults, least 6 months duration, active stable class II or III classical or definite rheumatoid arthritis.
Interventions	Nabumetone 1.000 mg (n= 186), naproxen 500 mg (n= 181).
Outcomes	Articular index, duration of morning stiffness, grip strength, walking time, and the physician s and patient s assessment of degree of rheumatoid arthritis activity, adverse events.
Notes	Both drugs were found to be efficacious in a comparable fashion. Both drugs were well tolerated in terms of patient withdrawal rates, which were 5 and 8 ercent, respectively. Gastrointestinal side effects were the most commonly encountered problem. Nabumetone holds promise as an important new therapeutic approach in arthritis.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised of numbers table.
Allocation concealment (selection bias)	Low risk	Author confirms information.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals >10%, patients had part of their data excluded from analyses.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	High risk	Criteria for diagnosis of RA not specified.

Williams et al., 2006

Methods	Multi-centre, randomized, double-blind, 5 parallel groups, washout of 2-7 days duration 12 weeks.
Participants	Randomised n= 1093, Completed n= 651. Mean age 56.2 yrs, M:F 257:836. Inclusion criteria: Adults, diagnosis of RA met the 1987 American College of Rheumatology (ACR), diagnosed >6 months, functional capacity between I and III, >6 tender/painful joints and an increase of 2 tender/ painful joints (or 20% increase in the number of tender/painful joints, whichever was greater); and ->3 swollen joints, with an increase of >2 swollen joints (or >20% increase in the number of swollen joints, whichever was greater) compared with those observed at the screening visit. >45 minutes of morning stiffness at baseline, with an increase in the duration of morning stiffness of >15 minutes compared with the screening visit, or a measurement of >40 mm on the patients' assessment of arthritis pain on a 100-mm VAS.
Interventions	Valdecoxib 10 mg (n= 226), valdecoxib 20 mg (n= 219), valdecoxib 40 mg (n= 209), placebo (n= 220), naproxen 500 mg (n= 219).
Outcomes	ACR-20 responder index, physicians' and patients' global assessments of disease activity, CRP, incidence of withdrawal due to treatment failure, adverse events.
Notes	Valdecoxib 10, 20, and 40 mg were efficacious for treating the signs and symptoms of RA in these patients. The efficacy of valdecoxib 20 and 40 mg QD was not significantly different from that of naproxen 500 mg BID. Valdecoxib was generally well tolerated in this study.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised of number was generated by computerized method.
Allocation concealment (selection bias)	Low risk	Author confirms information.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals >10%, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria.

Wojtulewski et al., 1996

Methods	Multi-centre, randomized, double-blind, 2 parallel groups, washout of 3-11 days duration 26 weeks.
Participants	Randomised n= 379, Completed n= 306. Inclusion criteria: Adults, RA, defined by American Rheumatism Association (ARA) diagnostic criteria, functional class I, II or III, six or more joints painful or tender on motion; three or more swollen joints; duration of morning stiffness of at least 45 min.
Interventions	Meloxicam 7.5 mg once daily (n= 199) with naproxen 750 mg (n= 180).
Outcomes	Physicians' and patients' global assessments of disease activity, number of painful and/or tender joints, the number of swollen joints, Grip strength, Pain in the morning and at night, duration of morning stiffness, analgesic consumption.
Notes	In conclusion, meloxicam 7.5 mg once daily is a promising treatment in rheumatoid arthritis, with efficacy comparable to naproxen 750 mg. Meloxicam has the advantage of a significantly lower incidence of GI and renal side effects.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals >10%, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria.

Zhao et al., 2000

Methods	Multi-centre, randomized, double-blind, 5 parallel groups, washout of 2-7 days duration 12 weeks.
Participants	Randomised n= 1149, Completed n= 688. Inclusion criteria: Adults, RA, defined by American College of Rheumatology (ACR), functional class I, II or III, with symptoms for > 3 months.
Interventions	Placebo (n= 231), celecoxib 100 mg (n= 240) , celecoxib 200 mg (n= 235), celecoxib 400 mg (n= 218), naproxen 500 mg (n= 225).
Outcomes	Health Assessment Questionnaire (HAQ) disability index, Short Form 36 (SF-36) and plasma levels of C-reactive protein, GI endoscopy evaluation, adverse reactions.
Notes	Celecoxib was better than placebo and comparable with naproxen in improving functional status and overall HRQOL among RA patients.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	High risk	Reported withdrawals >10%, included intention-to-treat.
Selective reporting (reporting bias)	High risk	Although it reports adverse events, it does not portray other important outcomes.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria.

Characteristics of included studies- steroidal anti-inflammatories

Bakker et al., 2012

Methods	Multi-centre, randomized, double-blind, placebo-controlled, 2 parallel groups, duration 52 weeks.
Participants	Randomised n=236, Completed n=170. Mean age 53.5 yrs, M:F 142:94. Inclusion criteria: Adults, early RA (duration <1 year).
Interventions	MTX and prednisone (n= 117), MTX and placebo (n= 119)
Outcomes	Radiographic erosive, response criteria, remission, and the need to add cyclosporine or a biologic agent to the treatment; adverse events.
Notes	Inclusion of low-dose prednisone in an MTX-based treatment strategy for tight control in early RA improves patient outcomes.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	Low risk	Reported withdrawals, included intention-to-treat.
Selective reporting (reporting bias)	High risk	The study protocol was not recorded. Although it reports adverse events, it does not portray other important outcomes.
Other bias	High risk	Criteria for diagnosis of RA not specified.

Buttgereit et al., 2013

Methods	Randomized, double-blind, placebo-controlled, 2 parallel groups, 1-week washout, duration 12 weeks.
Participants	Randomised n=350. Completed n=323. Mean age 57.3 yrs. M:F 294:56. Inclusion criteria: Adults, diagnosis and documented history of RA and who had been taking DMARDs for at least 6 months; morning stiffness of at least 45 min on at least 4 days within the 7 days of screening, a swollen joint count of □ 4 and a tender joint count of □ 4.
Interventions	Prednisone (5 mg) (n=231) or placebo (n=119)
Outcomes	Disease activity (DAS28); adverse events.
Notes	Low-dose prednisone added to existing DMARD treatment produced rapid and relevant improvements in RA signs and symptoms.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	Low risk	Reported withdrawals, included intention-to-treat.
Selective reporting (reporting bias)	High risk	The study protocol was not recorded; Although it reports adverse events, it does not portray other important outcomes.
Other bias	Low risk	Diagnosis and assesment consistent with ARA criteria.

Choy et al., 2008

Methods	Randomised, double-blind,
Participants	Randomised n=467. Complete n=379. Mean age 57.3 yrs. M:F 325:142. Inclusion criteria: Adults, with RA within 2 years of diagnosis by American College of rheumatology (ACR) criteria of less than 24 months with three of the following: >3 swollen joints, >6 tender joints, >45 min morning stiffness, erythrocyte sedimentation rate (ESR) >28 mm/h.
Interventions	Methotrexate anole (n=117), Methotrexate and ciclosporin (n=119), Methotrexate and predinisolone (n=115), Methotrexate, ciclosporin and predinisolonestarted (n=116)
Outcomes	Radiographic erosive; function (health assessment questionnaire); quality of life (SF-36); disease activity (DAS28), adverse events.
Notes	The methotrexate prednisolone combinations reduce erosive damage, however, the synergistic effect of two DMARDs is needed to improve quality of life.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly allocated to one of the four groups stratified by region.
Allocation concealment (selection bias)	Low risk	Sequence was generated by VF (statistician).
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	Low risk	Reported withdrawals, included intention-to-treat.
Selective reporting (reporting bias)	Low risk	The study protocol was not recorded but reports adverse events.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria.

Ding et al., 2012

Methods	Randomized, double-blind, placebo-controlled, 3 parallel groups, 1-week washout, duration 12 weeks
Participants	Randomised n=266. Completed n=251. Mean age 43yrs. Inclusion criteria: Adults with early active RA (2 years duration according to the revised 1987 American College of Rheumatology criteria); criteria were presence of 2 of the following 3 symptoms: swollen joint count 3; tender joint count 8; and average duration of morning stiffness 45 minutes, erythrocyte sedimentation rate 28 mm/h, and C-reactive protein level 1.5-fold the upper limit of normal. Not used DMARDs (MTX, sulfasalazine, and anti-malarial drugs) or GCs in the past 3 months.
Interventions	Placebo (n=90), 7.5 mg/d prednisone (n=88), and 15 mg/d prednisone(n=88). All groups received leflunomide 20 mg and methotrexate 10mg.
Outcomes	Adverse events.
Notes	In the treatment of RA, the incidence of skin rash, liver dysfunction, and oral ulcers may be decreased with combination therapy using LEF, MTX, and 7.5 mg prednisone, and blood pressure, blood glucose concentration, and bone density are not increased. Most important, 7.5 mg prednisone was synergistic with LEF and MTX, and such combination therapy could be a useful option as initial treatment of early active RA.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	Low risk	Described as double-blind.
Blinding of outcome assessment (detection bias)	Low risk	Described as double-blind.
Incomplete outcome data (attrition bias)	Low risk	Reported withdrawals, included intention-to-treat.
Selective reporting (reporting bias)	High risk	The study protocol was not recorded.
Other bias	Low risk	Diagnosis and assesment consistent with ACR criteria.

Hafström et al., 2014

Methods	Multi-centre, randomized, 2 parallel groups, duration 104 weeks.
Participants	Randomised n=225. Mean age 54.5 yrs, M:F 81:144. Inclusion criteria: Adults, early RA, defined by ACR criteria, duration of less than 1 year.
Interventions	7.5 mg prednisolone daily for 2 years (P-group; n=108) or no prednisolone (NoP-group; n=117).
Outcomes	Radiographic erosive,
Notes	The presence of RF and anti-CCP predicted radiographic progression in patients not treated with prednisolone but failed to predict progression in patients treated with this drug. The data suggest that early treatment with prednisolone may modulate not only inflammation but also autoimmunity-associated pathogenetic mechanisms.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Author confirms information.
Allocation concealment (selection bias)	High risk	Inappropriate method.
Blinding of participants and personnel (performance bias)	High risk	Not described as double-blind.
Blinding of outcome assessment (detection bias)	High risk	Not described as double-blind.
Incomplete outcome data (attrition bias)	High risk	Not reported withdrawals.
Selective reporting (reporting bias)	High risk	The study protocol was not recorded. Not reports adverse events.
Other bias	High risk	Insufficient information.

6 CONSIDERAÇÕES FINAIS

A artrite reumatoide é uma doença articular degenerativa, prevalente entre a população mundial e causa sintomas desagradáveis e limitantes que prejudicam diretamente a qualidade de vida e o bem estar dos pacientes.

O uso de evidências científicas pode direcionar as melhores estretégias terapêuticas para essa condição.

AINES e corticoides são frequentemente utilizados para controle da dor, principalmente por via oral. De acordo com os critérios de seleção usados no presente estudo foram encontrados principalmente ensaios clínicos que utilizaram esta via.

Este estudo pode beneficiar pesquisadores, gestores, prescritores, cuidadores e pacientes quanto as informações geradas, alertando que embora haja indícios da efetividade dos medicamentos naproxeno, predinisona e predinisolona e da segurança de celecoxibe como coadjuvantes do tratamento da artrite reumatoide; para maior confiança, estes achados devem ser confirmados.

O presente estudo demonstrou que há lacunas quanto ao uso destes medicamentos na artrite reumatoide, uma vez que as evidências disponíveis são de baixa qualidade, sugerindo que estudos primários adicionais poderiam confirmar tais achados.

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ANEXO A: Orientações para apresentação de teses do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba

As dissertações/teses do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba (PPGCF-Uniso) poderão ser apresentadas em dois formatos: o tradicional ou em formato de artigo(s) científico(s).

Os trabalhos de investigação que possam resultar em patentes poderão ser apresentados na forma convencional, a critério do grupo de pesquisadores envolvidos, reservadas as particularidades exigidas em relação ao sigilo.

O formato tradicional segue o padrão descrito nas normas do "Manual para normalização de trabalhos acadêmicos" da Universidade de Sorocaba.

As dissertações entregues no formato de artigo científico têm como exigência a publicação ou, no mínimo, a submissão prévia de pelo menos um artigo em revista científica com classificação mínima Qualis/Capes B2 (de acordo com a categorização da WebQualis mais recente, na data do envio/publicação) e podem ser inseridos no idioma e na formatação estabelecida pelo(s) respectivo(s) periódico(s). Os demais artigos podem não ter sido submetidos ainda.

As teses entregues no formato de artigo científico têm como exigência a publicação ou, no mínimo, a submissão prévia de pelo menos dois artigos em revista científica com classificação mínima Qualis/Capes B2 (de acordo com a categorização da WebQualis mais recente, na data do envio/publicação) e podem ser inseridos no idioma e na formatação estabelecida pelo(s) respectivo(s) periódico(s). Os demais artigos podem não ter sido submetidos ainda.

Para aclarar membros da banca que desconhecem esta versão alternativa da dissertação/tese recomenda-se anexar este documento no final das versões encaminhadas aos membros da banca.

A dissertação/tese no formato de artigo(s) científico(s) deverá possuir os elementos apresentados no Quadro 1.

Elementos textuais	*1. Introdução ou apresentação:* trata-se da parte inicial do texto com formulação clara e simples do tema investigado, constando a delimitação do assunto tratado, sua relevância e justificativa.
	2. Revisão de literatura: quando a revisão de literatura for concebida como artigo de revisão, este item deverá ser incluído no item resultado(s).
	3. Objetivos: geral e específico
	4. Material e Métodos (opcional). Quando parte dos resultados não for apresentada no formato de artigo, este item deverá ser incluído após os objetivos específicos. Quando o autor quiser apresentar o(s) método(s) de forma mais detalhada do que no artigo, este item pode também ser apresentado em separado.
	5. Resultados (pode ser apresentado no formato de artigos): deve(m) ser inserida(s) a(s) cópia(s) de artigo(s) derivado(s) da dissertação, previamente publicados, submetidos ou não para publicação em revistas científicas. Sugere-se que cada artigo seja antecedido de uma breve apresentação seguida dos elementos de identificação do artigo (autores, título, revista de publicação, volume, páginas). Os artigos anexados poderão ser apresentados nos formatos exigidos pelas revistas, as quais os artigos foram publicados e/ou submetidos. Parte dos resultados pode ser apresentada em separado dos artigos, quando conveniente.
	6. Discussão (opcional): O autor pode ampliar a discussão dos resultados, quando conveniente.
	7. Conclusão ou Considerações finais: esta parte deverá conter a conclusão do trabalho ou as considerações do autor sobre os resultados alcançados frente aos objetivos propostos.
Elementos pós-textuais	*8. Referências:* Devem seguir as normas do "Manual para normalização de trabalhos acadêmicos" da Universidade de Sorocaba. Não devem ser inseridas as referências apresentadas nos artigos.
	9. Apêndices (Opcional)
	10. Anexos (Opcional)