National Institute for Health and Care Excellence

Final

Rheumatoid arthritis in adults: diagnosis and management

Evidence review G Analgesics

NICE guideline NG100

Evidence review

July 2018

Final

This evidence review was developed by the National Guideline Centre

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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1 Analgesics in Rheumatoid Arthritis

1.1 Review question: In adults with rheumatoid arthritis, what is the clinical and cost effectiveness of analgesics?

1.2 Introduction

Analgesics (including NSAIDs, paracetamol and opioids) are sometimes used on top of disease-modifying treatments for relief of pain and stiffness in people with rheumatoid arthritis (RA) whose symptom control is not adequate. The previous guideline recommended analgesics other than NSAIDs to reduce a person's need for long term treatment with NSAIDs, and included cautionary recommendations about how and when NSAIDs should be used. However, the evidence on analgesia other than NSAIDs in the previous guideline was highly limited, meaning there is uncertainty about the effectiveness of different types of analgesia in rheumatoid arthritis. Given this uncertainty, the committee wished to update these recommendations to reflect the latest and most robust clinical evidence. The committee agreed to use the term NSAIDS to include both selective and non-selective COX II inhibitors.

1.3 PICO table

For full details, see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults with RA
Intervention(s)	• Non-steroidal anti-inflammatory drugs (NSAIDs) • Opioids • Paracetamol • Nefopam • Gabapentioniods • Tricyclic antidepressants • Selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants • Combinations of the above (interclass combinations)
Comparison(s)	Compared with each other (interclass) or placebo
Outcomes	CRITICAL: • Pain • Quality of life IMPORTANT: • Stiffness • Function • Adverse events (mortality, serious gastrointestinal events, serious cardiac and vascular events, impaired renal function) • Drug continuation Pain, quality of life, stiffness and function to be reported at 3 time point: less than or equal to 2 weeks, greater than 2 weeks and up to and including 6 weeks, and more than 6 weeks.
Study design	Randomised controlled trials (RCTs) Systematic reviews of RCTs

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1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[21] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

1.5 Clinical evidence

1.5.1 Included studies

A search was conducted for randomised controlled trials and systematic reviews of randomised controlled trials comparing analgesics with other analgesics (interclass) or placebo in adults with rheumatoid arthritis. Forty-eight studies were included in the review. However, only 41 of these studies reported results in a form that could be extracted and analysed in the review;[7 ,11 ,20 ,23 ,30 ,33 ,35 ,40 ,50 ,56-58 ,69 ,72-75 ,80-82 ,85 ,93 ,98 ,106 ,108 ,111 ,113 ,114 ,116-118 ,128 ,131 ,168 ,169 ,180 ,185 ,190 ,191 ,193 ,194] these are summarised in Table 2 below. The studies reported a wide range of comparisons, as follows:

Interclass comparisons:

- one study compared paracetamol with an NSAID
- one study compared opioid plus paracetamol plus NSAID with an NSAID
- one study compared an opioid plus an NSAID with an opioid plus paracetamol (no extractable data).

Placebo comparisons:

- one study compared an opioid with placebo (no extractable data)
- two studies compared opioid plus paracetamol with placebo
- three studies compared tricyclic antidepressants with placebo (1 with extractable data)
- thirty-nine studies compared an NSAID with placebo (36 with extractable data).

Evidence from these studies is summarised in the clinical evidence summary below (Table 3). See also the study selection flow chart in appendix B, forest plots in appendix D, study evidence tables in appendix E, GRADE tables in appendix G and excluded studies list in appendix H.

1.5.2 Excluded studies

See the excluded studies list in appendix I.

1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of randomised controlled trials with extractable data included in the evidence review

Study	Intervention and comparison	Population	Outcomes (extractable)	Comments
Paracetamol plus opioid plus NSAID versus NSAID				
Glowinski 1999[75]	Opioid (codeine) plus paracetamol plus NSAID (diclofenac) versus NSAID (diclofenac)	Adults with RA with permanent residual pain Age, mean: 57	• Pain: ≤2 weeks • Discontinuation due to inefficacy • Discontinuation due to adverse	Intervention duration: 1 week

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Study	Intervention and comparison	Population	Outcomes (extractable)	Comments
		n=60	events	
NSAID versus paracetamol				
Lee 1975[117]	NSAID (indomethacin) versus paracetamol	Participants with RA with mild, moderate or severe pain Age: not reported n=96	• Pain: 2 weeks • Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 2 weeks
NSAID versus placebo				
Anonymous 1967[7]	Indomethacin versus placebo	Participants with classical or definite peripheral RA. Age, median: 52 n=141	• Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 12 weeks
Anonymous 1980[11]	Ibuprofen or naproxen or sulindac versus placebo	Participants with Active RA Age, median: 52 n=400	• Pain: ≤2 weeks • Stiffness: ≤2 weeks • Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 2 weeks
Ballesteros 1990[20]	Aceclofenac versus Placebo	Participants with RA and flare Age: not reported n=60	• Pain: ≤2 weeks • Stiffness: ≤2 weeks • Function: ≤2 weeks	Intervention duration: 2 weeks
Bensen 2002[23]	Naproxen versus placebo Study also investigated valdecoxib efficacy but this medication was withdrawn voluntarily by the manufacturer in 2005.	Participants with adult onset RA Age, mean: 56 n=448 for groups extracted	• Adverse events: cardiac and vascular events • Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 12 weeks Valdecoxib groups not extracted.
Bickham 2016[30]	Etoricoxib versus placebo	Participants with RA. Age, mean: 54 n=1,404	• Pain: >2 weeks to ≤ 6 weeks • Adverse events: cardiac and vascular events • Discontinuation due to adverse events	Intervention duration: 6 weeks

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Study	Intervention and comparison	Population	Outcomes (extractable)	Comments
Bobrove 1983[33]	Indomethacin versus placebo	Participants with Classical or definite RA. Age: not reported n=218	• Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 2 weeks
Caldwell 1986[40]	Diclofenac or ibuprofen versus placebo	Participants with definite or classical RA, active disease or flare upon entry to trial after discontinuation of NSAIDs. Age, mean: not reported N=183 for diclofenac trial and n=228 for diclofenac/ibuprofen trial.	• Discontinuation due to inefficacy	Two relevant trials reported in this paper: diclofenac versus placebo and diclofenac versus ibuprofen versus placebo. Intervention duration: 6 weeks for diclofenac trial and 10 weeks for ibuprofen trial.
Collantes 2002[50]	Etoricoxib or naproxen versus placebo	Participants with RA Age, mean: 53 n=891	• Adverse events: gastrointestinal effects • Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 12 weeks
Doreen 1978[56]	Diclofenac versus placebo	Participants with RA and require NSAID treatment Age, mean: 49 n=44	• Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 2 weeks
Durrigl 1975[57]	Diclofenac or indomethacin versus placebo	Participants with RA Age, mean: 44 n=50	• Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 2 weeks
Edwards 1983[58]	Etodolac versus placebo	Participants with RA and functional class I, II or III and Steinbrocker progression stage II or III. Age, mean: 54 n=18	• Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 12 weeks
Furst 2002[69]	Diclofenac or meloxicam versus placebo	Participants with RA and flare after discontinuation of NSAID therapy Age, mean: 56	• Pain: >6 weeks • Function: >6 weeks • Adverse events:	Intervention duration: 12 weeks

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Study	Intervention and comparison	Population	Outcomes (extractable)	Comments
		n=894	mortality • Adverse events: gastrointestinal effects • Discontinuation due to inefficacy • Discontinuation due to adverse events	
Geusens 2002[73]	Naproxen versus placebo	Participants with RA and flare Age, mean: 54 n=431	• Adverse events: mortality • Adverse events: gastrointestinal effects • Adverse events: cardiac and vascular events • Adverse events: impaired renal function • Discontinuation due to adverse events	Intervention duration: 12 weeks
Geusens 2004[72]	Naproxen versus placebo	Participants with symptomatic RA and Class I, II or III according to ACR revised criteria. Also flare after NSAID discontinuation. Age, mean: 54 n=563	• Pain: >6 weeks • Function: >6 weeks • Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 26 weeks
Gibofsky 2007[74]	Naproxen versus placebo	Participants with RA and flare after discontinuation of NSAID therapy Age, mean: 57 n=338	• Pain: >6 weeks • Stiffness: >6 weeks • Function: >6 weeks • Adverse events: mortality • Discontinuation due to adverse events	Intervention duration: 12 weeks
Gordon 1983[80]	Etodolac versus placebo	Participants with RA and flare Age, mean: 55 n=16	• Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 12 weeks
Greenwald 2011[82]	Etoricoxib versus placebo	Participants with RA and flare after discontinuation of NSAID therapy Age, mean: 57	• Pain: >6 weeks • Stiffness: >6 weeks • Function: >6	Intervention duration: 12 weeks

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Study	Intervention and comparison	Population	Outcomes (extractable)	Comments
		n=761	weeks • Discontinuation due to inefficacy • Discontinuation due to adverse events	
Hawkey 2003[85]	Naproxen versus placebo	Participants with RA Age, mean: 52 N=660	• Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 12 weeks
Hunter 1996[93]	Aceclofenac versus placebo	Participants with active RA Age, mean: 57 n=73	• Pain >2 weeks to ≤ 6 weeks • Discontinuation due to adverse events	Intervention duration: 4 weeks
Jacob 1983[98]	Etodolac versus placebo	Participants with RA in Functional Class I, II or III and Steinbrocker Progression Stage II or III. Age, mean: 52 n=129	• Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 12 weeks
Kawai 2010[106]	Ketoprofen versus placebo	Participants with RA and wrist joint pain for at least 1 month Age, mean: 59 n=676	• Pain: ≤2 weeks • Discontinuation due to adverse events	Intervention duration: 2 weeks
Kirchheiner 1976[108]	Diclofenac or indomethacin versus placebo	Participants with classical of definite RA Age, mean: 56 n=182	• Adverse events: gastrointestinal effects • Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 4 weeks
Lanier 1987[111]	Nabumentone versus placebo	Participants with stable class II or III definite or classical RA Age: 51=/<50 years old, 61>50 years old. n=160	• Stiffness: >2 weeks to ≤ 6 weeks • Discontinuation due to adverse events	Intervention duration: 3 weeks
Lavie 1990[113]	Diclofenac or tenoxicam versus placebo	Participants with classical RA. Age, mean: 58 n=30	• Discontinuation due to adverse events	Intervention duration: 2 weeks

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Study	Intervention and comparison	Population	Outcomes (extractable)	Comments
Lee 1978[116]	Indomethacin or naproxen versus placebo	Participants with definite or classic RA Age, mean: not reported n=136	• Pain: ≤2 weeks • Stiffness: ≤2 weeks • Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 2 weeks
Lemmel 1997[118]	Meloxicam versus placebo	Participants with RA and ARA functional class I, II or II Age, mean: 55 n=468	• Stiffness >2 weeks to ≤ 6 weeks • Adverse events: gastrointestinal effects • Adverse events: cardiac and vascular events • Discontinuation due to adverse events	Intervention duration: 3 weeks
Matsumoto 2002[128]	Etoricoxib or naproxen versus placebo	Participants with RA and flare after discontinuation of previous therapy Age, mean: 56 n=816	• Adverse events: mortality • Adverse events: gastrointestinal effects • Adverse events: cardiac and vascular events • Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 12 weeks
Mehta 1992[131]	Naproxen versus placebo	Participants with RA Age, mean: 38 n=90	• Adverse events: gastrointestinal effects	Intervention duration: 8 weeks
Simon 1998[168]	Celecoxib versus placebo	Participants with RA and flare and Steinbrocker functional capacity classification of I-III Age, mean: 57 n=330	• Discontinuation due to adverse events	Intervention duration: 4 weeks
Simon 1999[169]	Celecoxib or naproxen versus placebo	Participants with RA and a functional class of I, II, or III.	• Pain: >6 weeks • Stiffness: >6 weeks • Function: >6	Intervention duration: 12 weeks

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Study	Intervention and comparison	Population	Outcomes (extractable)	Comments
		Age, mean: 57 n=1149	weeks • Adverse events: gastrointestinal effects • Discontinuation due to inefficacy • Discontinuation due to adverse events	
Turner 1987[180]	Nabumentone versus placebo	Participants with definite or classical RA. 20% flare on Articular Index after washout period. Age, mean: not reported n=46	• Discontinuation due to adverse events	Intervention duration: 3 weeks
Vetter 1982[185]	Etodolac versus placebo	Hospitalised people with at least 5/11 criteria for RA and flare after anti-rheumatic treatment discontinued. Age, mean: 60 n=24	• Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 4 weeks
Weintraub 1977[190]	Piroxicam versus placebo	Participants with classical or definite RA Age, mean: 48 n=19	• Adverse events: gastrointestinal effects	Intervention duration: 12 weeks
Weisman 1986[191]	Diclofenac versus placebo	Participants with classical or definite RA Age, mean: 51 n=182	• Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 6 weeks
Williams 2006[193]	Naproxen versus placebo	Participants with RA and flare after discontinuation of NSAIDs Age, mean: 57 n=439	• Function: >6 weeks • Adverse events: mortality • Adverse events: cardiac and vascular events	Intervention duration: 12 weeks
Wong 2007[194]	Indomethacin versus placebo	Participants with RA Age, mean: 52 n=25	• Discontinuation due to adverse events	Intervention duration: 2 weeks

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Study	Intervention and comparison	Population	Outcomes (extractable)	Comments
Tricyclic antidepressant versus placebo				
Grace 1985[81]	Tricyclic antidepressant (amitriptyline) versus placebo	Adults with RA with persistent pain despite NSAID analgesic therapy Age, mean: 59 n=36	• Discontinuation due to inefficacy • Discontinuation due to adverse events	Intervention duration: 12 weeks
Paracetamol plus opioid versus placebo				
Boureau 1991[35]	Opioid (codeine) plus paracetamol versus placebo	Adults with RA with persistent residual pain 'refractory to management with symptomatic analgesics' Age, mean: 57 n=40	• Discontinuation due to adverse events	Intervention duration: 1 week
Lee 2006[114]	Opioid (tramadol) plus paracetamol versus placebo	Adults with RA (≥ 6 months), stable dose of NSAID or DMARD, ≥40mm VAS for pain for 2 days before enrolment Age, mean (52), n=277	• Pain: ≤2 weeks • Function: ≤2 weeks • Discontinuation due to adverse events • Discontinuation due to inefficacy	Intervention duration: 1 week

See appendix D for full evidence tables.

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1.5.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Paracetamol plus opioid plus NSAID versus NSAID

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with NSAID	Risk difference with Paracetamol plus opioid plus NSAID (95% CI)
Pain score (change score): ≤2 weeks visual analogue scale (VAS). Scale from: 0 to 100.	58 (1 study) 1 weeks	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean change in pain score (VAS) in the control groups was -23.4	The mean change in VAS pain score in the intervention groups was 8.1 lower (20.29 lower to 4.09 higher)
Pain: >2 weeks to ≤ 6 weeks, >6 weeks – not reported	-	-	-	-	-
Quality of life: ≤2 weeks, >2 weeks to ≤ 6 weeks, >6 weeks – not reported	-	-	-	-	-
Discontinuation: inefficacy	60 (1 study) 1 weeks	⨁⨁⨁⊖ MODERATE[1] due to risk of bias	Not estimable8[4]	0 per 1000	0 fewer per 1,000 (from 60 fewer to 60 more)[3]
Discontinuation: adverse events	60 (1 study) 1 weeks	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 3 (0.33 to 27.23)	33 per 1000	67 more per 1,000 (from 22 fewer to 874 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Absolute effect calculated using risk difference
[4] Zero events in both groups and no relative effect could be calculated

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Table 4: Clinical evidence summary: NSAID versus paracetamol

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Paracetamol	Risk difference with NSAID (95% CI)
Pain (change score): ≤2 weeks Patient rated (none=1, mild=2, moderate=3, severe=4, very severe=5). Scale from: 1 to 5.	96 (1 study) 2 weeks	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean pain score in the control groups was 3.5	The mean pain score in the intervention groups was 0.6 lower (0.88 to 0.32 lower)
Pain: >2 weeks to ≤ 6 weeks, >6 weeks – not reported	-	-	-	-	-
Quality of life: ≤2 weeks, >2 weeks to ≤ 6 weeks, >6 weeks – not reported	-	-	-	-	-
Discontinuation: adverse events	79 (1 study) 2 weeks	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.3 (0.45 to 3.74)	132 per 1,000	39 more per 1,000 (from 72 fewer to 361 more)
Discontinuation: inefficacy	79 (1 study) 2 weeks	⊕⊕⊖⊖ LOW[1] due to risk of bias	RR 0.31 (0.14 to 0.7)	474 per 1,000	327 fewer per 1,000 (from 142 fewer to 407 fewer)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

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Table 5: Clinical evidence summary: NSAIDs versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with NSAID v placebo (95% CI)
Pain (change score): ≤2 weeks VAS. Scale from: 0 to 100.	676 (1 study) 2 weeks	⊕⊕⊕⊖ MODERATE[1] due to risk of bias		The mean pain : </=2 weeks in the control groups was -13.2	The mean pain : </=2 weeks in the intervention groups was 2.5 lower (4.94 to 0.06 lower)
Pain (change or final score): >2 weeks to ≤6 weeks VAS. Scale from: 0 to 100.	1009 (2 studies) 5 weeks	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean pain: >2 weeks to </= 6 weeks in the control groups was -20.26	The mean pain: >2 weeks to </= 6 weeks in the intervention groups was 8.81 lower (12.73 to 4.9 lower)
Pain(change score): >6 weeks VAS. Scale from: 0 to 100.	3238 (7 studies) 14 weeks	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean pain: >6 weeks in the control groups was -13.98	The mean pain: >6 weeks in the intervention groups was 8.76 lower (11.48 to 6.04 lower)
Pain (change or final): ≤2 weeks Varying scales: Patient Global Assessment of Pain, pain intensity on a 5 point scale by the physician, subjective rating scale converted to 5 point numerical result	471 (6 studies) 2 weeks	⊕⊖⊖⊖ VERY LOW[1,4] due to risk of bias, inconsistency		The mean pain: </=2 weeks in the control groups was 2.83 1-5 (1 = nil, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe)	The mean pain: </=2 weeks in the intervention groups was 1.04 standard deviations lower (1.47 to 0.61 lower)
Stiffness (final value): ≤2 weeks Scale from: 0 to 3.	468 (6 studies) 2 weeks	⊕⊖⊖⊖ VERY LOW[1,2,4] due to risk of bias, inconsistency, imprecision		The mean stiffness (final value): </=2 weeks in the control groups was 1.96 Duration assessed by scale 0 = absent, 1 = < 30 min, 2 = 30 min - 2 hr, 3 = > 2 hr	The mean stiffness (final value): </=2 weeks in the intervention groups was 0.15 lower (0.25 to 0.06 lower)[3]

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with NSAID v placebo (95% CI)
Stiffness (change): >2 weeks to ≤6 weeks Change score in minutes:	606 (3 studies) 3 weeks	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision		The mean stiffness: >2 weeks to </= 6 weeks in the control groups was -15 minutes	The mean stiffness: >2 weeks to </= 6 weeks in the intervention groups was 40.42 lower (56.4 to 24.44 lower)
Stiffness(change score): >6 weeks Change score in minutes	2246 (4 studies) 12 weeks	⊕⊕⊖⊖ LOW[1,4] due to risk of bias, inconsistency		The mean stiffness: >6 weeks in the control groups was -30 minutes	The mean stiffness: >6 weeks in the intervention groups was 29.13 lower (43.7 to 14.57 lower)[5]
Function (change score): >6 weeks HAQ. Scale from: 0 to 3.	4137 (8 studies) 12 weeks	⊕⊕⊕⊖ MODERATE[1] due to risk of bias		The mean function: >6 weeks in the control groups was -0.15	The mean function: >6 weeks in the intervention groups was 0.14 lower (0.18 to 0.1 lower)
Function (change score): ≤2 weeks 0 = normal activity, 1 = normal activity with pain, 2 = limited activity, 3 = disability. Scale from: 0 to 3.	58 (1 study) 2 weeks	⊕⊕⊖⊖ LOW[1] due to risk of bias		The mean function: </=2 weeks in the control groups was 93	The mean function: </=2 weeks in the intervention groups was 0.83 lower (1.07 to 0.59 lower)
Adverse events: mortality	2895 (7 studies) 12 weeks	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 0.18 (0.01 to 3.12)	2 per 1000	0 fewer per 1000 (from 10 fewer to 0 more)[7]
Adverse events: gastrointestinal effects	4158 (14 studies)	⊕⊖⊖⊖ VERY LOW[1,2,6] due to risk of	RR 2.23 (1.31	7 per 1000	9 more per 1000 (from 2 more to 21 more)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with NSAID v placebo (95% CI)
	10 weeks	bias, inconsistency, indirectness	to 3.79)		
Adverse events: cardiac and vascular events	3965 (7 studies) 10 weeks	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 1.39 (0.43 to 4.51)	3 per 1000	0 more per 1000 (from 0 fewer to 10 more)[7]
Adverse events: impaired renal function	407 (1 study) 12 weeks	⊕⊕⊖⊖ LOW[1] due to risk of bias	Not estimable[8]	0 per 1000	0 fewer per 1000 (from 10 more to 10 more)[7]
Discontinuation: adverse events	10288 (39 studies) 10 weeks	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.17 (0.98 to 1.4)	51 per 1000	9 more per 1000 (from 1 fewer to 20 more)
Discontinuation: inefficacy	7453 (31 studies) 8 weeks	⊕⊕⊖⊖ LOW[1,4] due to risk of bias, inconsistency	RR 0.52 (0.45 to 0.59)	380 per 1000	183 fewer per 1000 (from 156 fewer to 209 fewer)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
3 Scores estimated using a standardised mean difference of -0.86 (-1.37 to -0.36)
4 Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.
5 Scores estimated using a standardised mean difference of -0.30 (-0.45 to -0.15)

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Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with NSAID v placebo (95% CI)
6 No requirement for protein pump inhibitor (PPI) treatment in non-selective NSAID studies led to gastrointestinal adverse event outcomes to be considered indirect evidence 7 Absolute effect calculated using risk difference 8 Zero events in both groups and no relative effect could be calculated					

Table 6: Clinical evidence summary: Tricyclic antidepressants versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Tricyclic anti-depressants (95% CI)
Pain: ≤2 weeks, >2 weeks to ≤6 weeks, >6 weeks – not reported	-	-	-	-	-
Quality of life: ≤2 weeks, >2 weeks to ≤6 weeks, >6 weeks – not reported	-	-	-	-	-
Discontinuation: adverse events	36 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.67 (0.13 to 3.53)	167 per 1,000	55 fewer per 1,000 (from 145 fewer to 422 more)
Discontinuation: inefficacy	36 (1 study) 12 weeks	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 2 (0.2 to 20.15)	56 per 1,000	56 more per 1,000 (from 44 fewer to 1,000 more)
[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias [2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

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Table 7: Clinical evidence summary: Paracetamol plus opioid versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Opioid plus paracetamol (95% CI)
Pain (final score) (VAS): ≤2 weeks Scale from: 0 to 100.	267 (1 study) 1 weeks	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean pain score in the control groups was 53.81	The mean pain score in the intervention groups was 6.58 lower (11.44 to 1.72 lower)
Pain: >2 weeks to ≤6 weeks, >6 weeks – not reported	-	-	-	-	-
Quality of life: ≤2 weeks, >2 weeks to ≤6 weeks, >6 weeks - not reported	-	-	-	-	-
Function (final score) (common daily activities score in HAQ disability index) HAQ. Scale from: 0 to 3.	267 (1 study) 1 weeks	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision		The mean common daily activities score in the control groups was 1.89	The mean common daily activities score in the intervention groups was 0.14 lower (0.4 lower to 0.12 higher)
Discontinuation: adverse events	307 (2 studies) 1 weeks	⊕⊕⊖⊖ LOW[1,4] due to risk of bias, inconsistency	RR 2.79 (0.42 to 18.35)	47 per 1,000	83 more per 1000 (from 27 fewer to 807 more)
Discontinuation: inefficacy	267 (1 study) 1 weeks	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.33 (0.02 to 5.18)	15 per 1,000	10 fewer per 1000 (from 15 fewer to 63 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 Not the overall HAQ score. Score for common daily activities domain only.
4 Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Random effects (DerSimonian and Laird) model was employed.

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See appendix F for full GRADE tables.

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1.6 Economic evidence

1.6.1 Included studies

No relevant health economic studies were identified.

1.6.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.6.3 Unit costs

Table 8: UK costs of analgesics

Drug	Dose	Unit cost (£)
Paracetamol	500mg tablets	0.74 per 32 tablets
NSAIDs		
Celecoxib	100mg capsules	2.35 per 60 capsules
	200mg capsules	1.92 per 30 capsules
Diclofenac	50mg administered twice per day	3.27 per 28 tablets
Etodolac	300mg capsules	8.14 per 60 capsules
	600mg tablets	15.50 per 30 tablets
Etoricoxib	120mg tablets	24.11 per 28 tablets
	30mg tablets	13.99 per 28 tablets
	60mg tablets	20.11 per 28 tablets
	90mg tablets	22.96 per 28 tablets
Ibuprofen	200mg capsules	4.40 per 30 capsules
	200mg tablets	0.90 per 24 tablets
	400mg tablets	0.90 per 24 tablets
	600mg tablets	5.61 per 84 tablets
Indometacin	25mg four times daily Duration 14 days	1.00 per 28 capsules
Opioids		
Codeine + paracetamol	30mg + 500 mg daily	6.82 per 56 tablets
Tramadol + Paracetamol	37.5mg + 325mg daily	9.22 per 60 tablets
Anti-depressant		
Amitryptyline	Week 1 - 25mg daily; week 2 - 25mg twice daily; week 3 onwards - 25mg 3 times daily	

Sources: NHS Drug Tariff September 2016;[141] BNF November 2016[31]

1.7 Resource costs

The recommendations made in this review are not expected to have a substantial impact on resources.

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1.8 Evidence statements

1.8.1 Clinical evidence statements

- Paracetamol plus opioid plus NSAID versus NSAID

Evidence from 1 study showed that there was no clinically important difference between combined treatment with paracetamol, opioid and NSAID versus NSAID alone in terms of improving pain or discontinuation due to inefficacy; however, NSAID alone was associated with a clinically important benefit over the combination treatment in terms of discontinuation for adverse events (very low to moderate quality, n=60). No evidence was available for quality of life.

- NSAID versus paracetamol

Evidence from 1 study showed a clinically important benefit of NSAIDs over paracetamol in terms of pain and discontinuation due to inefficacy; however, paracetamol was associated with a clinically important benefit over NSAIDs in terms of discontinuation for adverse events (low to very low quality, n=96). No evidence was available for quality of life.

- NSAIDs versus placebo

NSAIDs were found to have a clinically important benefit in terms of discontinuations due to inefficacy. There was inconsistent evidence for the effect of NSAIDs versus placebo on pain, stiffness and function. Some measures of pain, stiffness and function showed a clinically important benefit of NSAIDs over placebo, but other measures of the same outcomes found no clinically important difference (reported in 11, 9 and 7 studies respectively; range of n=3,320-5,394; moderate to very low quality). NSAIDs were associated with a small but clinically important increased occurrence of 9 per thousand people in serious gastrointestinal events when compared to placebo (very low quality; 9 studies; n=5,072). No clinically important difference was seen for mortality, cardiac and vascular adverse events or discontinuation due to adverse events (reported in 5, 6 and 31 studies respectively; range of n= 2,895–10,288; very low quality). No evidence was available for quality of life.

- Tricyclic antidepressants versus placebo

Evidence from 1 study comparing tricyclic antidepressants with placebo suggested that tricyclic antidepressants were associated with a clinically important benefit in terms of fewer discontinuations due to adverse events but a clinically important increase discontinuations due to inefficacy (very low quality; n=36). However, there was considerable uncertainty in the direction of the effects, limiting the ability to draw firm conclusions. No evidence was available for pain or quality of life.

- Paracetamol plus opioid versus placebo

Evidence from 1 study suggested no clinically important difference between paracetamol plus opioid versus placebo in terms of pain but a clinically important benefit of paracetamol plus opioid in terms of function and discontinuation due to inefficacy (very low quality; n=277). Paracetamol plus opioid was associated with an increased occurrence of discontinuation due to adverse events (low quality; 2 studies; n=317). No evidence was available for quality of life.

1.8.2 Health economic evidence statements

No relevant economic evaluations were identified.

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1.9 The committee's discussion of the evidence

1.9.1 Interpreting the evidence

1.9.1.1 The outcomes that matter most

The committee agreed that the critical outcomes for decision-making were quality of life and pain. Stiffness and function were included as important outcomes. In addition, medication continuation and adverse events (mortality, serious gastrointestinal events, serious cardiac and vascular events, and impaired renal function) were considered important outcomes.

The committee agreed that pain, quality of life, stiffness and function should be reported at 3 different time points to enable judgement of efficacy across short or longer treatment periods. Therefore, the results were separated into 3 time periods: less than or equal to 2 weeks, greater than 2 weeks and up to and including 6 weeks, and more than 6 weeks.

No evidence was found for quality of life for any of the analgesic drugs considered.

1.9.1.2 The quality of the evidence

The majority of the evidence received a GRADE quality rating of low or very low. None of the evidence was considered high quality. Risk of bias was high or very high for all outcomes for reasons including selection bias due to no details of how randomisation was conducted or whether there was allocation concealment, lack of details about how blinding was carried out for subjective outcomes, and missing data due to treatment discontinuation. There were a small number of outcomes which contained inconsistent results that could not be explained by subgroup analysis.

Four studies in the NSAID versus placebo comparison were considered to have indirect populations due to participants being required to have a history of positive response to previous treatment with NSAIDs. Also, the lack of protein pump inhibitor (PPI) treatment in all of the non-selective COX II inhibitor NSAID studies led to gastrointestinal adverse event outcomes being considered indirect evidence. The BNF states that people at risk of gastro-intestinal ulceration (including the elderly), who use NSAID treatment, should receive gastroprotective treatment.

1.9.1.3 Benefits and harms

NSAIDs

The committee acknowledged that the evidence for NSAIDs compared to placebo was inconsistent in terms of pain relief, with the magnitude of the effect varying depending on the scoring system used. In general, NSAID treatment seemed to provide some reduction in pain but the results were often not sufficiently large to be considered clinically important. There was also some evidence of benefit of NSAIDs on stiffness and function (though this was somewhat inconsistent), and a clinically important reduction in people discontinuing due to inefficacy when taking NSAIDs compared to placebo. Overall, the committee's view was that NSAIDs may offer a small benefit in relieving symptoms for adults with RA. The 3 timepoints which data was separated into did not give an explanation of when NSAIDs were effective analgesics.

The committee discussed the evidence on adverse events of NSAIDs. There was no clinically important difference between NSAIDs and placebo for most adverse events (mortality, cardiac and vascular events, impaired renal function and discontinuation due to adverse events). However, NSAIDs were associated with an increased risk of serious gastrointestinal events. The committee noted that the absolute risk was small and on balance, the committee agreed that the benefit of NSAIDs for people whose symptom control

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is not adequate was likely to outweigh the risk of harm. The committee also noted that the risk of GI events may have been overestimated in the evidence as PPIs were not co-prescribed with non-selective NSAIDs in the included studies. Overall, the committee recommended that oral NSAIDs be considered in people with rheumatoid arthritis whose symptom control is not adequate.

The committee discussed whether the recommendation for NSAIDs should include the stipulation that PPIs be co-prescribed, as was recommended in the 2009 guideline and agreed this should remain.

To minimise the risk of adverse events, the committee agreed that NSAIDs should be used at the lowest doses and for the shortest possible time, and that risk factors for adverse events should be reviewed regularly, these include previous peptic ulcer, age over 60 years, use of oral steroids, anticoagulants and/or anti-platelet (aspirin or clopidogrel).

Other analgesics

The committee discussed the evidence for other analgesic treatments and noted that it was highly limited.

Paracetamol plus opioid treatment was compared with placebo in 2 studies. The combined treatment showed a clinical benefit over placebo for function and was associated with a clinically significant reduction in discontinuations due to inefficacy. However, it failed to show a benefit over placebo for the critical outcome of pain. It also showed a benefit over placebo in terms of fewer discontinuations due to adverse events, the GC considered this an unlikely finding which only served to highlight the weaknesses of the evidence.

Single small studies provided limited evidence for each of the following comparisons: tricyclic antidepressants versus placebo, NSAID versus paracetamol, and NSAID versus paracetamol plus opioid plus NSAID. The committee placed little weight on the highly limited, poor quality and inconsistent evidence for these comparisons. No evidence was found for nefopam, gabapentinoids or SSRI and SSNRI antidepressants.

The committee noted the 2009 recommendations to use analgesics other than NSAIDs (such as paracetamol, codeine or compound analgesics) which, at the time, was acknowledged to be based on “sparse” evidence. The committee discussed the evidence on the other analgesic treatments and decided that it was too weak to support recommendations for or against their usage. Therefore the 2009 recommendation was not sustained though a research recommendation investigating non-NSAID analgesic drugs was submitted.

General

The committee agreed that choice of analgesic tends to be based on individual effectiveness as well as the person’s risk profile, tolerance, and side effects. In particular, there are some groups of people for whom NSAIDs are unsuitable because of contraindications, comorbidities or tolerability, and other people who are currently benefiting from analgesic drugs other than NSAIDs. The committee agreed that these recommendations should not change the current individualised approach to analgesic drug choice. The committee agreed, based on their experience, that compound analgesics in particular were a potentially useful analgesic option in rheumatoid arthritis, notwithstanding the evidence being insufficient to support a recommendation.

The committee noted that there was a body of evidence on the usage of NSAIDs for short term symptom control but other analgesic drugs, such as paracetamol plus opioid, have not been adequately studied in rheumatoid arthritis. The committee agreed that the effectiveness of non NSAID analgesic drugs in controlling rheumatoid arthritis symptoms was a high priority for further research. Few studies were found for treatment strategies not utilising NSAIDs and the committee decided to make a research recommendation in this area to inform future guidance on analgesia in rheumatoid arthritis.

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1.9.2 Cost effectiveness and resource use

No relevant published economic evidence was identified.

The committee noted that NSAIDs are currently used by people with rheumatoid arthritis and are available either under prescription or over the counter. The committee highlighted that, although their unit cost is relatively low, follow-up costs due to adverse events may increase the NHS resource use in a small group of patients. The committee believed though that, if NSAIDs are offered at their lowest effective dose and for the shortest period possible, the benefits from using them to alleviate disease symptoms outweigh their overall costs.

The committee highlighted that the current approach is likely to continue but there may be an increase in prescribing of NSAIDs instead of other analgesic drugs for people with newly diagnosed RA. Overall however, the recommendation is not expected to have a significant resource impact to the NHS.

1.9.3 Other factors the committee took into account

The management of rheumatoid arthritis in pregnancy was identified as an equalities issue in the equalities impact assessment. No evidence was found for this population strata. The committee agreed that it should be an individualised and consultant-led service, with involvement of obstetric services and broader rheumatology MDT as indicated. Patients and their rheumatology team need to consider many aspects of each individual person's care. These include pre-conception advice and management of pharmacological therapies, assessment of potential impact of disease on the pregnancy, advice on disease course during pregnancy, and discussions regarding the disease and its treatment in the post-partum period. Particular attention should be paid to therapeutic management of rheumatoid arthritis to ensure potentially teratogenic therapies are not continued in the pre-conception stage or into early pregnancy. Alternative management strategies should be considered, depending on each patient's level of disease control and symptoms, for the duration of the pregnancy.

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Appendices

Appendix A: Review protocols

Table 9: Review protocol: Analgesics

ID	Field	Content
I	Review question	In adults with rheumatoid arthritis, what is the clinical and cost effectiveness of analgesics?
II	Type of review question	Intervention
III	Objective of the review	To establish the clinical and cost effectiveness of different classes of analgesic drugs for symptom management in RA.
IV	Eligibility criteria – population / disease / condition / issue / domain	Adults with rheumatoid arthritis according to validated classification criteria. Pregnant women will be treated as a stratum.
V	Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	• Paracetamol • NSAIDs • Opioids • Nefopam • Non-tricyclic anti-depressants (SSRIs & SSNRIs) • Gabapentinoids • Tricyclic anti-depressants • Combinations of the above All doses will be pooled in the analysis
VI	Eligibility criteria – comparator(s) / control or reference (gold) standard	Compared with each other (interclass) or placebo
VII	Outcomes and prioritisation	CRITICAL • Pain (Continuous) at >6 weeks • Pain (Continuous) at >2 to 6 weeks • Pain (Continuous) at ≤2 weeks • Quality of life (Continuous) at >6 weeks • Quality of life (Continuous) at >2 to 6 weeks • Quality of life (Continuous) at ≤2 weeks IMPORTANT • Stiffness (Continuous) at >6 weeks • Stiffness (Continuous) at >2 to 6 weeks • Stiffness at ≤2 weeks (Continuous) at ≤2 weeks • Function at >6 weeks (Continuous) at >6 weeks • Function at >2 to 6 weeks (Continuous) at >2 to 6 weeks • Function at ≤2 weeks (Continuous) at ≤2 weeks • Adverse events: mortality (Dichotomous) at longest time period reported • Adverse events: gastrointestinal effects (Dichotomous) at longest time

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		period reported • Adverse events: cardiac and vascular events (Dichotomous) at longest time period reported • Adverse events: impaired renal function (Continuous) at longest time period reported • Drug continuation (Dichotomous) at longest time period reported
VIII	Eligibility criteria – study design	Systematic Review of RCTs RCTs
IX	Other inclusion / exclusion criteria	The following studies will be excluded: • Mixed inflammatory arthritis populations, unless the results are presented separately for RA patients. • Populations with RA as well as another rheumatic disease (e.g. lupus). • Within class (intra-class) comparisons • Study uses doses of anti-depressants greater than those used in clinical practice for analgesic effect • Study of anti-depressants in patients who are depressed
X	Proposed sensitivity / subgroup analysis, or meta-regression	Subgroup analyses if there is heterogeneity: • Age (Not applicable; Not stated / Unclear; >65 years ; ≤65 years); Patients >65 years have increasing morbidity and mortality from side effects of NSAIDs because of impaired adaptation and other natural defence mechanisms. They are also less likely to tolerate opioid analgesia. • Route of administration (Not applicable; Not stated / Unclear; Oral; Topical; Transcutaneous); Transcutaneous and topical administration may be better tolerated and cause fewer side effects by bypassing the stomach and biliary system; for NSAIDs, a lower dose administered topically may be more effective by acting locally. • Duration of intervention use (Short-term use [<2 weeks]; Long-term use [>6 weeks]); Long-term use of analgesics and NSAIDs carries greater risk of side effects because of cumulative dose. • Within-class differences (Strong opioids; Weak opioids; Selective COX-2 inhibitors; Non-selective NSAIDs); Strong opioids may have greater efficacy but more side effects and poorer tolerability; COX-2 inhibitors are expected to cause less serious GI toxicity than non-selective NSAIDs (ulcers, haemorrhage, perforation, hospitalisation, death) for the same efficacy. They may also be better tolerated.
XI	Selection process – duplicate screening / selection / analysis	A sample of at least 10% of the abstract lists will be double-sifted by a senior research fellow and discrepancies rectified, with committee input where consensus is not reached, for more information please see the separate Methods report for this guideline.
XII	Data management (software)	• Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). • GRADEpro was used to assess the quality of evidence for each outcome. • Endnote was used for bibliography, citations, sifting and reference management
XIII	Information sources – databases and dates	Clinical search databases: Medline, Embase and the Cochrane Library. Date limits for search: None Language: English Health economics search databases: Medline, Embase, NHSEED and HTA

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		Date limits for search: Medline and Embase from 2014 NHSEED and HTA from 2001 Language: English
XIV	Identify if an update	This review is an update of a clinical area covered in NICE guideline: Rheumatoid arthritis in adults: management[139] published in 2009. However the protocol for this updated review differed from the previous review and thus the search was undertaken for all years.
XV	Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10014
XVI	Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
XVII	Search strategy – for one database	For details please see appendix B
XVIII	Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
XIX	Data items – define all variables to be collected	For details, please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
XX	Methods for assessing bias at outcome / study level	Standard study checklists were used to appraise individual studies critically. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
XXI	Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual.
XXII	Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
XXIV	Confidence in cumulative evidence	For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
XXV	Rationale / context – what is known	For details, please see the introduction to the evidence review.
XXVI	Describe contributions	A multidisciplinary committee (https://www.nice.org.uk/guidance/indevelopment/gid-

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	of authors and guarantor	ng10014/documents) developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Stephen Ward in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual.
XXVII	Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
XXVIII	Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
XXIX	Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
XXX	PROSPERO registration number	Not registered

Table 10: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	Populations, interventions and comparators must be as specified in the clinical review protocol above. Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) Unpublished reports will not be considered unless submitted as part of a call for evidence. Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2001, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).140 Inclusion and exclusion criteria If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

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Review question	All questions – health economic evidence
	Where there is discretion The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. Setting: UK NHS (most applicable). OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). OECD countries with predominantly private health insurance systems (for example, Switzerland). Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. Health economic study type: Cost–utility analysis (most applicable). Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). Comparative cost analysis. Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. Year of analysis: The more recent the study, the more applicable it will be. Studies published in 2001 or later but that depend on unit costs and resource data entirely or predominantly from before 2001 will be rated as 'Not applicable'. Studies published before 2001 will be excluded before being assessed for applicability and methodological limitations. Quality and relevance of effectiveness data used in the health economic analysis: The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017 (https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869).

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 11: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (Ovid)	1946 – 06 October 2017	Exclusions Randomised controlled trials Systematic review studies
Embase (Ovid)	1974 – 06 October 2017	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2017 Issue 10 of 12 CENTRAL to 2017 Issue 9 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

Medline (Ovid) search terms

1.	exp Arthritis, Rheumatoid/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/

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15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	Animals, Laboratory/
23.	exp animal experiment/
24.	exp animal model/
25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	analgesics/
30.	analgesic*.ti,ab.
31.	acetaminophen/
32.	(paracetamol or acetaminophen or acetominophen or panadol).ti,ab.
33.	exp anti inflammatory agents, non steroidal/
34.	(nsaid* or ((non-steroid* or nonsteroid*) adj (antiinflammatory or anti-inflammatory))).ti,ab.
35.	((cox 2 or cox2 or cox ii) adj inhibitor*).ti,ab.
36.	(cyclooxygenase adj2 inhibitor*).ti,ab.
37.	(ibuprofen or brufen or calprofen or ibuderm or ibugel or ibuleve or ibuspray or nurofen).ti,ab.
38.	(naproxen or diclofenac or voltarol or rheumatac or mefenamic or ponstan or mefenaminic or indomethacin or indometacin or indocid or ketoprofen or axorid or oruvail or piroxicam or feldene or meloxicam).ti,ab.
39.	(celecoxib or celebrex or etoricoxib or arcoxia or etodolac or eccoxolac or etopan or lodine).ti,ab.
40.	fenoprofen/
41.	meptazinol/
42.	(tiaprofenic or surgam or tenoxicam or mobiflex or nabumeton* or reliflex or aceclofenac or preservex or fenoprofen or flurbiprofen or froben or sulindac or tolfenamic or clotam or pethidin* or meperidin* or meptazinol or meptid).ti,ab.
43.	exp analgesics, opioid/
44.	(opioid* or opiate*).ti,ab.
45.	(tramadol or maxitram or tilodol or tramacet or zamadol or zydol or codeine or pentazocine or fortral or morphine or morphia or oxycodone or carexil or retelbon or zomestine or methadone or fentanyl or durogesic or fentalis or mezolar or opiodur or osmanil or hydromorphone or dihydromorphinone or palladone or buprenorphine or bupeaze or butrans or gabup or hapoctasin or panitaz or sevodyne or subutex or transtec or temgesic or diamorphine or dihydromorphine or paramorfan or paramorphan or dihydrocodeine).ti,ab.
46.	(anadin or co-codamol or cocodamol or co-dydramol or codydramol or paracodol or solpadeine or solpadol or ultramol or veganin or zapain).ti,ab.
47.	nefopam/
48.	nefopam.ti,ab.
49.	exp antidepressive agents/

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50.	(anti-depressant* or antidepressant* or antidepressive* or anti-depressive*).ti,ab.
51.	(tricyclic* or amitriptyline or butriptyline or clomipramine or desipramine or dosulepin or dothiepin or doxepin or imipramine or iprindole or lofepramine or nortriptyline or opipramol or protriptyline or trimipramine).ti,ab.
52.	exp serotonin uptake inhibitors/
53.	trazodone/
54.	(SSRI* or selective serotonin reuptake inhibitor* or serotonin uptake inhibitor*).ti,ab.
55.	(citalopram or dapoxetine or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline or trazodone or mirtazapine).ti,ab.
56.	exp "serotonin and noradrenaline reuptake inhibitors"/
57.	(snri* or ("serotonin and noradrenaline reuptake" adj inhibitor*)).ti,ab.
58.	(venlafaxine or sibutramine or duloxetine or atomoxetine or desvenlafaxine or milnacipran or levomilnacipran).ti,ab.
59.	exp gamma-aminobutyric acid/
60.	gabapentinoid*.ti,ab.
61.	(gabapentin or pregabalin).ti,ab.
62.	or/29-61
63.	28 and 62
64.	randomized controlled trial.pt.
65.	controlled clinical trial.pt.
66.	randomi#ed.ab.
67.	placebo.ab.
68.	drug therapy.fs.
69.	randomly.ab.
70.	trial.ab.
71.	groups.ab.
72.	or/64-71
73.	Clinical Trials as topic.sh.
74.	trial.ti.
75.	or/64-67,69,73-74
76.	Meta-Analysis/
77.	Meta-Analysis as Topic/
78.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
79.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
80.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
81.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
82.	(search* adj4 literature).ab.
83.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
84.	cochrane.jw.
85.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
86.	or/76-85
87.	63 and (75 or 86)

Embase (Ovid) search terms

1.	exp *rheumatoid arthritis/

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2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter.pt. or letter/
11.	note.pt.
12.	editorial.pt.
13.	case report/ or case study/
14.	(letter or comment*).ti.
15.	or/10-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animal/ not human/
19.	nonhuman/
20.	exp Animal Experiment/
21.	exp Experimental Animal/
22.	animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice).ti.
25.	or/17-24
26.	9 not 25
27.	*analgesic agent/
28.	analgesic*.ti,ab.
29.	*paracetamol/
30.	(paracetamol or acetaminophen or acetominophen or panadol).ti,ab.
31.	exp *nonsteroid antiinflammatory agent/
32.	(nsaid* or ((non-steroid* or nonsteroid*) adj (antiinflammatory or anti-inflammatory))).ti,ab.
33.	exp *cyclooxygenase 2 inhibitor/
34.	((cox 2 or cox2 or cox ii) adj inhibitor*).ti,ab.
35.	(cyclooxygenase adj2 inhibitor*).ti,ab.
36.	(ibuprofen or brufen or calprofen or ibuderm or ibugel or ibuleve or ibuspray or nurofen).ti,ab.
37.	(naproxen or diclofenac or voltarol or rheumatac or mefenamic or ponstan or mefenaminic or indomethacin or indometacin or indocid or ketoprofen or axorid or oruvail or piroxicam or feldene or meloxicam).ti,ab.
38.	(celecoxib or celebrex or etoricoxib or arcoxia or etodolac or eccoxolac or etopan or lodine).ti,ab.
39.	*pethidine/
40.	*meptazinol/
41.	(tiaprofenic or surgam or tenoxicam or mobiflex or nabumeton* or reliflex or aceclofenac or preservex or fenoprofen or flurbiprofen or froben or sulindac or tolfenamic or clotam or pethidin* or meperidin* or meptazinol or meptid).ti,ab.

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42.	*opiate/
43.	*buprenorphine/ or *cocodamol/ or *codeine/ or *diamorphine/ or *dihydrocodeine/ or exp *fentanyl derivative/ or *hydromorphone/ or *methadone/ or *morphine/ or *oxycodone/ or *oxycodone plus paracetamol/ or *paracetamol plus tramadol/ or *pentazocine/ or *tramadol/
44.	(opioid* or opiate*).ti,ab.
45.	(tramadol or maxitram or tilodol or tramacet or zamadol or zydol or codeine or pentazocine or fortral or morphine or morphia or oxycodone or carexil or retelbon or zomestine or methadone or fentanyl or durogesic or fentalis or mezolar or opiodur or osmanil or hydromorphone or dihydromorphinone or palladone or buprenorphine or bupeaze or butrans or gabup or hapoctasin or panitaz or sevodyne or subutex or transtec or temgesic or diamorphine or dihydromorphine or paramorfan or paramorphan or dihydrocodeine).ti,ab.
46.	(anadin or co-codamol or cocodamol or co-dydramol or codydramol or paracodol or solpadeine or solpadol or ultramol or veganin or zapain).ti,ab.
47.	*nefopam/
48.	nefopam.ti,ab.
49.	*antidepressant agent/ or exp *tricyclic antidepressant agent/
50.	(anti-depressant* or antidepressant* or antidepressive* or anti-depressive*).ti,ab.
51.	(tricyclic* or amitriptyline or butriptyline or clomipramine or desipramine or dosulepin or dothiepin or doxepin or imipramine or iprindole or lofepramine or nortriptyline or opipramol or protriptyline or trimipramine).ti,ab.
52.	exp *serotonin uptake inhibitor/
53.	(SSRI* or selective serotonin reuptake inhibitor* or serotonin uptake inhibitor*).ti,ab.
54.	(citalopram or dapoxetine or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline or trazodone or mirtazapine).ti,ab.
55.	exp *serotonin noradrenalin reuptake inhibitor/
56.	(snri* or ("serotonin and noradrenaline reuptake" adj inhibitor*)).ti,ab.
57.	(venlafaxine or sibutramine or duloxetine or atomoxetine or desvenlafaxine or milnacipran or levomilnacipran).ti,ab.
58.	*gabapentin/ or *pregabalin/
59.	gabapentinoid*.ti,ab.
60.	(gabapentin or pregabalin).ti,ab.
61.	or/27-60
62.	26 and 61
63.	random*.ti,ab.
64.	factorial*.ti,ab.
65.	(crossover* or cross over*).ti,ab.
66.	((doubl* or singl*) adj blind*).ti,ab.
67.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
68.	crossover procedure/
69.	single blind procedure/
70.	randomized controlled trial/
71.	double blind procedure/
72.	or/63-71
73.	systematic review/
74.	meta-analysis/
75.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
76.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.

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77.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
78.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
79.	(search* adj4 literature).ab.
80.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
81.	cochrane.jw.
82.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
83.	or/73-82
84.	62 and (72 or 83)

Cochrane Library (Wiley) search terms

#1.	[mh "Arthritis, Rheumatoid"]
#2.	(rheumatoid near/2 (arthritis or arthrosis)):ti,ab
#3.	(caplan* near/2 syndrome):ti,ab
#4.	(felty* near/2 syndrome):ti,ab
#5.	(rheumatoid near/2 factor):ti,ab
#6.	((inflammatory or idiopathic) near/2 arthritis):ti,ab
#7.	inflammatory polyarthritis:ti,ab
#8.	(or #1-#7)
#9.	[mh ^analgesics]
#10.	analgesic*:ti,ab
#11.	[mh ^acetaminophen]
#12.	(paracetamol or acetaminophen or acetominophen or panadol):ti,ab
#13.	[mh "anti inflammatory agents, non steroidal"]
#14.	(nsaid* or ((non-steroid* or nonsteroid* or non next steroid*) next (antiinflammatory or anti-inflammatory or "anti inflammatory"))):ti,ab
#15.	(("cox 2" or cox2 or "cox ii") next inhibitor*):ti,ab
#16.	(cyclooxygenase near/2 inhibitor*):ti,ab
#17.	(ibuprofen or brufen or calprofen or ibuderm or ibugel or ibuleve or ibuspray or nurofen):ti,ab
#18.	(naproxen or diclofenac or voltarol or rheumatac or mefenamic or ponstan or mefenaminic or indomethacin or indometacin or indocid or ketoprofen or axorid or oruvail or piroxicam or feldene or meloxicam):ti,ab
#19.	(celecoxib or celebrex or etoricoxib or arcoxia or etodolac or eccoxolac or etopan or lodine):ti,ab
#20.	[mh "analgesics, opioid"]
#21.	(opioid* or opiate*):ti,ab
#22.	(tramadol or maxitram or tilodol or tramacet or zamadol or zydol or codeine or pentazocine or fortral or morphine or morphia or oxycodone or carexil or retelbon or zomestine or methadone or fentanyl or durogesic or fentalis or mezolar or opiodur or osmanil or hydromorphone or dihydromorphinone or palladone or buprenorphine or bupeaze or butrans or gabup or hapoctasin or panitaz or sevodyne or subutex or transtec or temgesic or diamorphine or dihydromorphine or paramorfan or paramorphan or dihydrocodeine):ti,ab
#23.	(anadin or co-codamol or cocodamol or co-dydramol or codydramol or paracodol or solpadeine or solpadol or ultramol or veganin or zapain):ti,ab
#24.	[mh ^nefopam]
#25.	nefopam:ti,ab

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#26.	[mh "antidepressive agents"]
#27.	(anti-depressant* or antidepressant* or antidepressive* or anti-depressive*) .ti,ab
#28.	(tricyclic* or amitriptyline or butriptyline or clomipramine or desipramine or dosulepin or dothiepin or doxepin or imipramine or iprindole or lofepramine or nortriptyline or opipramol or protriptyline or trimipramine):ti,ab
#29.	[mh "serotonin uptake inhibitors"]
#30.	[mh ^trazodone]
#31.	(SSRI* or "selective serotonin reuptake" next inhibitor* or "serotonin uptake" next inhibitor*) .ti,ab.
#32.	(citalopram or dapoxetine or escitalopram or fluoxetine or fluvoxamine or paroxetine or sertraline or trazodone or mirtazapine):ti,ab
#33.	[mh ^trazodone]
#34.	[mh "serotonin and noradrenaline reuptake inhibitors"]
#35.	(snri* or ("serotonin and noradrenaline reuptake" next inhibitor*)):ti,ab
#36.	(venlafaxine or sibutramine or duloxetine or atomoxetine or desvenlafaxine or milnacipran or levomilnacipran):ti,ab
#37.	[mh "gamma-aminobutyric acid"]
#38.	gabapentinoid*:ti,ab
#39.	(gabapentin or pregabalin):ti,ab
#40.	(tiaprofenic or surgam or tenoxicam or mobiflex or nabumeton* or reliflex or aceclofenac or preservex or fenoprofen or flurbiprofen or froben or sulindac or tolfenamic or clotam or pethidin* or meperidin* or meptazinol or meptid):ti,ab
#41.	[mh ^fenoprofen]
#42.	[mh ^meptazinol]
#43.	(or #9-#42)
#44.	#8 and #43

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to rheumatoid arthritis population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies.

Table 12: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 06 October 2017	Exclusions Health economics studies
Embase	2014– 06 October 2017	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 2001 – 06 October 2017 NHSEED - 2001 – 31 March 2015	None

Medline (Ovid) search terms

1.	exp Arthritis, Rheumatoid/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.

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3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/
15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	Animals, Laboratory/
23.	exp animal experiment/
24.	exp animal model/
25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	Economics/
30.	Value of life/
31.	exp "Costs and Cost Analysis"/
32.	exp Economics, Hospital/
33.	exp Economics, Medical/
34.	Economics, Nursing/
35.	Economics, Pharmaceutical/
36.	exp "Fees and Charges"/
37.	exp Budgets/
38.	budget*.ti,ab.
39.	cost*.ti.
40.	(economic* or pharmaco?economic*).ti.
41.	(price* or pricing*).ti,ab.
42.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
43.	(financ* or fee or fees).ti,ab.
44.	(value adj2 (money or monetary)).ti,ab.
45.	or/29-44

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46.	exp models, economic/
47.	*Models, Theoretical/
48.	*Models, Organizational/
49.	markov chains/
50.	monte carlo method/
51.	exp Decision Theory/
52.	(markov* or monte carlo).ti,ab.
53.	econom* model*.ti,ab.
54.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
55.	or/46-54
56.	28 and (45 or 55)

Embase (Ovid) search terms

1.	exp *rheumatoid arthritis/
2.	(rheumatoid adj2 (arthritis or arthrosis)).ti,ab.
3.	(caplan* adj2 syndrome).ti,ab.
4.	(felty* adj2 syndrome).ti,ab.
5.	(rheumatoid adj2 factor).ti,ab.
6.	((inflammatory or idiopathic) adj2 arthritis).ti,ab.
7.	"inflammatory polyarthritis".ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter.pt. or letter/
11.	note.pt.
12.	editorial.pt.
13.	case report/ or case study/
14.	(letter or comment*).ti.
15.	or/10-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animal/ not human/
19.	nonhuman/
20.	exp Animal Experiment/
21.	exp Experimental Animal/
22.	animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice).ti.
25.	or/17-24
26.	9 not 25
27.	statistical model/
28.	exp economic aspect/
29.	27 and 28

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30.	*theoretical model/
31.	*nonbiological model/
32.	stochastic model/
33.	decision theory/
34.	decision tree/
35.	monte carlo method/
36.	(markov* or monte carlo).ti,ab.
37.	econom* model*.ti,ab.
38.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
39.	or/29-38
40.	*health economics/
41.	exp *economic evaluation/
42.	exp *health care cost/
43.	exp *fee/
44.	budget/
45.	funding/
46.	budget*.ti,ab.
47.	cost*.ti.
48.	(economic* or pharmaco?economic*).ti.
49.	(price* or pricing*).ti,ab.
50.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
51.	(financ* or fee or fees).ti,ab.
52.	(value adj2 (money or monetary)).ti,ab.
53.	or/40-52
54.	26 and (39 or 53)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Arthritis, Rheumatoid EXPLODE ALL TREES
#2.	((rheumatoid adj2 (arthritis or arthrosis)))
#3.	((caplan* adj2 syndrome))
#4.	((felty* adj2 syndrome))
#5.	((rheumatoid adj2 factor))
#6.	(((inflammatory or idiopathic) adj2 arthritis))
#7.	("inflammatory polyarthritis")
#8.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

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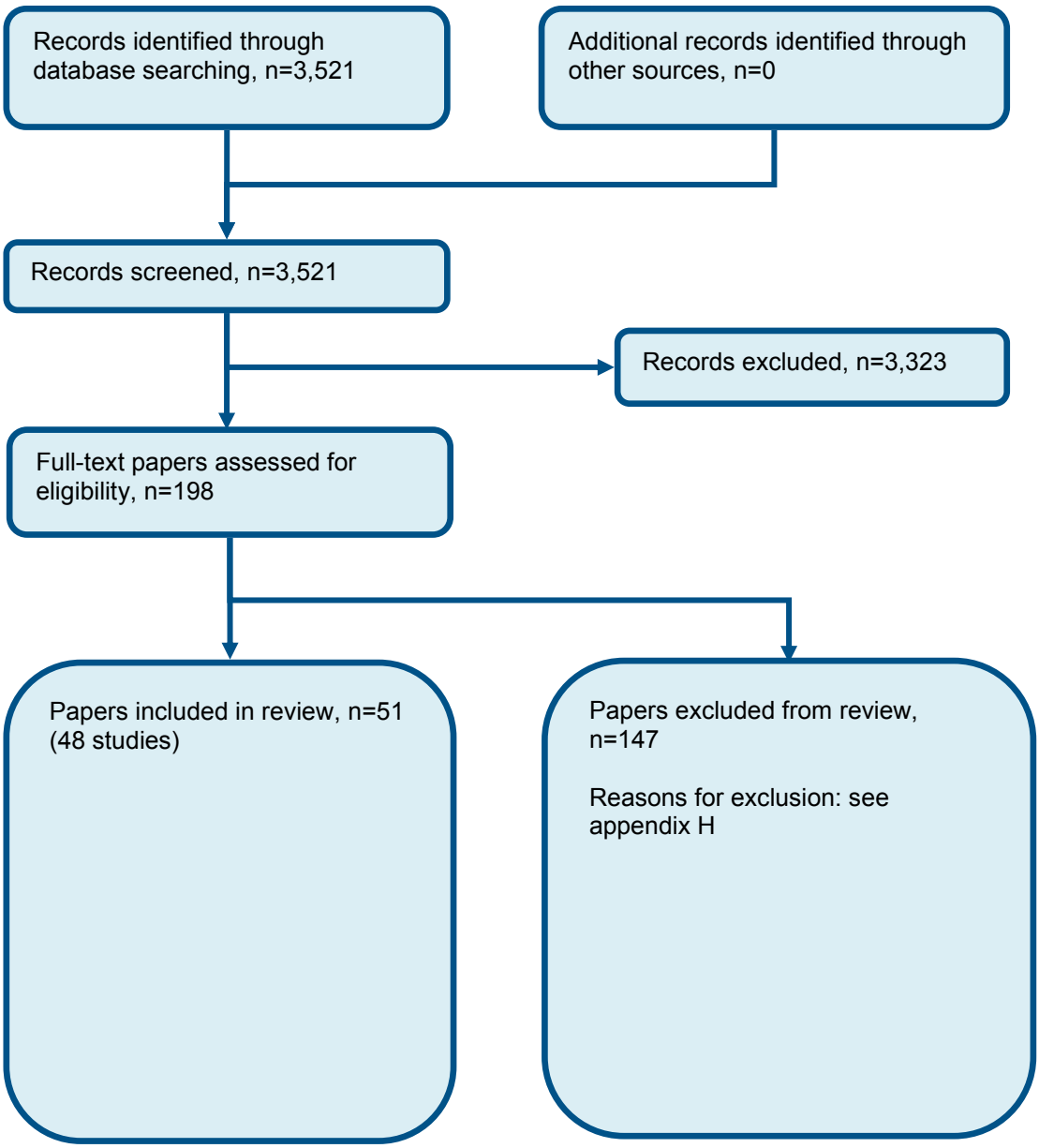
Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of analgesics for rheumatoid arthritis



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Appendix D: Clinical evidence tables

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Study	Anonymous 1967[7]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=141)
Countries and setting	Conducted in USA; Setting:
Line of therapy	Mixed line
Duration of study	Intervention time: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Classical or definite peripheral RA.
Exclusion criteria	20 exclusions in ARA criteria, for example, high concentration of erythematosus cells, scleroderma, infectious arthritis, Reiter's syndrome, gouty arthritis) . Also, arthritis for less than 6 months, pregnancy or childbirth, severe infection, major surgery within previous 6 months, anemia associated with RA, cancer, diabetes, serious kidney disease, serious liver disease, suspected peptic ulcer, psoriasis, sever hypertension, active tuberculosis, ulcerative colitis, known or suspected ankylosing spondylitis. Use of indomethacin previously, systemic or intra-articular glucocorticoid, phenylbutazone, antimalarial or gold treatment during prior 2 months.
Recruitment/selection of patients	Outpatients or domiciliary hospital patients
Age, gender and ethnicity	Age - Median (range): 52 (16-81). Gender (M:F): Male: 38, Female: 98. Ethnicity: Not detailed
Further population details	1. Age: Not applicable (Age range 16 to 81.).
Indirectness of population	No indirectness
Interventions	(n=71) Intervention 1: NSAIDs - indomethacin. Weeks 1,2: 50mg per day. Weeks 3,4: 200mg per day. Weeks: 5,6,7,8: 150mg per day. Weeks 9,10,11,12: 200mg per day. Dispensed in 25mg capsules. . Duration 12 weeks. Concurrent medication/care: No systemic or intra articular glucocorticoids, anti-malarials, gold, non-trial indomethacin. Salicylate therapy in accordance with clinical practice. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral (Capsules). 3. Within-class differences : Non-selective NSAIDs (n=65) Intervention 2: Placebo. Capsules containing 223mg lactose and 2mg magnesium. Schedules capsule intake matched to active treatment. . Duration 12 weeks. Concurrent medication/care: No systemic or intra articular glucocorticoids, anti-malarials, gold, non-trial indomethacin. Salicylate therapy in accordance with clinical practice. . Indirectness: No indirectness

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	Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Academic or government funding (Supported by Grant AM-03252 from the National Institute of Arthritis and Metabolic Diseases)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INDOMETHACIN versus PLACEBO Protocol outcome 1: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: inefficacy at 12 weeks; Group 1: 5/61, Group 2: 2/55 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups stated to be similar for age, disease duration and number of affected joints. ; Group 1 Number missing: 10; Group 2 Number missing: 10 - Actual outcome: Discontinuation: adverse events at 12 weeks; Group 1: 10/66, Group 2: 7/60 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups stated to be similar for age, disease duration and number of affected joints. ; Group 1 Number missing: 5; Group 2 Number missing: 5	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Anonymous 1980[11]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=400)
Countries and setting	Conducted in Australia, New Zealand; Setting: 10 centres
Line of therapy	Unclear
Duration of study	Intervention + follow up: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Stratified then randomised: Stratified by pain at baseline
Inclusion criteria	Active RA (presence of symptoms)
Exclusion criteria	Patients who had been started on, or had a chance in dose of, glucocorticoids or DMARDs within 3 months of commencement of trial; history of peptic ulceration.
Recruitment/selection of patients	Patients with RA invited to participate either through mail or when attended for follow-up.
Age, gender and ethnicity	Age - Mean (SD): NR. Gender (M:F): 99:223 (completers). Ethnicity: NR
Further population details	1. Age: Not applicable
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=150) Intervention 1: NSAIDs - naproxen . Either 250 mg twice daily, 500 mg at night, 250 mg morning and 500 mg at night (all three arms combined in this analysis). Duration 2 weeks. Concurrent medication/care: Assumed that DMARDs and glucocorticoids could be maintained as background if stable and if stable for last 3 months prior to trial. All other NSAID medication taken before study was discontinued for the duration of the trial. . Indirectness: Serious indirectness; Indirectness comment: No requirement for co-prescription with PPIs Further details: 1. Duration of intervention use: Short term use (<2 weeks) 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=100) Intervention 2: NSAIDs - sulindac. Either 100 mg twice daily, or 200 mg twice daily (two separate arms combined in this analysis). Duration 2 weeks. Concurrent medication/care: DMARDs and glucocorticoids at stable dose. All other NSAID medication stopped during trial. . Indirectness: Serious indirectness; Indirectness comment: No requirement to co-prescribe with PPIs Further details: 1. Duration of intervention use: Short term use (<2 weeks) 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs

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	(n=50) Intervention 3: NSAIDs - ibuprofen . 400 mg 3 times daily. Duration 2 weeks . Concurrent medication/care: DMARDs and glucocorticoids at stable doses. All other NSAID medication stopped during trial. . Indirectness: Serious indirectness; Indirectness comment: No requirement to co-prescribe with PPIs Further details: 1. Duration of intervention use: Short term use (<2 weeks) 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=50) Intervention 4: Placebo. Matching placebo. Duration 2 weeks. Concurrent medication/care: DMARDs and glucocorticoids at stable dose. All other NSAID medication stopped during trial. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Study funded by industry ("Generous support of Syntex Australia Ltd" and sulindac tablets provided by Merck Sharp and Dohme (NZ) Ltd.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NAPROXEN versus PLACEBO

Protocol outcome 1: Pain at <2 weeks
- Actual outcome: Pain score at 2 weeks; Group 1: mean 2.69 (SD 0.7); n=122,
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Refers to methods 'described elsewhere' that indicate trial was randomised. ITT: withdrawn patients were given maximum possible pain and morning stiffness scores for missing days. ; Indirectness of outcome: No indirectness ; Baseline details: Baseline pain scores comparable. Other confounding/ prognostic factors not reported. ; Blinding details: Branding of known ibuprofen tablets removed, naproxen tablets obtained in different form, sulindac tablets new and unknown to patients. ; Group 1 Number missing: 58, Reason: 28 forms not returned, 30 patients withdrawn (25 due to inefficacy); Group 2 Number missing: 33, Reason: 10 forms not returned, 23 patients withdrawn (20 due to inefficacy)

Protocol outcome 2: Stiffness at <2 weeks
- Actual outcome: Stiffness score at 2 weeks; Group 1: mean 2.6 (SD 0.77); n=122,
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Refers to methods 'described elsewhere' that indicate trial was randomised. ITT: withdrawn patients were given maximum possible pain and morning stiffness scores for missing days. ; Indirectness of outcome: No indirectness ; Baseline details: Baseline stiffness scores comparable. Other confounding/ prognostic factors not reported. ; Blinding details: Branding of known ibuprofen tablets removed, naproxen tablets obtained in different form, sulindac tablets new and unknown to patients. ; Group 1 Number missing: 58, Reason: 28 forms not returned, 30 patients withdrawn (25 due to inefficacy); Group 2 Number missing: 33, Reason: 10 forms not returned, 23 patients withdrawn (20 due to inefficacy)

Protocol outcome 3: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation: adverse events at 2 weeks; Group 1: 11/122, Group 2: 7/40

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Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Refers to methods 'described elsewhere' that indicate trial was randomised. ITT: withdrawn patients were given maximum possible pain and morning stiffness scores for missing days. ; Indirectness of outcome: No indirectness ; Baseline details: confounding/ prognostic factors not reported. ; Blinding details: Branding of known ibuprofen tablets removed, naproxen tablets obtained in different form, sulindac tablets new and unknown to patients. ; Group 1 Number missing: 47, Reason: 28 forms not returned, 19 patients withdrawn due to inefficacy alone; Group 2 Number missing: 26, Reason: 10 forms not returned, 16 patients withdrawn due to inefficacy alone
- Actual outcome: Discontinuation: inefficacy at 2 weeks; Group 1: 25/122, Group 2: 20/40
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Refers to methods 'described elsewhere' that indicate trial was randomised. ITT: withdrawn patients were given maximum possible pain and morning stiffness scores for missing days. ; Indirectness of outcome: No indirectness ; Baseline details: confounding/ prognostic factors not reported. ; Blinding details: Branding of known ibuprofen tablets removed, naproxen tablets obtained in different form, sulindac tablets new and unknown to patients. ; Group 1 Number missing: 33, Reason: 28 forms not returned, 5 patients withdrawn due to adverse events alone; Group 2 Number missing: 13, Reason: 10 forms not returned, 3 patients withdrawn due to adverse events alone

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SULINDAC versus PLACEBO

Protocol outcome 1: Pain at <2 weeks
- Actual outcome: Pain score at 2 weeks; Group 1: mean 2.83 (SD 0.71); n=81,
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Refers to methods 'described elsewhere' that indicate trial was randomised. ITT: withdrawn patients were given maximum possible pain and morning stiffness scores for missing days. ; Indirectness of outcome: No indirectness ; Baseline details: Baseline pain scores comparable. Other confounding/ prognostic factors not reported. ; Blinding details: Branding of known ibuprofen tablets removed, naproxen tablets obtained in different form, sulindac tablets new and unknown to patients. ; Group 1 Number missing: 26, Reason: 19 forms not returned, 17 patients withdrawn (13 due to inefficacy); Group 2 Number missing: 33, Reason: 10 forms not returned, 23 patients withdrawn (20 due to inefficacy)

Protocol outcome 2: Stiffness at <2 weeks
- Actual outcome: Stiffness score at 2 weeks; Group 1: mean 2.8 (SD 0.77); n=81,
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Refers to methods 'described elsewhere' that indicate trial was randomised. ITT: withdrawn patients were given maximum possible pain and morning stiffness scores for missing days. ; Indirectness of outcome: No indirectness ; Baseline details: Baseline stiffness scores comparable. Other confounding/ prognostic factors not reported. ; Blinding details: Branding of known ibuprofen tablets removed, naproxen tablets obtained in different form, sulindac tablets new and unknown to patients. ; Group 1 Number missing: 26, Reason: 19 forms not returned, 17 patients withdrawn (13 due to inefficacy); Group 2 Number missing: 33, Reason: 10 forms not returned, 23 patients withdrawn (20 due to inefficacy)

Protocol outcome 3: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation: adverse events at 2 weeks; Group 1: 8/81, Group 2: 7/40
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Refers to methods 'described elsewhere' that indicate trial was randomised. ITT: withdrawn patients were given maximum

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possible pain and morning stiffness scores for missing days. ; Indirectness of outcome: No indirectness ; Baseline details: Other confounding/ prognostic factors not reported. ; Blinding details: Branding of known ibuprofen tablets removed, naproxen tablets obtained in different form, sulindac tablets new and unknown to patients. ; Group 1 Number missing: 28, Reason: 19 forms not returned, 9 patients withdrawn due to inefficacy alone; Group 2 Number missing: 26, Reason: 10 forms not returned, 16 patients withdrawn due to inefficacy alone
- Actual outcome: Discontinuation: inefficacy at 2 weeks; Group 1: 13/81, Group 2: 20/40
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Refers to methods 'described elsewhere' that indicate trial was randomised. ITT: withdrawn patients were given maximum possible pain and morning stiffness scores for missing days. ; Indirectness of outcome: No indirectness ; Baseline details: Other confounding/ prognostic factors not reported. ; Blinding details: Branding of known ibuprofen tablets removed, naproxen tablets obtained in different form, sulindac tablets new and unknown to patients. ; Group 1 Number missing: 23, Reason: 19 forms not returned, 4 patients withdrawn due to adverse events alone; Group 2 Number missing: 13, Reason: 10 forms not returned, 3 patients withdrawn due to adverse events alone

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IBUPROFEN versus PLACEBO

Protocol outcome 1: Pain at <2 weeks
- Actual outcome: Pain score at 2 weeks; Group 1: mean 2.83 (SD 0.7); n=40,
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Refers to methods 'described elsewhere' that indicate trial was randomised. ITT: withdrawn patients were given maximum possible pain and morning stiffness scores for missing days. ; Indirectness of outcome: No indirectness ; Baseline details: Outcome comparable at baseline. Other confounding / prognostic factors not reported; Blinding details: Branding of known ibuprofen tablets removed, naproxen tablets obtained in different form, sulindac tablets new and unknown to patients. ; Group 1 Number missing: 18, Reason: 10 forms not returned, 8 patients withdrawn (9 due to inefficacy); Group 2 Number missing: 33, Reason: 10 forms not returned, 23 patients withdrawn (20 due to inefficacy)

Protocol outcome 2: Stiffness at <2 weeks
- Actual outcome: Stiffness score at 2 weeks; Group 1: mean 3 (SD 0.76); n=40,
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Refers to methods 'described elsewhere' that indicate trial was randomised. ITT: withdrawn patients were given maximum possible pain and morning stiffness scores for missing days. ; Indirectness of outcome: No indirectness ; Baseline details: Outcome NOT comparable at baseline (placebo lower). Other confounding / prognostic factors not reported; Blinding details: Branding of known ibuprofen tablets removed, naproxen tablets obtained in different form, sulindac tablets new and unknown to patients. ; Group 1 Number missing: 18, Reason: 10 forms not returned, 8 patients withdrawn (9 due to inefficacy); Group 2 Number missing: 33, Reason: 10 forms not returned, 23 patients withdrawn (20 due to inefficacy)

Protocol outcome 3: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation: adverse events at 2 weeks; Group 1: 3/40, Group 2: 7/40
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Refers to methods 'described elsewhere' that indicate trial was randomised. ITT: withdrawn patients were given maximum possible pain and morning stiffness scores for missing days. ; Indirectness of outcome: No indirectness ; Baseline details: Other confounding / prognostic factors not reported; Blinding details: Branding of known ibuprofen tablets removed, naproxen tablets obtained in different form, sulindac tablets new and

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unknown to patients. ; Group 1 Number missing: 15, Reason: 10 forms not returned, 5 patients withdrawn due to inefficacy only; Group 2 Number missing: 26, Reason: 10 forms not returned, 16 patients withdrawn due to inefficacy only - Actual outcome: Discontinuation: inefficacy at 2 weeks; Group 1: 6/40, Group 2: 20/40 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Refers to methods 'described elsewhere' that indicate trial was randomised. ITT: withdrawn patients were given maximum possible pain and morning stiffness scores for missing days. ; Indirectness of outcome: No indirectness ; Baseline details: Other confounding / prognostic factors not reported; Blinding details: Branding of known ibuprofen tablets removed, naproxen tablets obtained in different form, sulindac tablets new and unknown to patients. ; Group 1 Number missing: 12, Reason: 10 forms not returned, 2 patients withdrawn due to adverse events only; Group 2 Number missing: 13, Reason: 10 forms not returned, 3 patients withdrawn due to adverse events only	
Protocol outcomes not reported by the study	Pain at >6 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Ballesteros 1990[20]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Spain; Setting: NR
Line of therapy	Unclear
Duration of study	Intervention time: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged between 27 and 60 years with RA showing clear signs of activity when they were not treated with anti-inflammatory drugs
Exclusion criteria	Proven hypersensitivity to NSAIDs, significant renal or liver impairment, treated with anti-inflammatory drugs in one month prior to study commencement
Recruitment/selection of patients	Patients 'chosen at random'
Age, gender and ethnicity	Age - Mean (SD): Aceclofenac - 41 (7.3), Placebo - 42 (7.2). Gender (M:F): 25:35. Ethnicity: NR
Further population details	1. Age: ≤65 years (Range 27-60 years).
Extra comments	NR
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: NSAIDs - aceclofenac. 2 x 100mg tablets per day. Duration 2 weeks. Concurrent medication/care: NR, other than that most patients in NSAID arm had at least intermittent antacid consumption (mean 1.07 (SD 0.92) on a scale where 0 = none, 1 = intermittant, 2 = constant). Indirectness: Serious indirectness; Indirectness comment: No mention of co-prescription with PPI Further details: 1. Duration of intervention use: Short term use (<2 weeks) 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=30) Intervention 2: Placebo. 2 tablets per day. Duration 2 weeks. Concurrent medication/care: NR. Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs
Funding	Funding not stated

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACECLOFENAC versus PLACEBO

Protocol outcome 1: Pain at <2 weeks
- Actual outcome: Pain at rest at 2 weeks; Group 1: mean 0.98 (SD 0.41); n=29, Group 2: mean 1.79 (SD 0.49); n=29; 5 point scale 0 = absent, 1 = mild, 2 = moderate, 3 = intense, 4 = unbearable Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Confounding factors other than age and sex (comparable) not reported. 0.17 difference in groups at baseline (NSAID group worse score); Blinding details: "double blind". Assume patient was blinded. ; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 1, Reason: NR
- Actual outcome: Pain during movement at 2 weeks; Group 1: mean 0.86 (SD 0.44); n=29, Group 2: mean 1.86 (SD 0.44); n=29; 5 point scale 0 = absent, 1 = mild, 2 = moderate, 3 = intense, 4 = unbearable Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Confounding factors other than age and sex (comparable) not reported. 0.04 difference in groups at baseline (NSAID group worse score); Blinding details: "double blind". Assume patient was blinded. ; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 1, Reason: NR

Protocol outcome 2: Stiffness at <2 weeks
- Actual outcome: Duration of stiffness at 2 weeks; Group 1: mean 1.17 (SD 0.47); n=29, Group 2: mean 1.96 (SD 0.18); n=29; Duration assessed by scale 0 = absent, 1 = < 30 min, 2 = 30 min - 2 hr, 3 = > 2 hr Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Confounding factors other than age and sex (comparable) not reported. 0.11 difference in groups at baseline (NSAID group worse score); Blinding details: "double blind". Assume patient was blinded. ; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 1, Reason: NR

Protocol outcome 3: Function at <2 weeks
- Actual outcome: Degree of disability at 2 weeks; Group 1: mean 1.1 (SD 0.55); n=29, Group 2: mean 1.93 (SD 0.37); n=29; 4 point scale 0 = normal activity, 1 = normal activity with pain, 2 = limited activity, 3 = disability Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Confounding factors other than age and sex (comparable) not reported. 0.38 difference in groups at baseline (NSAID group worse score); Blinding details: "double blind". Assume patient was blinded. ; Group 1 Number missing: 1, Reason: NR; Group 2 Number missing: 1, Reason: NR

Protocol outcomes not reported by the study	Pain at >6 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Function at >6 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported; Drug continuation at Longest time period reported

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Study	Bensen 2002[23]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1090 randomised of which 222 were in the placebo group, 226 naproxen group (Valdecoxib groups not extracted))
Countries and setting	Conducted in USA; Setting: Not described.
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Adult onset RA, defined by ACR criteria, for at least 6 months
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who were of legal age of consent and had adult onset RA, defined by ACR criteria for at least 6 months. Stable RA on conventional NSAID therapy for at least 1 month and a Functional Capacity Classification between I and II at the screening assessment. Patients with RA in a flare state at the baseline assessment, within 2-7 days following discontinuation of conventional NSAID, full-dose aspirin or celecoxib, or 4-7 days following discontinuation of oxaprozin, piroxicm or rofecoxib were included in the study. An RA flare state was defined as a Patient's and Physician's Global Assessment of Disease Activity of 'fair', 'poor', or 'very poor' at the baseline visit, with a minimum of six tender/painful joints and an increase of two joints (or 20%) over the screening visit, and three swollen joints with an increase of two joints (or 20%) over the screening visit. In addition, patients had to have either a minimum of 45 min of morning stiffness at baseline with a minimum increase of ≥15 min compared with screening or have Patient's Assessment of Arthritis Pain-VAS of ≥40mm (where 0= no pain and 100=most severe pain) with a minimum increase of 10mm compared with screening.
Exclusion criteria	Any other form of inflammatory arthritis, or secondary or non-inflammatory arthritis that interfered with the evaluation of study medication in the treatment of RA. Patients with a history of malignancy, active GI disease, chronic or acute renal/hepatic disorders (including uncontrolled hypertension) or significant coagulation disorder were also excluded, as were patients who had received treatment for GI ulceration within 30 days of the first study dose. Received warfarin within 30 days, oral glucocorticoids within 4 weeks or intra-articular glucocorticoids within 8 weeks, anti-neoplastics within 12 weeks, or anti-inflammatory analgesics within 48 hr of study drug administration were not eligible.
Recruitment/selection of patients	Not described.
Age, gender and ethnicity	Age - Mean (SD): Placebo 55.7 (12.0), Naproxen 55.4 (12.7). Gender (M:F): Placebo 23% male, naproxen 19%. Ethnicity: The following are for Placebo and Naproxen respectively: caucasian 76%, 78%, Black 9%, 8%, Asian 0%, <1%, Hispanic 15%, 11%, Other <1%, 2%.

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Further population details	1. Age: Not applicable
Extra comments	Low dose aspirin (<325mg) for non-arthritic reasons were allowed to continue their aspirin regimen. Patients were allowed to continue their DMARD therapy but those who changed their dosing or started taking any of the following during the outlined time periods prior to study drug administration were excluded: gold salts or anti-malarial drugs within 4 months, methotrexate >25mg/week, sulphasalazaline >3g/day, azathioprine, penicillamine, etanercept, leflunomide or antibiotics (e.g. monocycline or doxycycline) within 12 weeks, glucosamine chondroitin with 4 weeks.
Indirectness of population	No indirectness
Interventions	(n=222) Intervention 1: Placebo. Not described, but stated to be double blind. Study period was preceded by a screening visit, a 2-7 day washout period and baseline visit.. Duration 12 weeks. Concurrent medication/care: Concomitant medication: methotrexate 55%, other DMARDs 25%.. Indirectness: No indirectness Further details: 1. Duration of intervention use: 2. Route of administration: 3. Within-class differences : (n=226) Intervention 2: NSAIDs - naproxen . 500mg b.i.d. stated to be double blind. No further information given. Study period was preceded by a screening visit, a 2-7 day washout period and baseline visit.. Duration 12 weeks. Concurrent medication/care: Concomitant medication: methotrexate 49%, other DMARDs 26%.. Indirectness: No indirectness Further details: 1. Duration of intervention use: 2. Route of administration: 3. Within-class differences :
Funding	Study funded by industry (Sponsored by Pharmacia Corporation and Pfizer Inc. 3 authors were all employees of the Pharmacia Corporation, and 2 authors acted in the capacity of consultants for Pharmacia)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NAPROXEN versus PLACEBO

Protocol outcome 1: Adverse events: cardiac and vascular events at Longest time period reported
- Actual outcome: Adverse events: cardiac and vascular events at 12 weeks; Group 1: 1/226, Group 2: 0/222; Comments: Single patient in the naproxen group, event not specified. Described overall as thromboembolic events (angina pectoris, coronary artery disorder, and/or myocardial infarction).)
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Downgraded due to no description of randomization and allocation concealment and high differential rate in missing data between the two groups.; Indirectness of outcome: No indirectness ; Baseline details: For Naproxen and placebo groups respectively: age 55.4 (12.7) years, 55.7 (12.0) years, weight 79.3 (18.3)kg, 78.3 (18.3)kg, disease duration, 9.9 (8.7) years, 10.3 (8.6) years, history of upper GI bleeding 0.9%, 1.4%, history of Gastroduodenal ulcer 8.0%, 8.1%.; Blinding details: Only stated to be double blind. No further information was given. Unclear no placebo tablets/ care received alongside medication etc.; Group 1 Number missing: 89, Reason: adverse events 13,treatment failure 57, pre-existing violation 8, noncompliance 11; Group 2 Number missing: 130, Reason: adverse events 10, treatment failure 102, lost to follow up 2, pre-existing violation 10, noncompliance 6

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Protocol outcome 2: Drug continuation at Longest time period reported - Actual outcome: Withdrawal: adverse events at 12 weeks; Group 1: 13/226, Group 2: 10/222; Comments: The study does not describe what the adverse events were that led to withdrawal. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Downgraded due to no description of randomization and allocation concealment and high differential rate in missing data between the two groups.; Indirectness of outcome: No indirectness ; Baseline details: For Naproxen and placebo groups respectively: age 55.4 (12.7) years, 55.7 (12.0) years, weight 79.3 (18.3)kg, 78.3 (18.3)kg, disease duration, 9.9 (8.7) years, 10.3 (8.6) years, history of upper GI bleeding 0.9%, 1.4%, history of Gastroduodenal ulcer 8.0%, 8.1%.; Blinding details: Only stated to be double blind. No further information was given. Unclear no placebo tablets/ care received alongside medication etc.; Group 1 Number missing: 76, Reason: treatment failure 57, pre-existing violation 8, noncompliance 11; Group 2 Number missing: 120, Reason: treatment failure 102, lost to follow up 2, pre-existing violation 10, noncompliance 6 - Actual outcome: Withdrawal: inefficacy at 12 weeks; Group 1: 57/226, Group 2: 102/222 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Downgraded due to no description of randomization and allocation concealment. No definition given for 'treatment failure'.; Indirectness of outcome: No indirectness ; Baseline details: For Naproxen and placebo groups respectively: age 55.4 (12.7) years, 55.7 (12.0) years, weight 79.3 (18.3)kg, 78.3 (18.3)kg, disease duration, 9.9 (8.7) years, 10.3 (8.6) years, history of upper GI bleeding 0.9%, 1.4%, history of Gastroduodenal ulcer 8.0%, 8.1%.; Blinding details: Only stated to be double blind. No further information was given. Unclear no placebo tablets/ care received alongside medication etc.; Group 1 Number missing: 32, Reason: adverse events 13, pre-existing violation 8, noncompliance 11; Group 2 Number missing: 28, Reason: adverse events 10, lost to follow up 2, pre-existing violation 10, noncompliance 6	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Bickham 2016[30]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1404)
Countries and setting	Conducted in Argentina, Austria, Canada, Colombia, Czech Republic, Finland, Germany, Guatemala, India, Lithuania, Mexico, Panama, Peru, Poland, Romania, Russia, Slovakia, South Africa, Taiwan, United Kingdom, USA
Line of therapy	Mixed line
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA 1987 criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	18 years and older, diagnosis of RA at least 6 months prior to study screening, demonstrated prior clinical response to NSAIDs, demonstrated symptom flare upon discontinuation of previous NSAID treatment.
Exclusion criteria	None detailed.
Recruitment/selection of patients	Conducted in 211 study centres.
Age, gender and ethnicity	Age - Mean (SD): 53.8 (12). Gender (M:F): Male: 232, Female: 1172. Ethnicity: White: 1059, Asian: 164, Black: 33, Multi-Racial: 126, Other: 22
Further population details	1. Age: Not applicable (Ages ranged from 18 to 84.).
Extra comments	. Randomisation stratified by concomitant use of DMARDs. Proportion of DMARD users capped at 50% for whole study population.
Indirectness of population	No indirectness
Interventions	(n=118) Intervention 1: Placebo. No details. Duration 6 weeks. Concurrent medication/care: No details Further details: 1. Duration of intervention use: Not applicable (6 week treatment). 2. Route of administration: Not stated / Unclear (Not stated). 3. Within-class differences : Not applicable (Placebo). (n=1286) Intervention 2: NSAIDs - etoricoxib. 2 groups: 60mg or 90mg. 818 people in the 60mg group and 468 in the 90mg group.. Duration 6 weeks. Concurrent medication/care: No details Further details: 1. Duration of intervention use: Long term use (>6 weeks) (6 weeks). 2. Route of administration: Oral 3. Within-class differences : Selective COX-2 inhibitors
Funding	Study funded by industry (Study funded by Merck & Co.)

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RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ETORICOXIB versus PLACEBO

Protocol outcome 1: Pain at >6 weeks
- Actual outcome: Pain Score at 6 weeks; Group 1: mean -29.2362 (SD 25.5295); n=1286, Group 2: mean -20.26 (SD 20.95); n=118
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for gender, age, race, RA duration, ARA functional class, use of biologics, use of methotrexate, use of glucocorticoid, use of DMARDs; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Adverse events: cardiac and vascular events at Longest time period reported
- Actual outcome: Adverse events: congestive heart failure, pulmonary edema, cardiac failure at 6 weeks; Group 1: 0/1270, Group 2: 0/116
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for gender, age, race, RA duration, ARA functional class, use of biologics, use of methotrexate, use of glucocorticoid, use of DMARDs; Group 1 Number missing: 16; Group 2 Number missing: 2

Protocol outcome 3: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation due to hypertension/edema at 6 weeks; Group 1: 16/1286, Group 2: 2/118
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for gender, age, race, RA duration, ARA functional class, use of biologics, use of methotrexate, use of glucocorticoid, use of DMARDs; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Bobrove 1983[33]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=218)
Countries and setting	Conducted in USA; Setting: Multicentre
Line of therapy	Mixed line
Duration of study	Intervention time: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Classical or definite RA. Anti-inflammatory drugs previously taken were withdrawn and participants were required to exhibit a flare.
Exclusion criteria	Participants with a history of peptic ulcer disease, gastrointestinal heamorrhage, known intolerance to Indomethacin, concurrent illness that could confound efficacy or tolerance evaluation.
Age, gender and ethnicity	Age - Range: 21-70 years of age. Gender (M:F): Male: 69, Female: 149. Ethnicity: Not stated
Further population details	1. Age: Not applicable (Range of ages included was 21-70).
Indirectness of population	No indirectness
Interventions	(n=53) Intervention 1: NSAIDs - indomethacin. Osmosin A: 1 tablet per day at bedtime. Contains 85mg of indomethacin, delivered over 10 to 12 hours (OROS). Dose increased to twice daily, in the morning and evening, if response not adequate. . Duration 2 weeks. Concurrent medication/care: None detailed. Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (2 weeks). 2. Route of administration: Oral (Tablet). 3. Within-class differences: Not applicable (n=56) Intervention 2: NSAIDs - indomethacin. Osmosin B: 1 tablet per day at bedtime. Contains 85mg of indomethacin, delivered over 8 hours (OROS). Dose increased to twice daily, in the morning and evening, if response not adequate. . Duration 2 weeks. Concurrent medication/care: None detailed. Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (2 weeks). 2. Route of administration: Oral (Tablet). 3. Within-class differences: Not applicable (n=55) Intervention 3: NSAIDs - indomethacin. 25mg 3 times daily. Increased to 50mg 3 times daily for inadequate response. . Duration 2 weeks. Concurrent medication/care: Not detailed. . Indirectness: No indirectness

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	Further details: 1. Duration of intervention use: Short term use (<2 weeks) (2 weeks). 2. Route of administration: Oral (Tablet). 3. Within-class differences : Non-selective NSAIDs (n=54) Intervention 4: Placebo. Given at the same timepoints as the indomethacin treatment. . Duration 2 weeks. Concurrent medication/care: None detailed. Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (2 weeks). 2. Route of administration: Oral (Tablet). 3. Within-class differences : Not applicable (n=164) Intervention 5: NSAIDs - indomethacin. 3 treatment groups with similar numbers in each. Indomethacin: 25mg 3 times daily. Increased to 50mg 3 times daily for inadequate response. Osmosin A: 1 tablet per day at bedtime. Contains 85mg of indomethacin, delivered over 10 to 12 hours (OROS). Dose increased to twice daily, in the morning and evening, if response not adequate. Osmosin B: 1 tablet per day at bedtime. Contains 85mg of indomethacin, delivered over 8 hours (OROS). Dose increased to twice daily, in the morning and evening, if response not adequate. . Duration 2 weeks. Concurrent medication/care: None detailed. Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (2 weeks). 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INDOMETHACIN versus PLACEBO Protocol outcome 1: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: inefficacy at 2 weeks; Group 1: 3/152, Group 2: 10/52 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Stated that there are no statistically significant differences between the 4 treatment groups for age, gender, duration of illness, baseline efficacy, or tolerance. ; Group 1 Number missing: 12; Group 2 Number missing: 2 - Actual outcome: Discontinuation: adverse events at 2 weeks; Group 1: 10/158, Group 2: 3/45 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Stated that there are no statistically significant differences between the 4 treatment groups for age, gender, duration of illness, baseline efficacy, or tolerance. ; Group 1 Number missing: 6; Group 2 Number missing: 9	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported;

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Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported	

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Study	Boureau 1991[35]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in France
Line of therapy	Not applicable
Duration of study	Intervention time: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Met the American Rheumatology Association (ARA) criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18 and over, presented with rheumatoid arthritis, stabilised for at least 1 month without changes to basic and anti-inflammatory therapy. Presented with persistent residual pain refractory to management with symptomatic analgesics. Judged pain over the past 24 hours to be moderate or worse on a 5 point scale.
Exclusion criteria	Contraindication to codeine, history of abuse of opioid analgesics, contraindication to paracetamol, use of an anti-inflammatory other than the usual one 48 hours preceding the start of the trial, an intellectual level preventing full understanding of the pain assessment scales and study procedure.
Recruitment/selection of patients	Multicentre (4 centres)
Age, gender and ethnicity	Age - Mean (SD): 58.6 (1.9) for paracetamol/codeine group, 55.1 (2.8) for placebo group. Gender (M:F): 4 male, 36 female. . Ethnicity: Not stated
Further population details	1. Age: Not stated / Unclear (Age range not specified but might have spanned 65 year cut off).
Extra comments	Interrupted previous analgesic treatment during study.
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Opioid + paracetamol. Codeine: 500mg administered over 3 daily treatments. Paracetamol: 30mg administered over 3 daily treatments. Duration 7 days. Concurrent medication/care: No other analgesic treatment utilised. Other treatments utilised (numbers apply to overall study not this specific treatment group): Auranofin (n=15), penicillamine (n=10), hydroxychloroquine (n=4), azathioprine (n=2), levamisole (n=2), sulfalazine (n=1), methotrexate (n=1). Combined with glucocorticoid (n=17) or NSAIDs (n=22). . Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (7 days). 2. Route of administration: Not stated / Unclear 3. Within-class differences: Not applicable (Weak opiate in codeine combined with paracetamol). (n=20) Intervention 2: Placebo. Not stated. . Duration 7 days. Concurrent medication/care: No analgesic

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	treatment utilised. Other treatments utilised (numbers apply to overall study not this specific treatment group): Auranofin (n=15), penicillamine (n=10), hydroxychloroquine (n=4), azathioprine (n=2), levamisole (n=2), sulfalazine (n=1), methotrexate (n=1). Combined with glucocorticoid (n=17) or NSAIDs (n=22). . Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (7 days). 2. Route of administration: Not stated / Unclear 3. Within-class differences: Not applicable (Placebo).
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CODEINE + PARACETAMOL versus PLACEBO Protocol outcome 1: Drug continuation at Longest time period reported - Actual outcome: Discontinuation (permanent): due to AEs at 7 days; Group 1: 2/20, Group 2: 2/20 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, weight, gender, disease duration, analgesic treatment, pre-treatment pain. ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Caldwell 1986-1[40]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=183)
Countries and setting	Conducted in USA
Line of therapy	Mixed line
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged 21-65 with definite or classical RA, active disease or flare upon entry to trial after discontinuation of NSAIDs.
Exclusion criteria	Pregnant women or women of childbearing potential not using a reliable method of contraception. People with active intestinal disease or significantly altered endocrine, renal or cardiovascular function. People with a history of hypersensitivity to aspirin, NSAIDs, acetaminophen. People requiring other NSAIDs or immunosuppressants.
Age, gender and ethnicity	Age - Range: Inclusion criteria range: 21 to 65 years of age. Gender (M:F): Not detailed. . Ethnicity: Not reported
Further population details	1. Age: Not applicable (People 65 years old could be included in the trial population).
Extra comments	Minimum washout was 2 days and maximum 4 weeks.
Indirectness of population	No indirectness
Interventions	(n=89) Intervention 1: NSAIDs - diclofenac. 150mg daily. . Duration 6 weeks. Concurrent medication/care: Antiarthritic medications permitted including gold and d-pencillamine if doses were stable for 6 months. Adrenocorticosteroids were permitted if dose had been stable for 3 months. Maximum dose allowed was 7.5mg. Further details: 1. Duration of intervention use: Long term use (>6 weeks) (6 weeks). 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=94) Intervention 2: Placebo. No details. . Duration 6 weeks. Concurrent medication/care: Antiarthritic medications permitted including gold and d-pencillamine if doses were stable for 6 months. Adrenocorticosteroids were permitted if dose had been stable for 3 months. Maximum dose allowed was 7.5mg. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (6 weeks). 2. Route of

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	administration: Oral 3. Within-class differences : Not applicable
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus PLACEBO Protocol outcome 1: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: inefficacy at 6 weeks; Group 1: 27/89, Group 2: 38/94 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Caldwell 1986-2[40]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=228)
Countries and setting	Conducted in USA
Line of therapy	Mixed line
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged 18-70 with definite or classical RA, active disease or flare upon entry to trial after discontinuation of NSAIDs.
Exclusion criteria	Pregnant women or women of childbearing potential not using a reliable method of contraception. People with active intestinal disease or significantly altered endocrine, renal or cardiovascular function. People with a history of hypersensitivity to aspirin, NSAIDs, acetaminophen. People requiring other NSAIDs or immunosuppressants.
Age, gender and ethnicity	Age - Range: Inclusion criteria range: 18 to 70 years of age. Gender (M:F): Not detailed. . Ethnicity: Not detailed
Further population details	1. Age: Not applicable (People 65 years old could be included in the trial population).
Extra comments	Minimum washout was 2 days and maximum 2 weeks.
Indirectness of population	No indirectness
Interventions	(n=75) Intervention 1: NSAIDs - diclofenac. 150mg daily. . Duration 10 weeks. Concurrent medication/care: Antiarthritic medications permitted including gold and d-pencillamine if doses were stable for 6 months. Adrenocorticosteroids were permitted if dose had been stable for 3 months. Maximum dose allowed was 5mg. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (10 weeks). 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=74) Intervention 2: NSAIDs - ibuprofen . 2.4mg per day. Duration 10 weeks. Concurrent medication/care: Antiarthritic medications permitted including gold and d-pencillamine if doses were stable for 6 months. Adrenocorticosteroids were permitted if dose had been stable for 3 months. Maximum dose allowed was 5mg.. Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (10 weeks). 2. Route of

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	administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=79) Intervention 3: Placebo. No details. Duration 10 weeks. Concurrent medication/care: Antiarthritic medications permitted including gold and d-pencillamine if doses were stable for 6 months. Adrenocorticosteroids were permitted if dose had been stable for 3 months. Maximum dose allowed was 5mg.. Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (10 weeks). 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus PLACEBO Protocol outcome 1: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: inefficacy at 10 weeks; Group 1: 19/75, Group 2: 38/79 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IBUPROFEN versus PLACEBO Protocol outcome 1: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: inefficacy at 10 weeks; Group 1: 19/74, Group 2: 38/79 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Collantes 2002[50]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=891)
Countries and setting	Conducted in Multiple countries; Setting: 67 sites over 28 countries.
Line of therapy	1st line
Duration of study	Intervention time: 12 weeks with an option to enter a further 40 week trial extension (if withdrew due to lack of efficacy or completed the trial)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Criteria for RA as specified by the 1987 revised criteria of the American Rheumatism Association.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≥18 years and fulfilled diagnostic criteria for RA as specified by the 1987 revised criteria of the American Rheumatism Association. Established diagnosis of RA for at least 6 months prior to entering the study, 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).
Exclusion criteria	History of angina or congestive heart failure, with symptoms that occurred at rest or minimal activity, and/or who had a history of myocardial infarction, coronary angioplasty, or coronary bypass within the past year. Stroke, transient ischemic attack or hepatitis in the previous two years. Uncontrolled hypertension at screening. Any medical condition which, in the opinion of the investigator could have confounded study results or caused undue risk to the patients (e.g. comorbid conditions for which NSAIDs are contraindicated). any evidence of GI bleeding (hemoccult screen done prior to allocation). At randomization patients could not be taking concomitant warfarin, ticlopidine, clopidogrel or digoxin.
Recruitment/selection of patients	Not reported.
Age, gender and ethnicity	Age - Mean (SD): Placebo 52 (12), Etoricoxib 53 (12), Naproxen 52 (12) years. Gender (M:F): % women: Placebo 82%, Etoricoxib 90mg 81%, Naproxen 1000mg 82%. Ethnicity: Not reported
Further population details	1. Age: Not stated / Unclear (Inclusion criteria would include participants above and below 65 years of age.).
Extra comments	Participants asked to discontinue current NSAIDs and return for evaluation if symptoms worsen (disease flare). Flare requirement was ≥6 tender joints, ≥3 swollen joints, 20% increase in number of tender and swollen joints. In addition the investigator assessment of disease activity must have noted either 1) morning stiffness ≥45 minutes plus increased duration of at least 15 minutes since screening, 2) a score of >40mm on VAS pain score and increase of 10mm since screening.
Indirectness of population	No indirectness
Interventions	(n=353) Intervention 1: NSAIDs - etoricoxib. 90mg once daily. Duration 12 weeks. Concurrent

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	medication/care: Participants on stable doses of disease modifying therapy (except TNF inhibitors) and glucocorticoids were allowed to continue therapy. Low dose (100mg/day) aspirin was permitted. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral 3. Within-class differences : Selective COX-2 inhibitors (n=181) Intervention 2: NSAIDs - naproxen . 500mg twice daily. Duration 12 weeks. Concurrent medication/care: Participants on stable doses of disease modifying therapy (except TNF inhibitors) and glucocorticoids were allowed to continue therapy. Low dose (100mg/day) aspirin was permitted. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=357) Intervention 3: Placebo. No details. Duration 12 weeks. Concurrent medication/care: Participants on stable doses of disease modifying therapy (except TNF inhibitors) and glucocorticoids were allowed to continue therapy. Low dose (100mg/day) aspirin was permitted. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Funding not stated (There is no funding described. However, many of the authors are employees and have held stocks or shares for Merck & Co. Inc. Some authors have received funding from various pharmaceutical companies for studies, acting as a consultant or speaker.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ETORICOXIB versus PLACEBO

Protocol outcome 1: Pain at >6 weeks
- Actual outcome: Pain score at 12 weeks; Mean; -9.62 (95%CI -12.73 to -6.51);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for gender, age, duration of RA, rheumatoid factor positive, ARA functional class, other RA medication, disease activity. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Function at >6 weeks
- Actual outcome: Health Assessment Questionnaire at 12 weeks; Mean; -0.2 (95%CI -0.28 to -0.13);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for gender, age, duration of RA, rheumatoid factor positive, ARA functional class, other RA medication, disease activity. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events: gastrointestinal effects at Longest time period reported

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- Actual outcome: Adverse events: gastroduodenal ulcer at 12 weeks; Group 1: 1/295, Group 2: 0/242
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for gender, age, duration of RA, rheumatoid factor positive, ARA functional class, other RA medication, disease activity. ; Group 1 Number missing: 58; Group 2 Number missing: 115

Protocol outcome 4: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation: adverse events at 12 weeks; Group 1: 8/302, Group 2: 10/252
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for gender, age, duration of RA, rheumatoid factor positive, ARA functional class, other RA medication, disease activity. ; Group 1 Number missing: 51; Group 2 Number missing: 105
- Actual outcome: Discontinuation: inefficacy at 12 weeks; Group 1: 44/338, Group 2: 90/332
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for gender, age, duration of RA, rheumatoid factor positive, ARA functional class, other RA medication, disease activity. ; Group 1 Number missing: 15; Group 2 Number missing: 25

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NAPROXEN versus PLACEBO

Protocol outcome 1: Pain at >6 weeks
- Actual outcome: Pain score at 12 weeks; Mean; -10.46 (95%CI -14.25 to -6.66);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for gender, age, duration of RA, rheumatoid factor positive, ARA functional class, other RA medication, disease activity. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Function at >6 weeks
- Actual outcome: Health Assessment Questionnaire at 12 weeks; Mean; -0.29 (95%CI -0.38 to -0.2);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for gender, age, duration of RA, rheumatoid factor positive, ARA functional class, other RA medication, disease activity. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Adverse events: gastrointestinal effects at Longest time period reported
- Actual outcome: Adverse events: gastroduodenal ulcer at 12 weeks; Group 1: 0/151, Group 2: 0/242
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Due to non-slective NSAID utilised without PPI treatment; Baseline details: Groups similar for gender, age, duration of RA, rheumatoid factor positive, ARA functional class, other RA medication, disease activity. ; Group 1 Number missing: 20; Group 2 Number missing: 115

Protocol outcome 4: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation: adverse events at 12 weeks; Group 1: 4/155, Group 2: 10/252

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Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for gender, age, duration of RA, rheumatoid factor positive, ARA functional class, other RA medication, disease activity. ; Group 1 Number missing: 26; Group 2 Number missing: 105 - Actual outcome: Discontinuation: inefficacy at 12 weeks; Group 1: 19/170, Group 2: 90/332 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for gender, age, duration of RA, rheumatoid factor positive, ARA functional class, other RA medication, disease activity. ; Group 1 Number missing: 11; Group 2 Number missing: 25	
Protocol outcomes not reported by the study	Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

ISBN: 978-1-4731-3003-6

Study	Doreen 1978[56]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=44)
Countries and setting	Conducted in United Kingdom
Line of therapy	Mixed line
Duration of study	Intervention time: 2 weeks
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with RA and require NSAID treatment.
Exclusion criteria	People under the age of 16, suffering from disease likely to adversely influence the drug trial, taking D-penicillamine or immunosuppressant drugs, pregnancy.
Age, gender and ethnicity	Age - Mean (SD): Diclofenac group: 48, placebo group: 49. Gender (M:F): Male: 11, Female: 27. Ethnicity: Not stated
Further population details	1. Age: Not stated / Unclear (Age range not stated).
Extra comments	1 member of the diclofenac group had psoriatic arthroplasty rather than RA
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: NSAIDs - diclofenac. 25mg tablets 3 times per day. After day 7 assessment this could be increased to a maximum of 6 times per day. . Duration 2 weeks. Concurrent medication/care: Paracetamol allowed freely as a rescue medication. Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (2 weeks). 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=23) Intervention 2: Placebo. Matching placebo tablets taken 3 times per day. Duration 2 weeks. Concurrent medication/care: Paracetamol allowed freely as a rescue medication. Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (2 weeks). 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus PLACEBO

ISBN: 978-1-4731-3003-6

Protocol outcome 1: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: adverse events at 2 weeks; Group 1: 1/21, Group 2: 1/22 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, gender, RA latex test results, mean duration of RA, pre-trial analgesic use, gold or chloroquine or glucocorticoid use. ; Group 1 Number missing: 0; Group 2 Number missing: 1 - Actual outcome: Discontinuation: inefficacy at 2 weeks; Group 1: 0/20, Group 2: 1/22 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, gender, RA latex test results, mean duration of RA, pre-trial analgesic use, gold or chloroquine or glucocorticoid use. ; Group 1 Number missing: 1; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

ISBN: 978-1-4731-3003-6

Study	Durrigl 1975[57]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Croatia; Setting: 2 center study.
Line of therapy	Mixed line
Duration of study	Intervention time: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with RA.
Exclusion criteria	Uncooperative. Signs of sever hepatic or renal disease, manifest diabetes, alcoholism, cardiac failure, severe hypertension, possible or diagnosed gastro-duodenal ulcer, ulcerative colitis. Pregnant women, people who received immunosuppressive therapy or penicillamine in preceding 12 months, gold or anti-malarial's in preceding 3 months, ACTH or glucocorticoids in 6 weeks prior to trial. People with severe infections or known indomethacin intolerance and those who had recent major surgery. People requiring anticoagulant therapy. People with abnormalities of the pre-treatment laboratory examination.
Recruitment/selection of patients	24 from one centre and 26 from other.
Age, gender and ethnicity	Age - Median (range): 44 (21-75). Gender (M:F): Mlae: 2, Female: 48. Ethnicity: Not detailed
Further population details	1. Age: Not applicable (Range 21-75 years old).
Extra comments	5 people received non-medication therapy during the trial. No people received concomitant medication.
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: NSAIDs - diclofenac. 25mg 3 times per day. Duration 2 week. Concurrent medication/care: Paracetamol up to 3 times per day as rescue therapy. Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (2 weeks). 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=16) Intervention 2: NSAIDs - indomethacin. 25mg 3 times per day. Duration 2 weeks. Concurrent medication/care: Paracetamol up to 3 times per day as rescue therapy. Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (2 weeks). 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=17) Intervention 3: Placebo. Double dummy method utilised. . Duration 2 weeks. Concurrent

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	medication/care: Paracetamol up to 3 times per day as rescue therapy. Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (2 weeks). 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus PLACEBO

Protocol outcome 1: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation: adverse events at 2 weeks; Group 1: 0/17, Group 2: 0/17
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for gender. Stated to be similar for age, weight, type and duration of RA, concomitant disease, non-drug therapy and RA severity. ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Discontinuation: inefficacy at 2 weeks; Group 1: 0/17, Group 2: 0/17
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for gender. Stated to be similar for age, weight, type and duration of RA, concomitant disease, non-drug therapy and RA severity. ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INDOMETHACIN versus PLACEBO

Protocol outcome 1: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation: adverse events at 2 weeks; Group 1: 1/15, Group 2: 0/17
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for gender. Stated to be similar for age, weight, type and duration of RA, concomitant disease, non-drug therapy and RA severity. ; Group 1 Number missing: 1; Group 2 Number missing: 0
- Actual outcome: Discontinuation: inefficacy at 2 weeks; Group 1: 1/15, Group 2: 0/17
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for gender. Stated to be similar for age, weight, type and duration of RA, concomitant disease, non-drug therapy and RA severity. ; Group 1 Number missing: 1; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

ISBN: 978-1-4731-3003-6

Study	Edwards 1983[58]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=18)
Countries and setting	Conducted in USA
Line of therapy	Mixed line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with RA, functional class I, II or III and Steinbrocker progression stage II or III. RA activity had 3 of the following criteria: 1) at least 6 painful or tender joints on motion, 2) at least 3 swollen joints, 3) at least 45 minutes of morning stiffness, 4) erythrocyte sedimentation rate greater than 28mm/hr. In addition a positive response to 1 or more NSAIDs required.
Exclusion criteria	Not detailed
Age, gender and ethnicity	Age - Mean (range): Etodolac group: 51 (31-63), aspirin group: 55 (39-66), placebo group: 55 (30-65). Gender (M:F): Male: 9, Female: 9.. Ethnicity: White: 17, Black: 1.
Further population details	1. Age: Not applicable (Age spans 65 year cut-off).
Extra comments	Washout period of up to 2 weeks.
Indirectness of population	Serious indirectness: Positive response to 1 or more NSAIDs required.
Interventions	(n=6) Intervention 1: NSAIDs - etodolac. 4 weeks of dose titration followed by 8 weeks at a fixed dose. Mean dose was 390mg/day. Administered twice per day. . Duration 12 weeks. Concurrent medication/care: Concurrent use of gold salts or D-pencillamine was allowed provided it had been taken for 6 months previously or for 2 months on a stable dose. Physical therapy and aids already used were continued. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral 3. Within-class differences : Selective COX-2 inhibitors (n=6) Intervention 2: Placebo. Matching placebo. Duration 12 weeks. Concurrent medication/care: Concurrent use of gold salts or D-pencillamine was allowed provided it had been taken for 6 months previously or for 2 months on a stable dose. Physical therapy and aids already used were continued. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of

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	administration: Oral 3. Within-class differences : Not applicable
Funding	Funding not stated
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Furst 2002[69]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=894)
Countries and setting	Conducted in USA; Setting: NR
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: NR
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	18 to 80 years of age, currently using NSAID therapy for RA, 3 or more of following criteria: (1) 6+ tender joints, (2) 3+ swollen joints, (3) pain at least 20mm on VAS, (4) morning stiffness 45+ mins, (5) ESR > 28 mm or CRP > 1.2 mg/dl. Upon discontinuing NSAID therapy prior to the study, a flare meeting certain criteria had to be observed w/in 2 weeks.
Exclusion criteria	NR
Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Range of means: 55-57 . Gender (M:F): 213:681. Ethnicity: "white" (range): 80% - 87%
Further population details	1. Age: Not applicable
Extra comments	RA duration, yrs, range of means: 9.6 - 10.4 RF+, range of %: 49.7% - 56.5% Any DMARD use, range of %: 55.8% - 66.3% Prednisone use, range of %: 26.6% - 36.2%
Indirectness of population	No indirectness
Interventions	(n=536) Intervention 1: NSAIDs - meloxicam. 7.5mg, 15mg or 22.5mg (3 arms combined in this analysis). Duration 12 weeks. Concurrent medication/care: DMARDs initiated at least 3 months before trial and/or prednisone < 10mg/day stable for at least one month before trial could be continued at stable dose during trial. IA glucocorticoids were not permitted. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) 2. Route of administration: Oral 3. Within-class differences : Selective COX-2 inhibitors (n=181) Intervention 2: NSAIDs - diclofenac. 75 mg twice daily. Duration 12 weeks. Concurrent medication/care: DMARDs initiated at least 3 months before trial and/or prednisone < 10mg/day stable for at least one month before trial could be continued at stable dose during trial. IA glucocorticoids were not

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	permitted. . Indirectness: Serious indirectness; Indirectness comment: No mention of co-prescription with PPIs Further details: 1. Duration of intervention use: Long term use (>6 weeks) 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=177) Intervention 3: Placebo. placebo. Duration 12 weeks. Concurrent medication/care: DMARDs initiated at least 3 months before trial and/or prednisone < 10mg/day stable for at least one month before trial could be continued at stable dose during trial. IA glucocorticoids were not permitted. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Study funded by industry ("Supported by" Boehringer Ingelheim Pharmaceuticals Inc)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MELOXICAM versus PLACEBO

Protocol outcome 1: Pain at >6 weeks
- Actual outcome: Pain, VAS at 12 weeks; Group 1: mean -23.56 mm (SD 28.13); n=535, Group 2: mean -14.4 mm (SD 27.94); n=173; Visual Analogue Scale 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for outcome at baseline. Use of prednisone higher in placebo group but comparable for other factors. ; Blinding details: No details; Group 1 Number missing: 192, Reason: 1 no post dose efficacy evaluation, 191 discontinued (127 inefficacy, 47 adverse events, 17 other); Group 2 Number missing: 89, Reason: 4 no post dose efficacy evaluation, 85 discontinued (61 inefficacy, 14 adverse events, 10 other)

Protocol outcome 2: Function at >6 weeks
- Actual outcome: Function, HAQ at 12 weeks; Group 1: mean -0.35 (SD 0.53); n=535, Group 2: mean -0.24 (SD 0.53); n=173; Stanford Health Assessment Questionnaire 0-3 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in outcome at baseline, but less than differences after treatment. Use of prednisone higher in placebo group but comparable for other factors. ; Blinding details: No details; Group 1 Number missing: 192, Reason: 1 no post dose efficacy evaluation, 191 discontinued (127 inefficacy, 47 adverse events, 17 other); Group 2 Number missing: 89, Reason: 4 no post dose efficacy evaluation, 85 discontinued (61 inefficacy, 14 adverse events, 10 other)

Protocol outcome 3: Adverse events: mortality at Longest time period reported
- Actual outcome: Mortality at 12 weeks; Group 1: 0/536, Group 2: 0/177
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Use of prednisone higher in placebo group but comparable for other factors. ; Blinding

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details: No details; Group 1 Number missing: 0, Reason: Assume 'vital status' followed up for all patients, including those discontinuing drug; Group 2 Number missing: 0, Reason: Assume 'vital status' followed up for all patients, including those discontinuing drug

Protocol outcome 4: Adverse events: gastrointestinal effects at Longest time period reported
- Actual outcome: Upper GI perforation, ulceration or bleeding at 12 weeks; Group 1: 4/536, Group 2: 0/177
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Unclear whether patients who discontinued were still followed up (ie whether ITT or ACA); Indirectness of outcome: No indirectness ; Baseline details: Use of prednisone higher in placebo group but comparable for other factors. ; Blinding details: No details; Group 1 Number missing: 191, Reason: 191 discontinued (127 inefficacy, 47 adverse events, 17 other); Group 2 Number missing: 85, Reason: 85 discontinued (61 inefficacy, 14 adverse events, 10 other)
- Actual outcome: GI hemorrhage at 12 weeks; Group 1: 5/536, Group 2: 1/177; Comments: Includes GI bleeding (upper and lower), rectal bleeding, and blood in stool
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Unclear whether patients who discontinued were still followed up (ie whether ITT or ACA); Indirectness of outcome: No indirectness ; Baseline details: Use of prednisone higher in placebo group but comparable for other factors. ; Blinding details: No details; Group 1 Number missing: 191, Reason: 191 discontinued (127 inefficacy, 47 adverse events, 17 other); Group 2 Number missing: 85, Reason: 85 discontinued (61 inefficacy, 14 adverse events, 10 other)

Protocol outcome 5: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation: adverse events at 12 weeks; Group 1: 47/536, Group 2: 14/177
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Use of prednisone higher in placebo group but comparable for other factors. ; Blinding details: No details; Group 1 Number missing: 144, Reason: 127 discontinued for inefficacy, 17 other reasons; Group 2 Number missing: 71, Reason: 61 discontinued for inefficacy, 10 other reasons
- Actual outcome: Discontinuation: inefficacy at 12 weeks; Group 1: 127/536, Group 2: 61/177
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Unclear whether patients who discontinued were still followed up (ie whether ITT or ACA); Indirectness of outcome: No indirectness ; Baseline details: Use of prednisone higher in placebo group but comparable for other factors. ; Blinding details: No details; Group 1 Number missing: 64, Reason: 47 discontinued due to adverse events, 17 other reasons; Group 2 Number missing: 24, Reason: 14 discontinued due to adverse events, 10 other reasons

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus PLACEBO

Protocol outcome 1: Pain at >6 weeks
- Actual outcome: Pain, VAS at 12 weeks; Group 1: mean -25.4 mm (SD 28.25); n=180, Group 2: mean -14.4 mm (SD 27.94); n=173; Visual Analogue Scale 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for outcome at baseline. Differences in background medication

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(use of prednisone and DMARDs higher in placebo group) but comparable for other factors. ; Blinding details: No details; Group 1 Number missing: 54, Reason: 1 no post dose efficacy evaluation, 52 discontinued (26 inefficacy, 20 adverse events, 7 other); Group 2 Number missing: 89, Reason: 4 no post dose efficacy evaluation, 85 discontinued (61 in efficacy, 14 adverse events, 10 other)

Protocol outcome 2: Function at >6 weeks
- Actual outcome: Function, HAQ at 12 weeks; Group 1: mean -0.32 (SD 0.54); n=180, Group 2: mean -0.24 (SD 0.53); n=173; Stanford Health Assessment Questionnaire (HAQ) 0-3 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Imbalance in outcome at baseline (0.1 difference). Differences in background medication (use of prednisone and DMARDs higher in placebo group) but comparable for other factors. ; Blinding details: No details; Group 1 Number missing: 54, Reason: 1 no post dose efficacy evaluation, 52 discontinued (26 inefficacy, 20 adverse events, 7 other); Group 2 Number missing: 89, Reason: 4 no post dose efficacy evaluation, 85 discontinued (61 in efficacy, 14 adverse events, 10 other)

Protocol outcome 3: Adverse events: mortality at Longest time period reported
- Actual outcome: Mortality at 12 weeks; Group 1: 0/181, Group 2: 0/177
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in background medication (use of prednisone and DMARDs higher in placebo group) but comparable for other factors. ; Blinding details: No details; Group 1 Number missing: 0, Reason: Assume 'vital status' followed up for all participants, including those discontinuing; Group 2 Number missing: 0, Reason: Assume 'vital status' followed up for all participants, including those discontinuing

Protocol outcome 4: Adverse events: gastrointestinal effects at Longest time period reported
- Actual outcome: Upper GI perforation, ulceration or bleeding at 12 weeks; Group 1: 0/181, Group 2: 0/177
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Unclear whether data on discontinued patients was included in analysis (ie whether were still followed up -whether ITT or ACA unclear); Indirectness of outcome: Serious indirectness, Comments: Due to non-slective NSAID utilised without PPI treatment; Baseline details: Differences in background medication (use of prednisone and DMARDs higher in placebo group) but comparable for other factors. ; Blinding details: No details; Group 1 Number missing: 53, Reason: 53 discontinued (26 inefficacy, 20 adverse events, 7 other); Group 2 Number missing: 85, Reason: 85 discontinued (61 in efficacy, 14 adverse events, 10 other)
- Actual outcome: GI hemorrhage at 12 weeks; Group 1: 4/181, Group 2: 1/177; Comments: Includes GI bleeding (upper and lower), rectal bleeding, and blood in stool
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Unclear whether data on discontinued patients was included in analysis (ie whether were still followed up -whether ITT or ACA unclear); Indirectness of outcome: Serious indirectness, Comments: Due to non-slective NSAID utilised without PPI treatment; Baseline details: Differences in background medication (use of prednisone and DMARDs higher in placebo group) but comparable for other factors. ; Blinding details: No details; Group 1 Number missing: 53, Reason: 53 discontinued (26 inefficacy, 20 adverse events, 7 other); Group 2 Number missing: 85, Reason: 85 discontinued (61 in efficacy, 14 adverse events, 10 other)

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Protocol outcome 5: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: adverse events at 12 weeks; Group 1: 20/181, Group 2: 14/177 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Differences in background medication (use of prednisone and DMARDs higher in placebo group) but comparable for other factors. ; Blinding details: No details; Group 1 Number missing: 33, Reason: 26 discontinued for inefficacy, 7 other reasons; Group 2 Number missing: 71, Reason: 61 discontinued for inefficacy, 10 other reasons - Actual outcome: Discontinuation: inefficacy at 12 weeks; Group 1: 26/181, Group 2: 61/177 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Differences in background medication (use of prednisone and DMARDs higher in placebo group) but comparable for other factors. ; Blinding details: No details; Group 1 Number missing: 27, Reason: 20 discontinued for adverse events, 7 other reasons; Group 2 Number missing: 24, Reason: 14 discontinued for adverse events, 10 other reasons	
Protocol outcomes not reported by the study	Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at <2 weeks; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

ISBN: 978-1-4731-3003-6

Study	Geusens 2002[73]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=431)
Countries and setting	Conducted in Multiple countries; Setting: 87 clinical centres
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1987 ACR criteria
Stratum	Overall
Subgroup analysis within study	Stratified then randomised: Allocation was stratified by concomitant cglucocorticoid use.
Inclusion criteria	≥ 18 years of age, diagnosis of RA after at 16 and at least 6 months prior to enrollment, history of therapeutic benefit from NSAIDs or COX-2 selective inhibitors and have required therapeutic doses on a regular basis (≥ 25 of 30 days prior to study entry), satisfaction of pre-specified disease activity and flare criteria.
Exclusion criteria	Patients taking warfarin, ticlopidine, clopidogrel or aspirin, patients previously exposed to rofecoxib, patients with confounding medical conditions: systemic lupos, spondylarthropathy, polymyalgia rheumatica, gout, Paget's disease, active GI bleeding or ulceration, a positve screen for stool occult blood, uncontrolled diabetes, MI, angioplasty or coronary bypass in past year, stroke in past 2 years, active hepatitis, malignancy, serum creatinine > 2.0 mg/dL, estimated creatinine clearance ≤ 30 mL/min, serum transaminases ≥ 150% of the upper limit of lab-normal range, allergy to acetaminophen, aspirin or NSAIDs.
Recruitment/selection of patients	1344 patients were screened and 1023 were randomised (592 to rofecoxib, outside the scope of this review). After informed consent, disease activity was assessed, followed by a NSAID-wash-out of 3 to 16 days. If pre-specified disease activity and flare criteria were satisfied, patients were randomised. Most common reasons for exclusion of screened patients: failure to meet RA flare or activity criteria, diagnosis of RA inconsistent with ACR criteria, withdrawal of consent, potentially confounding medical issues/medications.
Age, gender and ethnicity	Age - Mean (SD): Placebo - 53.7(11.53), Naproxen - 54.1 (12.39). Gender (M:F): 69:362. Ethnicity: NR
Further population details	1. Age: Not applicable

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Extra comments	. Mean duration of RA (SD): Placebo - 8.6 (7.27), Naproxen - 9.1 (7.72). ARA functional class II: Placebo - 59%, Naproxen - 57%. Methotrexate use: Placebo - 65%, Naproxen - 66% Systemic glucocorticoids use: Placebo - 59%, Naproxen - 54% Patient assessment of disease activity (100mm VAS, mean (SD)): Placebo - 75.80 (14.95), Naproxen - 73.45 (13.34)
Indirectness of population	No indirectness
Interventions	(n=142) Intervention 1: NSAIDs - naproxen . 500mg twice daily. Duration 12 weeks. Concurrent medication/care: Stable therapy (for the previous 6 months) with most DMARDs was permitted at study entry. TNF-sequestrant use within 3 months of entry was not permitted. Patients were allowed to continue chronic lose-dose oral corticosteriods if the use had been stable over past 30 days and anticipated to remain stable. Concomitant therapy with nonstudy NSAIDs or COX-2 inhibitors was not permitted. Paracetamol was provided as rescue therapy. . Indirectness: Serious indirectness; Indirectness comment: No co-prescription with PPIs (use of gastroprotective agents (including PPIs) was not permitted on entry but was allowed as necessary to treat digestive symptoms arising during the trial) Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=289) Intervention 2: Placebo. Matched placebo. Duration 12 weeks. Concurrent medication/care: Stable therapy (for the previous 6 months) with most DMARDs was permitted at study entry. TNF-sequestrant use within 3 months of entry was not permitted. Patients were allowed to continue chronic lose-dose oral glucocorticoids if the use had been stable over past 30 days and anticipated to remain stable. Concomitant therapy with nonstudy NSAIDs or COX-2 inhibitors was not permitted. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Other author(s) funded by industry (Four of nine authors were at Merck and Co.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NAPROXEN versus PLACEBO

Protocol outcome 1: Adverse events: mortality at Longest time period reported
- Actual outcome: Mortality at 12 weeks; Group 1: 0/142, Group 2: 1/289
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See population. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Adverse events: gastrointestinal effects at Longest time period reported
- Actual outcome: Upper GI perforations, ulcers or bleeding at 12 weeks; Group 1: 4/135, Group 2: 0/276

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Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Due to non-slective NSAID utilised without PPI treatment; Baseline details: See population. ; Group 1 Number missing: 7, Reason: 7 discontinued due to (other) AEs, unknown number missing due to inefficacy; Group 2 Number missing: 13, Reason: 13 discontinued due to (other) AEs, unknown number missing due to inefficacy (10% higher rate than in naproxen group). Protocol outcome 3: Adverse events: cardiac and vascular events at Longest time period reported - Actual outcome: Myocardial infarction or stroke at 12 weeks; Group 1: 0/131, Group 2: 0/276 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See population. ; Group 1 Number missing: 11, Reason: 11 discontinued due to AEs, unknown number missing due to inefficacy; Group 2 Number missing: 13, Reason: 13 discontinued due to AEs, unknown number missing due to inefficacy (10% higher rate than in naproxen group). Protocol outcome 4: Adverse events: impaired renal function at Longest time period reported - Actual outcome: Acute renal failure at 12 weeks; Group 1: 0/131, Group 2: 0/276 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See population. ; Group 1 Number missing: 11, Reason: 11 discontinued due to AEs, unknown number missing due to inefficacy; Group 2 Number missing: 13, Reason: 13 discontinued due to AEs, unknown number missing due to inefficacy (10% higher rate than in naproxen group). Protocol outcome 5: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: adverse events at 12 weeks; Group 1: 11/142, Group 2: 13/289 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See population. ; Group 1 Number missing: 0, Reason: Unknown number missing due to lack of efficacy; Group 2 Number missing: 0, Reason: Unknown number missing due to lack of efficacy	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks

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Study	Geusens 2004[72]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=563)
Countries and setting	Conducted in Multiple countries
Line of therapy	Mixed line
Duration of study	Intervention time: 26 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Participants aged 18 or over with symptomatic RA. Class I, II or III according to ACR revised criteria with symptoms for at least 3 months, and receiving regular NSAID therapy. 3-14 day screening after NSAIDs and analgesics discontinued (paracetamol allowed as rescue medication). After screening, only participants with at least 3 swollen joints and an increase of at least 2 or 20% in number of swollen joints since screening, at least 6 tender joints and an increase of 2 or 20% of tender joints since screening. Additionally participants were required to have pain intensity of >/=40mm on 100mm VAS during 24 hours prior to baseline and an increase in pain intensity of either >/=20% or >/=10mm.
Exclusion criteria	Participants receiving >/=3 DMARDs, systemic glucocorticoids, gastroprotective medication, misoprostol, any NSAID other than low-dose aspirin for cardiovascular prophylaxis. Also patients with history of GI ulceration or bleeding, known hypersensitivity to NSAIDs, significant medical problem. Also pregnant or nursing women or those without reliable contraceptive protection.
Age, gender and ethnicity	Age - Mean (SD): Naproxen group: 54 (12), placebo group: 53 (11). Gender (M:F): Male: 118, Female: 445. Ethnicity: Caucasian: 96%
Further population details	1. Age: Not stated / Unclear (Age range not stated).
Indirectness of population	No indirectness
Interventions	(n=279) Intervention 1: NSAIDs - naproxen . 500mg twice per day. Duration 26 weeks. Concurrent medication/care: Paracetamol permitted as a rescue medication (</=2g per day). Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (26 weeks). 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=284) Intervention 2: Placebo. Double dummy technique. Duration 26 weeks. Concurrent medication/care: Paracetamol permitted as a rescue medication (</=2g per day). Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (26 weeks). 2. Route of

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	administration: Oral 3. Within-class differences : Not applicable
Funding	Study funded by industry (Study supported by Novartis Pharma AG, Switzerland.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NAPROXEN versus PLACEBO

Protocol outcome 1: Pain at >6 weeks
- Actual outcome: Pain intensity at 26 weeks; Group 1: mean -24.1 (SD 23.83); n=279, Group 2: mean -18.8 (SD 24.71); n=284; VAS 100mm 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups comparable for age, gender, race, BMI, disease duration, RA pain, disease activity, CRP, HAQ. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Function at >6 weeks
- Actual outcome: Function at 26 weeks; Group 1: mean -0.3 (SD 0.58); n=279, Group 2: mean -0.2 (SD 0.54); n=284; Health Assessment Questionnaire (HAQ) 0-3 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups comparable for age, gender, race, BMI, disease duration, RA pain, disease activity, CRP, HAQ. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation: adverse events at 26 weeks; Group 1: 30/222, Group 2: 20/178
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups comparable for age, gender, race, BMI, disease duration, RA pain, disease activity, CRP, HAQ. ; Group 1 Number missing: 57; Group 2 Number missing: 106
- Actual outcome: Discontinuation: inefficacy at 26 weeks; Group 1: 42/244, Group 2: 93/251
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups comparable for age, gender, race, BMI, disease duration, RA pain, disease activity, CRP, HAQ. ; Group 1 Number missing: 45; Group 2 Number missing: 33

Protocol outcomes not reported by the study	Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

ISBN: 978-1-4731-3003-6

Study	Gibofsky 2007[74]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=In the two treatment groups of interest: 338)
Countries and setting	Conducted in Canada, USA; Setting: 61 centres in Canada and USA between 2003 and 2005.
Line of therapy	Mixed line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1987 ACR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with RA >/= 18 years old, diagnosed over 6 months before study, with stable therapy including an NSAID for at least 4 weeks, with DMARD therapy as part of this for at least 12 weeks. DMARDs accepted were methotrexate, cyclosporine, leflunomide, anakinra, TNF inhibitor. Patients discontinues from NSAID therapy and notified investigator when/if a flare occurred. These patients were then included in the study. Patients required to have a functional Capacity Classification of I or III that had not changed 1 month before screening. Women of a child bearing potential were required to be using effective contraception and have a negative pregnancy test. Patients receiving aspirin for cardioprophylaxis were allowed to continue this regimen throughout the study. Use of acetaminophen as a rescue medication was permitted.
Exclusion criteria	Any other form of inflammatory arthritis, secondary noninflammatory arthritis, history of malignancy, active GI disease, chronic or acute renal or hepatic disorders, uncontrollable hypertension, diabetes, significant coagulation disorder, received treatment for GI ulceration, received warfarin or other anticoagulants within 30 days, were taking lithium or oral glucocorticoids within 4 weeks or intra-articular or intramuscular glucocorticoids within 8 weeks, or antineoplastic agents within 12 weeks.
Age, gender and ethnicity	Age - Mean (SD): Naproxen group: 57 (11), placebo group: 56 (12). Gender (M:F): Male: 76, Female: 26. Ethnicity: In the two treatment groups of interest: White: 271, Black: 36, Asian: 3, Other: 28
Further population details	1. Age: Not stated / Unclear (Age range in groups not stated but likely to be participnats above and below 65.).
Indirectness of population	No indirectness
Interventions	(n=167) Intervention 1: NSAIDs - naproxen . 500mg twice per day. Duration 12 weeks. Concurrent medication/care: Discontinued NSAID therapy. Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=171) Intervention 2: Placebo. Double dummy approach to keep blinding. . Duration 12 weeks. Concurrent

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	medication/care: Discontinued NSAID therapy. Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Study funded by industry (Sponsored and managed by Pfizer Inc., New York, USA.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NAPROXEN versus PLACEBO

Protocol outcome 1: Pain at >6 weeks
- Actual outcome: Pain score at 12 weeks; Group 1: mean -30.8 (SD 28.6); n=166, Group 2: mean -14.9 (SD 29.12); n=169; VAS 100mm 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, weight, height, race, duration of disease, concomitant medication. Minor difference in terms of gender. ; Group 1 Number missing: 1, Reason: Not detailed; Group 2 Number missing: 2, Reason: Not detailed

Protocol outcome 2: Stiffness at >6 weeks
- Actual outcome: Duration of morning stiffness at 12 weeks; Group 1: mean -4.4 hours (SD 6.44); n=166, Group 2: mean -1 hours (SD 6.37); n=169
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, weight, height, race, duration of disease, concomitant medication. Minor difference in terms of gender. ; Group 1 Number missing: 1, Reason: Not detailed; Group 2 Number missing: 2, Reason: Not detailed

Protocol outcome 3: Function at >6 weeks
- Actual outcome: HAQ disability index at 12 weeks; Group 1: mean -0.4 (SD 0.52); n=166, Group 2: mean -0.2 (SD 0.52); n=169
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, weight, height, race, duration of disease, concomitant medication. Minor difference in terms of gender. ; Group 1 Number missing: 1, Reason: Not detailed; Group 2 Number missing: 2, Reason: Not detailed

Protocol outcome 4: Adverse events: mortality at Longest time period reported
- Actual outcome: Adverse events: mortality at 12 weeks; Group 1: 0/150, Group 2: 1/163
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, weight, height, race, duration of disease, concomitant medication. Minor difference in terms of gender. ; Group 1 Number missing: 17, Reason: 16 discontinued treatment due to adverse events. 1 not detailed. ; Group 2 Number missing: 8, Reason: 7 other patients discontinued treatment due to adverse events. 1 not detailed.

Protocol outcome 5: Drug continuation at Longest time period reported

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- Actual outcome: Discontinuation: adverse events at 12 weeks; Group 1: 16/166, Group 2: 8/170 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, weight, height, race, duration of disease, concomitant medication. Minor difference in terms of gender. ; Group 1 Number missing: 1, Reason: Not detailed; Group 2 Number missing: 1, Reason: Not detailed	
Protocol outcomes not reported by the study	Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at <2 weeks; Function at <2 weeks; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

ISBN: 978-1-4731-3003-6

Study	Glowinski 1999[75]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in France; Setting: Multicentre (7 centres)
Line of therapy	Mixed line
Duration of study	Intervention time: 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged between 18 and 75 years old, RA diagnosis, ambulatory, stabilised for at least 2 months by treatment and therefore are not altering medication regime, present with permanent residual pain, judged pain over previous 24 hours to be equal or greater than "moderate pain".
Exclusion criteria	Contraindication to codeine, history of abuse of opioid analgesics, contraindication to paracetamol, use of an oxicam anti-inflammatory agent unless 48 hour gap before start of study, forecast surgery or synoviorthesis or local infiltration, intellectual level preventing full understanding of the pain assessment scales and study procedure.
Age, gender and ethnicity	Age - Mean (SD): Paracetmaol-Codeine group: 55 (16), diclofenac group: 59 (10). Gender (M:F): Male: 10, Female: 50. Ethnicity: Not detailed
Further population details	1. Age: Not applicable (Inclusion range was 18 to 75 years old. Actual participant age range not specified.).
Indirectness of population	No indirectness

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Interventions	(n=30) Intervention 1: Opioid + paracetamol. Paracetamol (500mg) and codeine (30mg) administered 3 time daily at 8am, 1pm, 7pm. Diclofenac (50mg) administered once per day at 7pm. Placebo at 8am. . Duration 7 days. Concurrent medication/care: Previous analgesic treatment and NSAID treatment stopped during study. Further details: 1. Duration of intervention use: Short term use (<2 weeks) (7 days). 2. Route of administration: Oral (Tablets). 3. Within-class differences : Not applicable (Mixture of opioid, NSAID and paracetamol). (n=30) Intervention 2: NSAIDs - diclofenac. 50mg administered twice per day at 8am and 7pm. Placebo at 8am, 1pm and 7pm. . Duration 7 days. Concurrent medication/care: Previous analgesic treatment and NSAID treatment stopped during study. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (7 days). 2. Route of administration: Oral (Tablets). 3. Within-class differences : Non-selective NSAIDs (Diclofenac).
Funding	Study funded by industry (Study supported by a grant from Laboratoires UPSA)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARACETAMOL + CODEINE + DICLOFENAC versus DICLOFENAC

Protocol outcome 1: Pain at <2 weeks
- Actual outcome: Pain on horizontal 100mm VAS at 7 days; Group 1: mean -31.5 (SD 24.1); n=28, Group 2: mean -23.4 (SD 23.2); n=30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, weight, gender, treatments, pre-study pain, joint tenderness, type of pain. Disease duration was higher in the paracetamol codeine group. Mean 10.6 years vs 7 years. ; Group 1 Number missing: 3, Reason: 3 discontinued for adverse events; Group 2 Number missing: 1, Reason: 1 discontinued for adverse events

Protocol outcome 2: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation: due to inefficacy at 7 days; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, weight, gender, treatments, pre-study pain, joint tenderness, type of pain. Disease duration was higher in the paracetamol codeine group. Mean 10.6 years vs 7 years. ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Discontinuation: due to adverse events at 7 days; Group 1: 3/30, Group 2: 1/30
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, weight, gender, treatments, pre-study pain, joint tenderness, type of pain. Disease duration was higher in the paracetamol codeine group. Mean 10.6 years vs 7 years. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the	Pain at >6 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at

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study	<2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Gordon 1983[80]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=16)
Countries and setting	Conducted in USA; Setting: NR
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA diagnostic criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with RA in Functional Class I, II or III and Steinbrocker Progression Stage II or II, and if disease activity characterised by presence of three of the following: (1) at least six painful or tender joints on motion, 2) three swollen joints, (3), duration of morning stiffness of at least 3/4 hour, and (4) ESR greater than 28 mm/hr. Positive response to one or more NSAIDs in the past was required.
Exclusion criteria	NR
Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Mean (range): Etodolac - 54 (45-64), Placebo - 55 (37-65). Gender (M:F): 3:13. Ethnicity: 62.5% white, 37.5% black
Further population details	1. Age: ≤65 years (Age range 37 - 65).
Extra comments	Days to flare (washout period), mean: Etodolac - 4.6, Placebo - 6.8 Family history RA: Etodolac - 2/8, Placebo - 1/8 Duration RA, av. months: Etodolac - 110, Placebo - 133 Investigator's opinion of condition "poor": Etodolac - 4/8, Placebo - 3/8 Patient's opinion of condition "poor": Etodolac - 4/8, Placebo - 3/8
Indirectness of population	No indirectness
Interventions	(n=8) Intervention 1: NSAIDs - etodolac. Two week washout period followed by four week titration period, and eight week maintenance period. Etodolac tablets were administered twice daily. Test drugs were titrated in each patient to the level which gave optimal relief of symptoms. Four dose levels (100, 200, 300 to 400 mg / day). All patients began at the lowest level and were titrated upward until the maximal response was achieved. Mean total after titration was 338 mg/day. . Duration 12 weeks. Concurrent medication/care: D-penicillamine and gold salts permitted if had been taken for six months or more, remained at a constant regimen for at least two months prior to the study, and the dosage would not change during the study. 6/8

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	patients on gold salts, none on D-penicillamine. Non-narcotic, analgesic acetaminophen (650 mg 4 times daily) was permitted only during the washout and titration periods. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) 2. Route of administration: Oral 3. Within-class differences : Selective COX-2 inhibitors (n=8) Intervention 2: Placebo. Matching placebo in accordance with same regime. Duration 12 weeks. Concurrent medication/care: D-penicillamine and gold salts permitted if had been taken for six months or more, remained at a constant regimen for at least two months prior to the study, and the dosage would not change during the study. 3/8 patients on gold salts, none on D-penicillamine. Non-narcotic, analgesic acetaminophen (650 mg 4 times daily) was permitted only during the washout and titration periods. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ETODOLAC versus PLACEBO Protocol outcome 1: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: adverse events at 12 weeks; Group 1: 0/4, Group 2: 0/2 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in % use of gold and # days to flare at baseline. ; Blinding details: All tablets were identical and administered in same schedule. Said to be 'double blind'. ; Group 1 Number missing: 4, Reason: withdrawal due to inefficacy, these patients do not have the same opportunity to experience an adverse event; Group 2 Number missing: 6, Reason: withdrawal due to inefficacy, these patients do not have the same opportunity to experience an adverse event - Actual outcome: Discontinuation: inefficacy at 12 weeks; Group 1: 4/8, Group 2: 6/8 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in % use of gold and # days to flare at baseline. ; Blinding details: All tablets were identical and administered in same schedule. Said to be 'double blind'. ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Grace 1985[81]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=36)
Countries and setting	Conducted in Canada; Setting: Outpatient clinic
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Persistent pain despite adequate NSAID analgesic therapy
Exclusion criteria	NR
Recruitment/selection of patients	Patients referred to outpatient clinic by family doctors
Age, gender and ethnicity	Age - Mean (range): AD: 58 (27-72), P: 59 (28-76). Gender (M:F): 7:29. Ethnicity: NR
Further population details	1. Age: Not applicable
Extra comments	64% functional class II; ESR mean 59 (mm/1st hr), range 22-103. All patients seropositive for rheumatoid factor, all had articular erosions on x-ray. .
Indirectness of population	No indirectness
Interventions	(n=18) Intervention 1: Tricyclic anti-depressants - Amitriptyline. Week 1 - 25mg daily; week 2 - 25mg twice daily; week 3 onwards - 25mg 3 times daily. . Duration 12 weeks. Concurrent medication/care: None of the patients were receiving chrysotherapy, penicillamine, oral glucocorticoid therapy at the time of the study. None had recently received intra-articular glucocorticoid injections. Implied that all patients were maintained on NSAID therapy. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) 2. Route of administration: Oral 3. Within-class differences : Not applicable (n=18) Intervention 2: Placebo. Matched placebo. Duration 12 weeks. Concurrent medication/care: None of the patients were receiving chrysotherapy, penicillamine, oral glucocorticoid therapy at the time of the study. None had recently received intra-articular glucocorticoid injections. Implied that all patients were maintained on NSAID therapy. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) 2. Route of administration: Oral 3. Within-class differences : Not applicable

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Funding	Principal author funded by industry (Lead author funded by Parke Davis (Pfizer), other authors funded by Arthritis Society of Canada)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRICYCLIC AD: AMITRIPTYLINE versus PLACEBO Protocol outcome 1: Drug continuation at Longest time period reported - Actual outcome: Withdrawal due to adverse events at 12 weeks; Group 1: 2/18, Group 2: 3/18 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Comparable for sex, age, functional class, ESR (though variance data not reported, only range); Blinding details: Identical placebo tablets, neither patient nor physician was aware of the nature of the medication. ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Withdrawal due to inefficacy at 12 weeks; Group 1: 2/18, Group 2: 1/18 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Comparable for sex, age, functional class, ESR (though variance data not reported, only range); Blinding details: Identical placebo tablets, neither patient nor physician was aware of the nature of the medication. ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study (subsidiary papers)	Greenwald 2011[82] (Kvien 2015[110])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=761)
Countries and setting	Conducted in Canada, Colombia, Switzerland, USA; Setting: 90 sites
Line of therapy	Mixed line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: >/= 4 criteria from ARA 1987 revised
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	>/= 18 years old, diagnosis of RA, ARA function class I, II or III. Negative pregnancy test. Prior to randomisation patients underwent NSAID therapy withdrawal and were included if they had a flare. A flare was defined as >/=6 tender joints with a 20% increase post flare, >/=3 swollent joints with 20% increase post flare, Investigator's Global Assessment of Disease Activity of fair, poor or very poor, >/=45 minutes of morning stiffness with >/= 15 minute increase post flare or Patient's Assessment of pain >40mm with post flare increase of >10mm.
Exclusion criteria	Non RA inflammatory disease, morbid obesity, clinical malabsorption, GI bleeding, active gastric ulcer, heart disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure, uncontrolled hypertension, most forms of neoplastic disease. Rituximab and epratzumab not allowed within 15 months of enrollment. Low dose aspirin used concomitantly with warfarin or heparin. Use of non-study NAIDs, recent use of narcotics, use of prednisone, recent changes to RA medication.
Recruitment/selection of patients	Recruited from 2006-2008
Age, gender and ethnicity	Age - Mean (SD): 57 (12). Gender (M:F): Male: 148, Female: 613. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear (Age range not stated but likely to be people in the groups above and below 65 years old.).
Extra comments	Female patients expected to use appropriate contraception. antirheumatic therapy stable dose during trial.
Indirectness of population	No indirectness
Interventions	(n=161) Intervention 1: Placebo. Matching tablets taken once per day. Duration 12 weeks. Concurrent medication/care: Acetaminophen/paracetamol (APAP) 500mg up to eight times per day was provided to patients throughout the study as 'rescue therapy'. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral 3. Within-class differences : Not applicable

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	(n=600) Intervention 2: NSAIDs - etoricoxib. 4 treatment groups of roughly the same size. 10mg or 30mg or 60mg or 90mg once daily. . Duration 12 weeks. Concurrent medication/care: Acetaminophen/paracetamol (APAP) 500mg up to eight times per day was provided to patients throughout the study as 'rescue therapy'. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral 3. Within-class differences : Selective COX-2 inhibitors
Funding	Study funded by industry (The work was supported by Merck Sharp & Dohme Corp)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ETORICOXIB versus PLACEBO

Protocol outcome 1: Pain at >6 weeks
- Actual outcome: Pain score at 12 weeks; Group 1: mean -23.5622 (SD 24.033); n=600, Group 2: mean -16.79 (SD 23.37); n=161
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, gender, duration of RA, ARA functional class, rheumatoid factor positive, methotrexate use, glucocorticoid use, CRP, DMARD use, biologic therapy, baseline assessment of pain. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Stiffness at >6 weeks
- Actual outcome: Duration of morning stiffness at 12 weeks; Group 1: mean -44.18 minutes (SD 75.44); n=600, Group 2: mean -30 minutes (SD 97.11); n=161
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, gender, duration of RA, ARA functional class, rheumatoid factor positive, methotrexate use, glucocorticoid use, CRP, DMARD use, biologic therapy, baseline assessment of pain. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Function at >6 weeks
- Actual outcome: Function at 12 weeks; Group 1: mean -0.318 (SD 0.444); n=600, Group 2: mean -0.14 (SD 0.45); n=161; Health Assessment Questionnaire (HAQ) 0-3 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, gender, duration of RA, ARA functional class, rheumatoid factor positive, methotrexate use, glucocorticoid use, CRP, DMARD use, biologic therapy, baseline assessment of pain. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation: lack of efficacy at 12 weeks; Group 1: 245/557, Group 2: 84/147
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, gender, duration of RA, ARA functional class,

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rheumatoid factor positive, methotrexate use, glucocorticoid use, CRP, DMARD use, biologic therapy, baseline assessment of pain. ; Group 1 Number missing: 43; Group 2 Number missing: 14 - Actual outcome: Discontinuation: adverse events at 12 weeks; Group 1: 24/334, Group 2: 3/66 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, gender, duration of RA, ARA functional class, rheumatoid factor positive, methotrexate use, glucocorticoid use, CRP, DMARD use, biologic therapy, baseline assessment of pain. ; Group 1 Number missing: 266; Group 2 Number missing: 95	
Protocol outcomes not reported by the study	Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at <2 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study (subsidiary papers)	Hawkey 2003[85] (Anonymous 2003[14])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=660)
Countries and setting	Conducted in Multiple countries; Setting: 48 sites across 18 countries
Line of therapy	Mixed line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Inadequate method of assessment/diagnosis: Confirmed clinical diagnosis of RA
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Between 18 and 85 years old with RA, at least 3 months of NSAID therapy,
Exclusion criteria	Oesophageal, gastric or duodenal ulcer, pyloric obstruction, erosive oesophagitis at baseline endoscopy. Creatine levels >2mg/dl, creatinine clearance </=30ml/min, bleeding diathesis. Requirement for anticoagulants, low dose aspirin, ticlopidine, or clopidogrel. Unstable medical disease including current angina, congestive heart failure. Previous upper gastrointestinal surgery, faecal occult blood, history of inflammatory bowel disease, history of myocardial infarction, coronary angiopasty, coronary heart bypass graft in the previous year, cerebrovascular event or active hepatic disease within 2 years. Malignancy within 5 years.
Age, gender and ethnicity	Age - Mean (SD): 52. Gender (M:F): Male: 119, Female: 541. Ethnicity: Placebo group: 48% White, rofecoxib group: 52% White, naproxen group: 52% White.
Further population details	1. Age: Not applicable (Inclusion criteria for age is 21 to 85 years old.).
Indirectness of population	No indirectness

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Interventions	(n=220) Intervention 1: NSAIDs - naproxen . 50mg twice daily. Duration 12 weeks. Concurrent medication/care: Stable doses of antirheumatic were permitted. However non-study NSAIDs and antisecretory or cryoprotective drugs were not permitted. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=221) Intervention 2: Placebo. Matching placebo medication utilised. . Duration 12 weeks. Concurrent medication/care: Stable doses of antirheumatic were permitted. However non-study NSAIDs and antisecretory or cryoprotective drugs were not permitted. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NAPROXEN versus PLACEBO Protocol outcome 1: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: adverse events at 12 weeks; Group 1: 22/208, Group 2: 9/204 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for gender, age, number from USA, race, history of GI events, H pylori positive, tobacco use, glucocorticoid use. Prior NSAID use was less in naproxen group. ; Group 1 Number missing: 12; Group 2 Number missing: 17 - Actual outcome: Discontinuation: inefficacy at 12 weeks; Group 1: 2/188, Group 2: 11/206 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for gender, age, number from USA, race, history of GI events, H pylori positive, tobacco use, glucocorticoid use. Prior NSAID use was less in naproxen group. ; Group 1 Number missing: 32; Group 2 Number missing: 15	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Hunter 1996[93]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=73)
Countries and setting	Conducted in United Kingdom; Setting:
Line of therapy	Mixed line
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 4 ARA criteria for rheumatoid arthritis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged 18-75, with active rheumatoid arthritis, history of response to NSAID in previous year. Active disease defined by having at least 3 of: a) 6 or more tender or painful joints on motion, b) 3 or more swollen joints, c) morning stiffness for at least 1 hour, d) plasma viscosity >/= 1.76cps or C reactive protein >/= 0.7mg/dl or ESR >/= 20mm/hour.
Exclusion criteria	Arthritis before age of 16 or less than 3 months in duration, arthritis associated with UC, ankylosing spondylitis, psoriasis, inflammatory bowel disease, pregnancy, lactation, women taking inadequate contraception, history of blood dyscrasia, recent major surgery, serious renal hepatic or cardiovascular disease, active gastro-intestinal disease, concurrent anti-coagulant therapy, diabetes treated with oral hypoglycaemic agents or inadequately stabilised on diet or insulin, concurrent ACE inhibitor therapy, previous hypersensitivity or contraindication to NSAIDs, unexpected laboratory abnormality, treatment with intra-articular or parenteral glucocorticoids within 4 weeks, prior treatment with piroxicam or long acting indomethacin within 72 hours, history of malignancy, history of alcohol or drug abuse, skin disorders precipitated or aggravated by drug use, use of gold therapy in preceding 4 months, use of systemic glucocorticoids in preceding 3 months, penicillamine or sulphasalazine in preceding 2 months, history of poor compliance.
Recruitment/selection of patients	Recruited 1991-992 from out patient clinics of participating units
Age, gender and ethnicity	Age - Mean (SD): Aceclofenac group: 55 (11), placebo group: 58 (10). Gender (M:F): Male: 36, Female: 37. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear (Participant age range not stated but likely to be participants older and youonger than 65 years.).
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: NSAIDs - aceclofenac. One tablet of 100mg twice per day taken at intervals of approximately 12 hours. . Duration 4 weeks. Concurrent medication/care: Washout period of 14 days without

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	NSAID treatment. Further details: 1. Duration of intervention use: Not stated / Unclear (4 weeks). 2. Route of administration: Oral (Tablet). 3. Within-class differences : Selective COX-2 inhibitors (n=35) Intervention 2: Placebo. Taken twice per day with intervals of approximately 12 hours. . Duration 4 weeks. Concurrent medication/care: Washout period of 14 days without NSAID treatment. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Not applicable (4 weeks). 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Study funded by industry (Study sponsored by Prodesfarma, Baercelona, Spain.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACECLOFENAC versus PLACEBO

Protocol outcome 1: Pain at >6 weeks
- Actual outcome: Pain score at 4 weeks; Group 1: mean 42 (SD 21.9); n=38,
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, height, weight, joint tenderness, pain, morning stiffness duration, joint swelling. Groups stated to be similar for concurrent illnesses, additional medication use for unrelated illnesses. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation: adverse events at 4 weeks; Group 1: 3/32, Group 2: 4/23
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, height, weight, joint tenderness, pain, morning stiffness duration, joint swelling. Groups stated to be similar for concurrent illnesses, additional medication use for unrelated illnesses. ; Group 1 Number missing: 5, Reason: Unclear why withdrew; Group 2 Number missing: 12, Reason: Unclear why withdrew

Protocol outcomes not reported by the study	Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Jacob 1983[98]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=129)
Countries and setting	Conducted in Puerto Rico, USA; Setting: 14 centres
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA diagnostic criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with RA in Functional Class I, II or III and Steinbrocker Progression Stage II or II, and if disease activity characterised by presence of three of the following: (1) at least six painful or tender joints on motion, (2) three swollen joints, (3), duration of morning stiffness of at least 3/4 hour, and (4) ESR greater than 28 mm/hr. Positive response to one or more NSAIDs in the past was required.
Exclusion criteria	NR
Recruitment/selection of patients	NR
Age, gender and ethnicity	Age - Mean (SD): Etodolac - 50 (10.5), Placebo - 53 (10). Gender (M:F): 89:40. Ethnicity: 74% white, 22% black, 4% other
Further population details	1. Age: Not applicable
Extra comments	. Duration of RA, years (SD): Etodolac - 6.7 (5.7), Placebo - 10.1 (9.1)
Indirectness of population	No indirectness
Interventions	(n=64) Intervention 1: NSAIDs - etodolac. Two week washout period followed by four week titration period, and eight week maintenance period. Etodolac tablets were administered twice daily. Test drugs were titrated in each patient to the level which gave optimal relief of symptoms. Four dose levels (100, 200, 300 to 400 mg / day). All patients began at the lowest level and were titrated upward until the maximal response was achieved. Mean total after titration was 307 mg/day. Duration 12 weeks. Concurrent medication/care: D-penicillamine and gold salts permitted if had been taken for six months or more, remained at a constant regimen for at least two months prior to the study, and the dosage would not change during the study. Non-narcotic, analgesic acetaminophen (650 mg 4 times daily) was permitted only during the washout and titration periods (mean dose 1539 mg). Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) 2. Route of administration: Oral 3. Within-class differences : Selective COX-2 inhibitors

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	(n=65) Intervention 2: Placebo. Matching placebo in accordance with same regime. Duration 12 weeks. Concurrent medication/care: Concurrent medication/care: D-penicillamine and gold salts permitted if had been taken for six months or more, remained at a constant regimen for at least two months prior to the study, and the dosage would not change during the study. Non-narcotic, analgesic acetaminophen (650 mg 4 times daily) was permitted only during the washout and titration periods. Mean dose used 1556 mg. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) 2. Route of administration: Oral 3. Within-class differences : Selective COX-2 inhibitors
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ETODOLAC versus PLACEBO Protocol outcome 1: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: adverse events at 12 weeks; Group 1: 5/45, Group 2: 4/38 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Substantial difference in disease duration (see pop panel), differences in mean age. Most confouding/prognostic factors not reported. ; Group 1 Number missing: 19, Reason: Largely for inefficacy, some participants for other reasons 'not related to drug'. exact numbers not calculable; Group 2 Number missing: 27, Reason: Vast majority for inefficacy, some participants for other reasons 'not related to drug'. exact numbers not calculable - Actual outcome: Discontinuation: inefficacy at 12 weeks; Group 1: 16/56, Group 2: 24/58 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Substantial difference in disease duration (see pop panel), differences in mean age. Most confouding/prognostic factors not reported. ; Group 1 Number missing: 8, Reason: some participants for adverse events, others for reasons 'not related to drug'. exact numbers not calculable; Group 2 Number missing: 7, Reason: some participants for adverse events, others for reasons 'not related to drug'. exact numbers not calculable	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Jacob 1986[97]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=264)
Countries and setting	Conducted in USA; Setting: Outpatients
Line of therapy	2nd line
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: American Rheumatism Association criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients were required to have documented active RA of more than three months duration based on at least five of the ARA diagnostic criteria for adult RA, to have a prior positive response to one or more NSAIDs, and to be in ARA functional class 1, 2 or 3 and in stage II or III of the Steinbrocker Progression Scale.
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Drug 50mg/d = 50 ± 12; drug 100mg/d = 54 ±10; drug 200mg/d = 52 ± 11; asp = 53 ± 12; placebo 53 ± 13. Gender (M:F): 105:159. Ethnicity: White 81%, black 17%, other 1.5%
Further population details	1. Age: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=161) Intervention 1: NSAIDs - etodolac. Etodolac 50g, 100g or 200g. All tablets were administered at 7am, 12 noon, 5pm, and 10pm. Etodolac was given in two equal doses at 7am and 5pm, with matching placebo tablets given at other times to mimic the qid dosing of the aspirin and placebo groups. . Duration 6 weeks . Concurrent medication/care: Long acting antirheumatic drugs and low dose glucocorticoids were permitted if patients had been receiving a fixed dose for at least two months before study entry. Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) 2. Route of administration: Oral 3. Within-class differences : Not stated / Unclear (n=51) Intervention 2: Placebo. Placebo. All tablets were administered at 7am, 12 noon, 5pm, and 10pm. . Duration 6 weeks. Concurrent medication/care: Long acting antirheumatic drugs and low dose glucocorticoids were permitted if patients had been receiving a fixed dose for at least two months before study entry. Indirectness: No indirectness

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	Further details: 1. Duration of intervention use: Long term use (>6 weeks) 2. Route of administration: Oral 3. Within-class differences : Not stated / Unclear
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ETODOLAC versus PLACEBO Protocol outcome 1: Pain at >6 weeks - Actual outcome: Pain intensity at 6 weeks; Mean; , Comments: 50mg 0.06, placebo 0.2 (least squares mean change from baseline) 100mg 0.77 200mg 1.19 No variance data reported; Risk of bias: All domain - ; Indirectness of outcome: No indirectness Protocol outcome 2: Stiffness at >6 weeks - Actual outcome: Morning stiffness at 6 weeks; Mean; , Comments: 50mg 0.97, placebo -1.19 (least squares mean change from baseline) 100mg -0.07 200mg 2.73 No variance data reported (positive values represent improvement); Risk of bias: All domain - ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported; Drug continuation at Longest time period reported

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Study	Kawai 2010[106]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=676)
Countries and setting	Conducted in Japan; Setting: 80 centres
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1987 ACR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults (≥20 years of age) treated with NSAID without dosage modification for at least 8 weeks, fixed doses of DMARDs and/or systemic corticosteriod for a specified period, physiotherapy (if any) without modification for at least 8 weeks, wrist joint pain persisting for at least 1 month with VAS pain score ≥ 20mm but ≤ 80mm before start of treatment.
Exclusion criteria	Current or previous treatment with any anti-tumour necrosis factor agent, concomitant or previous aspirin induced asthma, known allergy to benzophenone or related compounds (including ketoprofen), known allergy to any topical preparations or adhesives, any concomitant illness that might affect the local response to the study treatment, any wound or dermatitis affecting the study joint, and confirmed or potential pregnancy, recent delivery, current breast feeding or a desire to become pregnant.
Recruitment/selection of patients	2-4 weeks before enrollment, patients were screened for eligibility with regard to demographic and clinical characteristics. Patients discontinued all non-study NSAIDs 1 or 2 weeks before treatment period (depending whether long or short acting). Patients also discontinued all topical analgesic or anti-inflammatory preparations applied to both upper extremities (excluding shoulders) at least 2 weeks before starting treatment. A 4 week washout period was required if the patient was receiving intra-articular therapy with sodium hyaluronate for the study joint or injectable glucocorticoids at any site. Patients who were confirmed eligible were enrolled and randomised.
Age, gender and ethnicity	Age - Mean (SD): Ketoprofen - 58 (13), Placebo - 59 (11). Gender (M:F): 116:560. Ethnicity: Not detailed
Further population details	1. Age: Not applicable
Extra comments	. RA stage I: Ketoprofen - 9.5%, Placebo - 6.8% RA stage IV: Ketoprofen - 27.5%, Placebo - 30.5% Functional class II: Ketoprofen - 66%, Placebo - 67.2% Wrist joint pain (VAS score), mean (SD): Ketoprofen - 50.1 (15.1), Placebo - 49.8 (14.7)
Indirectness of population	No indirectness

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Interventions	(n=338) Intervention 1: NSAIDs - ketoprofen. 70cm² patch containing 20mg of ketoprofen applied once daily to more painful wrist joint. Comprised of backing cloth and a matrix later containing 2% ketoprofen in non-aqueous base. Developed by Hisamitsu Pharmaceutical Company, Japan. . Duration 2 weeks. Concurrent medication/care: DMARD and/or oral glucocorticoid therapy permitted at stable doses. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) 2. Route of administration: Transcutaneous (Patch). 3. Within-class differences : Non-selective NSAIDs (n=338) Intervention 2: Placebo. Matching placebo patch. Duration 2 weeks. Concurrent medication/care: DMARD and/or glucocorticoid therapy at stable doses. Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) 2. Route of administration: Transcutaneous 3. Within-class differences : Not applicable
Funding	Study funded by industry (Hisamitsu Pharmaceutical Co., Inc)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: KETOPROFEN versus PLACEBO

Protocol outcome 1: Pain at <2 weeks
- Actual outcome: Pain, VAS at 2 weeks; Group 1: mean -15.7 mm (SD 16); n=338, Group 2: mean -13.2 mm (SD 16.4); n=338; Visual Analogue Scale 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT, imputation method unclear; Indirectness of outcome: No indirectness ; Baseline details: See population panel. Comparable at baseline. ; Blinding details: "To ensure objectivity of assessment, all patients and investigators were blinded to the treatment assigned until after completion of the study."; Group 1 Number missing: 13, Reason: Withdrawals: 9 adverse events, 3 patients request, 1 other reasons; Group 2 Number missing: 11, Reason: Withdrawals: 7 adverse events, 1 patients request, 3 other reasons

Protocol outcome 2: Drug continuation at Longest time period reported
- Actual outcome: Withdrawal: adverse events at 2 weeks; Group 1: 9/338, Group 2: 7/338
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT, imputation method unclear; Indirectness of outcome: No indirectness ; Baseline details: See population panel. Comparable at baseline. ; Blinding details: "To ensure objectivity of assessment, all patients and investigators were blinded to the treatment assigned until after completion of the study."; Group 1 Number missing: 4, Reason: Other withdrawals: 3 patients request, 1 other reasons; Group 2 Number missing: 4, Reason: Other withdrawals: 1 patients request, 3 other reasons

Protocol outcomes not reported by the study	Pain at >6 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac

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and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported	

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Study	Kirchheiner 1976[108]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=182)
Countries and setting	Conducted in Sweden
Line of therapy	Mixed line
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with classical of definite RA.
Exclusion criteria	Sever hepatic or renal disease, overt diabetes mellitus, cardiac failure, sever hypertension, proven or suspected gastrointestinal ulcer, ulcerative colitis, pregnancy, known sensitivity to acetylsalicylic acid or indomethacin. People who received gold immunosuppressive or antimalarial treatment during 3 months prior to trial. Or required glucocorticoid therapy or experienced rebound phenomenon due to cessation of glucocorticoid therapy during the 2 weeks prior to trial.
Recruitment/selection of patients	The majority of participants were out-patients.
Age, gender and ethnicity	Age - Mean (SD): Diclophenac group: 55 (13), indomethacin group: 56 (11), placebo group: 58 (11). Gender (M:F): Male: 28, Female: 154. Ethnicity: Not detailed
Further population details	1. Age: Not applicable (Age ranged from 21-82 years old).
Extra comments	1 week washout period before study began. Use of antirheumatic, analgesic and muscle relaxing drugs prohibited.
Indirectness of population	No indirectness
Interventions	(n=62) Intervention 1: NSAIDs - diclofenac. 25mg 3 times per day. This could be raised to 50mg 3 times per day after a week if efficacy was inadequate. Treatment was stopped if higher does was considered unsatisfactory after 1 week. . Duration 4 weeks. Concurrent medication/care: Acetylsalicylic acid permitted as a rescue medication. Indirectness: No indirectness Further details: 1. Duration of intervention use: Not applicable (4 weeks). 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=63) Intervention 2: NSAIDs - indomethacin. 25mg 3 times per day. This could be raised to 50mg 3 times per day after a week if efficacy was inadequate. Treatment was stopped if higher does was considered unsatisfactory after 1 week. . Duration 4 weeks. Concurrent medication/care: Acetylsalicylic acid permitted

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	as a rescue medication. Indirectness: No indirectness Further details: 1. Duration of intervention use: Not applicable (4 weeks). 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=57) Intervention 3: Placebo. Double dummy technique with identical placebo tablets. . Duration 4 weeks. Concurrent medication/care: Acetylsalicylic acid permitted as a rescue medication. Indirectness: No indirectness Further details: 1. Duration of intervention use: Not applicable (4 weeks). 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Equipment / drugs provided by industry (Tablets provided by Ciba-Geigy who became Novartis.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus PLACEBO

Protocol outcome 1: Adverse events: gastrointestinal effects at Longest time period reported
- Actual outcome: Adverse events: gastrointestinal bleeding at 4 weeks; Group 1: 0/52, Group 2: 0/39
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Due to non-slective NSAID utilised without PPI treatment; Baseline details: Groups similar for age, duration of disease, gender. No details of severity of RA or previous antirheumatic or analgesic treatment. ; Group 1 Number missing: 10; Group 2 Number missing: 18

Protocol outcome 2: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation: adverse events at 4 weeks; Group 1: 5/57, Group 2: 4/43
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, duration of disease, gender. No details of severity of RA or previous antirheumatic or analgesic treatment. ; Group 1 Number missing: 5; Group 2 Number missing: 14
- Actual outcome: Discontinuation: inefficacy at 4 weeks; Group 1: 5/57, Group 2: 14/53
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, duration of disease, gender. No details of severity of RA or previous antirheumatic or analgesic treatment. ; Group 1 Number missing: 5; Group 2 Number missing: 4

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INDOMETHACIN versus PLACEBO

Protocol outcome 1: Adverse events: gastrointestinal effects at Longest time period reported
- Actual outcome: Adverse events: gastrointestinal bleeding at 4 weeks; Group 1: 0/49, Group 2: 0/39
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Due to non-slective NSAID utilised without PPI treatment; Baseline details: Groups similar for age, duration of disease, gender. No details of severity of RA or previous antirheumatic or analgesic treatment. ;

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Group 1 Number missing: 14; Group 2 Number missing: 18 Protocol outcome 2: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: inefficacy at 4 weeks; Group 1: 6/55, Group 2: 14/53 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, duration of disease, gender. No details of severity of RA or previous antirheumatic or analgesic treatment. ; Group 1 Number missing: 8; Group 2 Number missing: 4 - Actual outcome: Discontinuation: adverse events at 4 weeks; Group 1: 8/57, Group 2: 4/43 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, duration of disease, gender. No details of severity of RA or previous antirheumatic or analgesic treatment. ; Group 1 Number missing: 6; Group 2 Number missing: 14	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Lanier 1987[111]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=160)
Countries and setting	Conducted in USA; Setting: Multicentre.
Line of therapy	Mixed line
Duration of study	Intervention time: 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Stable class II or III definite or classical RA. 18-70 years old, weighing between 90 and 250 pounds. Participants who were treated with NSAIDs or DMARDs were required to be stabilised for at least 6 months. Treatment with gold or glucocorticoids were permitted during the study: no new patients received these treatments during the study. Washout for 1 to 10 days with minimum for 20% flare. Determined using Ritchie Articular Index.
Exclusion criteria	Participants who were pregnant, history of allergy to aspirin, active or recent peptic ulcer, significant cardiac or hepatic or renal disease, those receiving high dose systemic glucocorticoids, or immunosupressive drugs.
Recruitment/selection of patients	Private practice outpatients.
Age, gender and ethnicity	Age - Other: 51 </=50 years old, 61 >50 years old. . Gender (M:F): Male: 31, Female: 82. Comprised of 113 evaluated in efficacy analysis. Ethnicity: White: 96, Black: 17. Comprised of 113 evaluated in efficacy analysis
Further population details	1. Age: Not stated / Unclear (Age range of eligable participants was 18-70 years old).
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: NSAIDs - nabumentone. 2 500mg tablets per day at bedtime. . Duration 3 weeks. Concurrent medication/care: Up to 10 325mg acetaminophen tablets permitted each day. Indirectness: No indirectness Further details: 1. Duration of intervention use: Not applicable (3 weeks). 2. Route of administration: Oral (Tablets). 3. Within-class differences : Non-selective NSAIDs (n=80) Intervention 2: Placebo. Identical placebo tablets. Duration 3 weeks. Concurrent medication/care: Up to 10 325mg acetaminophen tablets permitted each day. Indirectness: No indirectness Further details: 1. Duration of intervention use: Not applicable (3 weeks). 2. Route of administration: Oral 3. Within-class differences : Not applicable

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Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NABUMENTONE versus PLACEBO Protocol outcome 1: Stiffness at <2 weeks - Actual outcome: Morning stiffness at 3 weeks; Group 1: mean -1.3 hours (SD 1.56); n=61, Group 2: mean -0.4 hours (SD 1.41); n=50 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for race, gender, ARA class and ongoing therapy. Participants above or below 50 showed some difference with the placebo group having a higher percentage below 50 years old. ; Group 1 Number missing: 19; Group 2 Number missing: 30 Protocol outcome 2: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: adverse events at 3 weeks; Group 1: 0/70, Group 2: 0/69; Comments: No analysed estimated from total of 139 who received study medication Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for race, gender, ARA class and ongoing therapy. Participants above or below 50 showed some difference with the placebo group having a higher percentage below 50 years old. ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Lavie 1990[113]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Israel; Setting:
Line of therapy	Mixed line
Duration of study	Intervention time: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with RA. Defined as classical RA.
Exclusion criteria	Not detailed.
Recruitment/selection of patients	Recruited from the outpatient clinic at Rambam Medical Centre.
Age, gender and ethnicity	Age - Mean (SD): Tenoxicam group: 57 (13), diclofenac group: 59 (12), placebo group: 56 (13). Gender (M:F): Participants available for analysis: Male: 5, Female: 23. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear (Age range not stated but includes patients younger than 65 years old and might include patients older than 65 years.).
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: NSAIDs - tenoxicam. 20mg tablet in morning and placebo in afternoon. . Duration 2 weeks. Concurrent medication/care: NSAIDs discontinued 7 days before start of trial. Paracetamol permitted (up to 6 500mg tablets per day). . Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (2 weeks). 2. Route of administration: Oral 3. Within-class differences : Selective COX-2 inhibitors (n=10) Intervention 2: NSAIDs - diclofenac. 50mg twice daily. . Duration 2 weeks. Concurrent medication/care: NSAIDs discontinued 7 days before start of trial. Paracetamol permitted (up to 6 500mg tablets per day). . Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (2 weeks). 2. Route of administration: Oral 3. Within-class differences : Selective COX-2 inhibitors (n=10) Intervention 3: Placebo. Twice daily. . Duration 2 weeks. Concurrent medication/care: NSAIDs discontinued 7 days before start of trial. Paracetamol permitted (up to 6 500mg tablets per day). . Indirectness: No indirectness

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	Further details: 1. Duration of intervention use: Short term use (<2 weeks) (2 weeks). 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Study funded by industry (Financial support from F. Hoffmann-La Roche)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TENOXICAM versus PLACEBO Protocol outcome 1: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: adverse events at 2 weeks; Group 1: 1/10, Group 2: 0/10 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, and disease duration. Some difference in duration of disease, gender and Ristchie index. ; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus PLACEBO Protocol outcome 1: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: adverse events at 2 weeks; Group 1: 0/9, Group 2: 0/10 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, gender, Ritchie index and disease duration. Some difference in duration of disease. ; Group 1 Number missing: 1; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Lee 1975[117]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=96)
Countries and setting	Conducted in United Kingdom
Line of therapy	Mixed line
Duration of study	Intervention time: 14 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Participants with RA. Mild, moderate or severe pain.
Exclusion criteria	Receiving gold, glucocorticoid, or corticotrophin therapy. Past history of bleeding gastric or duodenal ulcers.
Age, gender and ethnicity	Age - Mean (SD): Not detailed. Gender (M:F): Not detailed. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear (Not stated.).
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: NSAIDs - indomethacin. 25mg four times daily. . Duration 14 days. Concurrent medication/care: All other antirheumatic drugs taken before the study were stopped for the duration of the trial. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (14 days). 2. Route of administration: Not stated / Unclear 3. Within-class differences : Non-selective NSAIDs (n=48) Intervention 2: Paracetamol. 1g four times daily. Duration 14 days. Concurrent medication/care: All other antirheumatic drugs taken before the study were stopped for the duration of the trial. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (14 days). 2. Route of administration: Not stated / Unclear 3. Within-class differences : Not applicable
Funding	Academic or government funding (Financial support from the Arthritis and Rheumatism Council for Research in Great Britain.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INDOMETHACIN versus PARACETAMOL

Protocol outcome 1: Pain at <2 weeks

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- Actual outcome: Mean pain score (none=1, mild=2, moderate=3, severe=4, very severe=5). Adjusted for initial patient rating of 3 for each group. at Over 14 day period; Group 1: mean 2.9 (SD 0.69); n=48, Group 2: mean 3.5 (SD 0.69); n=48 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Comments - Note: refers to methodology described in separate paper which indicates it was randomised. ; Indirectness of outcome: No indirectness ; Baseline details: Not detailed; Group 1 Number missing: 13, Reason: 13 withdrawals (5 for side effects, 4 for pain, 2 for both, 2 unknown). 14% of patients across the study did not return their scoring sheets. ; Group 2 Number missing: 20, Reason: 20 withdrawals (2 for side effects, 15 for pain, 3 for both). 14% of patients across the study did not return their scoring sheets. Protocol outcome 2: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: due to adverse events at Over 14 day period; Group 1: 7/41, Group 2: 5/38 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - Note: refers to methodology described in separate paper which indicates it was randomised. ; Indirectness of outcome: No indirectness ; Baseline details: Not detailed; Group 1 Number missing: 7, Reason: no detail; Group 2 Number missing: 10, Reason: no detail - Actual outcome: Discontinuation: due to pain at Over 14 day period; Group 1: 6/41, Group 2: 18/38 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - Note: refers to methodology described in separate paper which indicates it was randomised. ; Indirectness of outcome: No indirectness ; Baseline details: Not detailed; Group 1 Number missing: 7; Group 2 Number missing: 10	
Protocol outcomes not reported by the study	Pain at >6 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Lee 1978[116]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=136)
Countries and setting	Conducted in New Zealand
Line of therapy	Mixed line
Duration of study	Intervention time: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Definite or classic RA
Exclusion criteria	Begun or altered glucocorticoid, gold or d-pencillamine treatment within 3 months.
Recruitment/selection of patients	Groups stratified by pain severity based on initial pain rating: mild, moderate, severe.
Age, gender and ethnicity	Age - Mean (SD): Not detailed. Gender (M:F): Not detailed. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear (Age range not stated).
Indirectness of population	No indirectness
Interventions	(n=47) Intervention 1: NSAIDs - indomethacin. 25mg 4 times per day. Plain capsules. . Duration 2 weeks. Concurrent medication/care: Other NSAIDs discontinued for the duration of the study. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (2 weeks). 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=45) Intervention 2: NSAIDs - naproxen . 250mg twice per day. Tablets crushed and administered as capsules.. Duration 2 weeks. Concurrent medication/care: Other NSAIDs discontinued for the duration of the study. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (2 weeks). 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=44) Intervention 3: Placebo. Calcium gluconate tablets. 2 tablets, 3 times per day.. Duration 2 weeks. Concurrent medication/care: NSAIDs discontinued for the duration of the study. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (2 weeks). 2. Route of administration: Oral 3. Within-class differences : Not applicable

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Funding	Study funded by industry (Support from Syntex Pharmaceuticals)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INDOMETHACIN versus PLACEBO

Protocol outcome 1: Pain at <2 weeks
- Actual outcome: Pain Score at 2 weeks; Group 1: mean 2.79 (SD 0.66); n=44, Group 2: mean 3.39 (SD 0.64); n=41; Comments: Subjective rating scale converted to numerical result: nil, mild, moderate, severe, very severe. Mean pain score.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Other NSAID treatment discontinued. Only stable glucocorticoid, gold or pencillamine treatment permitted. Treatment groups stratified by initial pain rating. ; Blinding details: Placebo treatment was tablet while active treatment was capsule. ; Group 1 Number missing: 3; Group 2 Number missing: 3

Protocol outcome 2: Stiffness at <2 weeks
- Actual outcome: Stiffness score at 2 weeks; Group 1: mean 2.62 (SD 0.6); n=44, Group 2: mean 3.21 (SD 0.64); n=41; Comments: Subjective rating scale converted to numerical result: nil, mild, moderate, severe, very severe. Mean stiffness.
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Other NSAID treatment discontinued. Only stable glucocorticoid, gold or pencillamine treatment permitted. Treatment groups stratified by initial pain rating. ; Blinding details: Placebo treatment was tablet while active treatment was capsule. ; Group 1 Number missing: 3; Group 2 Number missing: 3

Protocol outcome 3: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation: inefficacy at 2 weeks; Group 1: 8/46, Group 2: 23/43
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Other NSAID treatment discontinued. Only stable glucocorticoid, gold or pencillamine treatment permitted. Treatment groups stratified by initial pain rating. ; Blinding details: Placebo treatment was tablet while active treatment was capsule. ; Group 1 Number missing: 1; Group 2 Number missing: 1
- Actual outcome: Discontinuation: adverse events at 2 weeks; Group 1: 6/44, Group 2: 3/23
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Other NSAID treatment discontinued. Only stable glucocorticoid, gold or pencillamine treatment permitted. Treatment groups stratified by initial pain rating. ; Blinding details: Placebo treatment was tablet while active treatment was capsule. ; Group 1 Number missing: 3; Group 2 Number missing: 21

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NAPROXEN versus PLACEBO

Protocol outcome 1: Pain at <2 weeks
- Actual outcome: Pain Score at 2 weeks; Group 1: mean 2.76 (SD 0.65); n=42, Group 2: mean 3.39 (SD 0.64); n=41; Comments: Subjective rating scale converted to numerical result: nil, mild, moderate, severe, very severe. Mean pain score.

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Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Other NSAID treatment discontinued. Only stable glucocorticoid, gold or pencillamine treatment permitted. Treatment groups stratified by initial pain rating. ; Blinding details: Placebo treatment was tablet while active treatment was capsule. ; Group 1 Number missing: 3; Group 2 Number missing: 3 Protocol outcome 2: Stiffness at <2 weeks - Actual outcome: Stiffness score at 2 weeks; Group 1: mean 2.77 (SD 0.65); n=42, Group 2: mean 3.21 (SD 0.64); n=41; Comments: Subjective rating scale converted to numerical result: nil, mild, moderate, severe, very severe. Mean morning stiffness rating. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Other NSAID treatment discontinued. Only stable glucocorticoid, gold or pencillamine treatment permitted. Treatment groups stratified by initial pain rating. ; Blinding details: Placebo treatment was tablet while active treatment was capsule. ; Group 1 Number missing: 3; Group 2 Number missing: 3 Protocol outcome 3: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: inefficacy at 2 weeks; Group 1: 8/43, Group 2: 23/43 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Other NSAID treatment discontinued. Only stable glucocorticoid, gold or pencillamine treatment permitted. Treatment groups stratified by initial pain rating. ; Blinding details: Placebo treatment was tablet while active treatment was capsule. ; Group 1 Number missing: 2; Group 2 Number missing: 1 - Actual outcome: Discontinuation: adverse events at 2 weeks; Group 1: 4/39, Group 2: 3/23 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Other NSAID treatment discontinued. Only stable glucocorticoid, gold or pencillamine treatment permitted. Treatment groups stratified by initial pain rating. ; Blinding details: Placebo treatment was tablet while active treatment was capsule. ; Group 1 Number missing: 6; Group 2 Number missing: 21	
Protocol outcomes not reported by the study	Pain at >6 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Lee 2006[114]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=277)
Countries and setting	Conducted in South Korea
Line of therapy	Mixed line
Duration of study	Intervention time: 1 week
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosed with RA for at least 6 months, stable dose of an NSAID or DMARD for at least 30 days before study began, symptomatic RA for at least 2 days before the beginning of the study as indicated by a ≥40mm VAS for pain.
Exclusion criteria	Using SSRIs, short acting analgesics, topical medications, or anesthetic within 5 half-lives of the given medication. Receipt of intra-articular injections of glucocorticoids within 2 months of study entry. Use of oral glucocorticoid within 4 weeks of study entry. However this was lifted if the oral glucocorticoid had been used at low levels 4 weeks before study entry. This dose was maintained throughout the study. Participants were excluded if DMARD treatment had started within 3 months of trial entry. However if DMARD usage had started and continuous for over 3 months then entry was allowed and DMARD treatment continued. Also excluded were participants with OA, ankylosing spondylitis, active gout, active pseudogout with infections of the joints, apparent avascular necrosis in the joints, joint replacement or arthroscopic procedure within 6 months. Previous failure or discontinuation of tramadol treatment due to adverse events, receipt of tramadol within 30 days of study entry, diagnosis of major psychiatric disorder, or any disorder that could compromise metabolism of study drug. History of substance abuse or chronic heavy alcohol abuse. Women were required to use an acceptable form of contraception and have a negative pregnancy test before study entry.
Recruitment/selection of patients	Participants were included from the investigators' medical practices and through advertisements at the study sites.
Age, gender and ethnicity	Age - Mean (SD): Tramadol group: 52 (12), placebo group: 52 (12). Gender (M:F): Male: 40, Female: 227. Ethnicity: Not reported
Further population details	1. Age: Not stated / Unclear (Range of age not stated).
Indirectness of population	No indirectness
Interventions	(n=209) Intervention 1: Opioid + paracetamol. Tramadol: 37.5mg, paracetamol: 325mg tablet daily (Ultracet). Duration 7 days. Concurrent medication/care: Stable doses of previous medications continued..

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	Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (7 days). 2. Route of administration: Oral (Tablet). 3. Within-class differences : Not applicable (Weak opioid and paracetamol). (n=68) Intervention 2: Placebo. Matching placebo taken daily. . Duration 7 days. Concurrent medication/care: Stable doses of previous medications continued.. Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (7 days). 2. Route of administration: Oral (Tablet). 3. Within-class differences : Not applicable (Placebo).
Funding	Study funded by industry (Supported by a grant from Janssen Korea Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRAMADOL + PARACETAMOL versus PLACEBO

Protocol outcome 1: Pain at <2 weeks
- Actual outcome: Mean daily pain intensity (100mm VAS) at Over 1 week of treatment; Group 1: mean 47.23 (SD 19.96); n=201, Group 2: mean 53.81 (SD 16.59); n=66
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, gender, weight, mean tender joints, swollen tender joints, use of DMARDs, use of glucocorticoids. ; Group 1 Number missing: 49, Reason: 8 excluded from ITT population, 41 discontinued and had last value carried forward (39 adverse events, 1 protocol violation, 1 insufficient pain relief) ; Group 2 Number missing: 5, Reason: 2 excluded from ITT population, 3 discontinued (2 adverse events, 1 insufficient pain relief)

Protocol outcome 2: Function at <2 weeks
- Actual outcome: Common daily activities (HAQ) at Over 1 week of treatment; Group 1: mean 1.75 (SD 0.97); n=201, Group 2: mean 1.89 (SD 0.94); n=66
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, gender, weight, mean tender joints, swollen tender joints, use of DMARDs, use of glucocorticoids. ; Group 1 Number missing: 49, Reason: 8 excluded from ITT population, 41 discontinued and had last value carried forward (39 adverse events, 1 protocol violation, 1 insufficient pain relief) ; Group 2 Number missing: 5, Reason: 2 excluded from ITT population, 3 discontinued and had last value carried forward (2 adverse events, 1 insufficient pain relief)

Protocol outcome 3: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation due to adverse events at Over 1 week of treatment; Group 1: 39/201, Group 2: 2/66
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, gender, weight, mean tender joints, swollen tender joints, use of DMARDs, use of glucocorticoids. ; Group 1 Number missing: 10, Reason: 8 not included in ITT analysis, 2 discontinued (1 pain relief inadequate, 1 protocol violation) ; Group 2 Number missing: 3, Reason: 2 not included in ITT analysis, 1 discontinued for insufficient pain relief

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- Actual outcome: Discontinuation due to pain at Over 1 week of treatment; Group 1: 1/201, Group 2: 1/66 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, gender, weight, mean tender joints, swollen tender joints, use of DMARDs, use of glucocorticoids. ; Group 1 Number missing: 48, Reason: 8 not included in ITT analysis, 39 discontinued due to AE, 1 discontinued due to protocol violation; Group 2 Number missing: 4, Reason: 2 not included in ITT analysis, 2 discontinued due to AEs	
Protocol outcomes not reported by the study	Pain at >6 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

ISBN: 978-1-4731-3003-6

Study	Lemmel 1997[118]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=468)
Countries and setting	Conducted in Multiple countries; Setting: 57 centres throughout Europe and 2 in Mexico
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1987 ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of RA for more than 6 months, ARA functional class I, II or II; evidence of at least moderate disease activity before and/or during washout period.
Exclusion criteria	Chemical, radiologic or surgical synovectomy in any large joint within previous 3 months or during study; pregnant or breastfeeding women; women not using adequate contraception; dermatomyositis, gout, Still's diase, systemic lupus erythematosus, or other disease that would interfere with evaluation; concomitant severe cardiac, hepatic, renal, hematologic or metabolic disease, cancer, mental disturbance, ulcerative colitis, bronchial asthma, or active peptic ulceration (within last 6 months); known hypersensitivity to analgesics, antipyretics, or NSAID; previous participation in another meloxicam trial; or simultaneous participation in another clinical trial.
Recruitment/selection of patients	500 patients were screened
Age, gender and ethnicity	Age - Mean (SD): Placebo - 55.26 (10.88), Meloxicam 7.5mg - 53.60 (11.23), Meoxicam 15 mg - 55.22 (10.04). Gender (M:F): NR. Ethnicity: NR
Further population details	1. Age: Not applicable
Extra comments	. Duration of RA, years (mean, SD): Placebo - 10.07 (8.61), Meloxicam 7.5mg - 9.99 (8.22), Meloxicam 15mg - 10.23 (8.88) Presence of concomitant disease: Placebo - 65%, Meloxicam 7.5mg - 62%, Meloxicam 15mg - 67% Use of concomitant therapy at baseline: Placebo - 35%, Meloxicam 7.5mg - 40%, Meloxicam 15mg - 43%
Indirectness of population	No indirectness
Interventions	(n=321) Intervention 1: NSAIDs - meloxicam. 7.5mg - 15mg (2 arms combined in this analysis). Duration 3 weeks. Concurrent medication/care: Patients could not be treated with IM or IV glucocorticoids or adrenocorticotropic hormone within one month of enrollment or during study. DMARDs were allowed as 2nd line therapy if dosage stable for 3 months prior to study and during study. Treatment with glucocorticoids ≤ 7.5mg / day and stabilised for 3 months with no changes during study. Paracetamol could be used as a

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	rescue medication as required. No other analgesics were allowed. . Indirectness: Serious indirectness; Indirectness comment: No mention of co-prescription with PPIs Further details: 1. Duration of intervention use: Not applicable 2. Route of administration: Oral 3. Within-class differences : Selective COX-2 inhibitors (n=147) Intervention 2: Placebo. Matched placebo. Duration 3 weeks. Concurrent medication/care: Patients could not be treated with IM or IV glucocorticoids or adrenocorticotropic hormone within one month of enrollment or during study. DMARDs were allowed as 2nd line therapy if dosage stable for 3 months prior to study and during study. Treatment with glucocorticoids ≤ 7.5mg / day and stabilised for 3 months with no changes during study. Paracetamol could be used as a rescue medication as required. No other analgesics were allowed. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Not applicable 2. Route of administration: Oral 3. Within-class differences : Not stated / Unclear
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MELOXICAM versus PLACEBO

Protocol outcome 1: Pain at <2 weeks
- Actual outcome: Pain during last 24h at 3 weeks; Group 1: mean -0.71 (SD 0.92); n=321,
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Score at 3 weeks (cf protocol outcome < 2 weeks); Baseline details: Balanced at baseline. But important
differences in use of concomitant therapy and 2nd line / glucocorticoid
treatment (all higher in intervention group), and in organ involvement,
rheumatoid nodules, RF positive and ESR at least 28 mm/h (all higher in placebo
group); Blinding details: All drugs were of identical appearance. Rescue treatment likely to lead to underestimation of effect. ; Group 1 Number missing: 14, Reason: Discontinued due to AEs. Whether any other data missing not reported. ; Group 2 Number missing: 7, Reason: Discontinued due to AEs. Whether any other data missing not reported.

Protocol outcome 2: Stiffness at <2 weeks
- Actual outcome: Morning stiffness (duration) at 3 weeks; Group 1: mean -47 min (SD 84); n=321, Group 2: mean -15 min (SD 94); n=147
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Balanced at baseline. But important
differences in use of concomitant therapy and 2nd line / glucocorticoid
treatment (all higher in intervention group), and in organ involvement,
rheumatoid nodules, RF positive and ESR at least 28 mm/h (all higher in placebo
group); Blinding details: All drugs were of identical appearance. Rescue treatment likely to lead to underestimation of effect. ; Group 1 Number missing:

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	14, Reason: Discontinued due to AEs. Whether any other data missing not reported. ; Group 2 Number missing: 7, Reason: Discontinued due to AEs. Whether any other data missing not reported. Protocol outcome 3: Adverse events: gastrointestinal effects at Longest time period reported - Actual outcome: GI ulcers or bleeding at 3 weeks; Group 1: 1/321, Group 2: 0/147; Comments: Esophageal ulcer revealed by gastroscopy. No clinically apparent ulcerations or bleeding in any group. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Balanced at baseline. But important differences in use of concomitant therapy and 2nd line / glucocorticoid treatment (all higher in intervention group), and in organ involvement, rheumatoid nodules, RF positive and ESR at least 28 mm/h (all higher in placebo group); Blinding details: All drugs were of identical appearance. ; Group 1 Number missing: 14, Reason: Discontinued due to AEs. Whether any other data missing not reported. ; Group 2 Number missing: 7, Reason: Discontinued due to AEs. Whether any other data missing not reported. Protocol outcome 4: Adverse events: cardiac and vascular events at Longest time period reported - Actual outcome: Cardiovascular disorders at 3 weeks; Group 1: 3/321, Group 2: 1/147 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Outcome included all adverse events in the "cardiovascular disorders, general" classification as per WHO adverse reaction terminology list. ; Indirectness of outcome: No indirectness; Baseline details: Balanced at baseline. But important differences in use of concomitant therapy and 2nd line / glucocorticoid treatment (all higher in intervention group), and in organ involvement, rheumatoid nodules, RF positive and ESR at least 28 mm/h (all higher in placebo group); Blinding details: All drugs were of identical appearance. ; Group 1 Number missing: 14, Reason: Discontinued due to AEs. Whether any other data missing not reported. ; Group 2 Number missing: 7, Reason: Discontinued due to AEs. Whether any other data missing not reported. Protocol outcome 5: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: adverse events at 3 weeks; Group 1: 14/321, Group 2: 7/147 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Balanced at baseline. But important differences in use of concomitant therapy and 2nd line / glucocorticoid treatment (all higher in intervention group), and in organ involvement, rheumatoid nodules, RF positive and ESR at least 28 mm/h (all higher in placebo group); Blinding details: All drugs were of identical appearance. ; Group 1 Number missing: ?, Reason: Whether any other data missing not reported. ; Group 2 Number missing: ?, Reason: Whether any other data missing not reported.
Protocol outcomes not reported by the study	Pain at >6 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Matsumoto 2002[128]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=816)
Countries and setting	Conducted in USA; Setting: 88 sites
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1987 ARA criteria
Stratum	Overall
Subgroup analysis within study	Stratified then randomised: Randomisation was stratified by low dose corticosteriod use or not.
Inclusion criteria	≥ 18 years, established diagnosis of RA for at least 6 months prior to study, taking NSAID therapy on regular basis (≥25 of past 30 days), satisfying disease activity and flare criteria after washout.
Exclusion criteria	History of angina or congestive heart failure with symptoms at rest of minimal activity; history of MI, coronary angioplasty or coronary bypass within past year; history of stroke, transient ischemic attack or hepatitis in previous 2 years; uncontrolled hypertension; comorbid condition that could confound results or cause risk (eg contradindicated for NSAIDs); evidence of active GI bleeding.
Recruitment/selection of patients	1147 patients screened and assessed for disease activity. Patients satisfying flare criteria after washout were randomised. Of 331 patients not randomised, 247 failed to meet inclusion criteria, 84 failed at randomisation visit (mostly for failing to meet flare criteria).
Age, gender and ethnicity	Age - Mean (SD): 56 years (SD NR). Gender (M:F): 188:628. Ethnicity: NR
Further population details	1. Age: Not applicable
Extra comments	. Mean RA duration: Placebo - 9 yrs, Etoricoxib - 9 yrs, Naproxen - 10 yrs. ARA functional class II: Placebo - 59%, Etoricoxib - 66%, Naproxen - 62% ARA functional class III: Placebo - 19%, Etoricoxib 13%, Naproxen - 17%. Methotrexate use: Placebo - 47%, Etoricoxib - 50%, Naproxen - 45% glucocorticoid use: Placebo - 32%, Etoricoxib - 29%, Naproxen - 43% Mean patient global assessment of disease activity (100mm VAS): Placebo - 66, Etoricoxib - 65, Naproxen - 63
Indirectness of population	No indirectness
Interventions	(n=170) Intervention 1: NSAIDs - naproxen . 50mg twice daily. Duration 12 weeks. Concurrent medication/care: Patients taking stable doses of DM therapy and low doses of glucocorticoids were allowed to continue therapy. Patients were permitted to take low dose aspirin. Patients could not be taking concomitant warfarin, ticlopidine, clopidrogel or digoxin. . Indirectness: Serious indirectness; Indirectness

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	comment: No mention of co-prescription with PPIs Further details: 1. Duration of intervention use: Long term use (>6 weeks) 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=323) Intervention 2: NSAIDs - etoricoxib. 90 mg once daily . Duration 12 weeks. Concurrent medication/care: Patients taking stable doses of DM therapy and low doses of glucocorticoids were allowed to continue therapy. Patients were permitted to take low dose aspirin. Patients could not be taking concomitant warfarin, ticlopidine, clopidrogel or digoxin. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) 2. Route of administration: Oral 3. Within-class differences : Selective COX-2 inhibitors (n=323) Intervention 3: Placebo. Placebo. Duration 12 weeks. Concurrent medication/care: Patients taking stable doses of DM therapy and low doses of glucocorticoids were allowed to continue therapy. Patients were permitted to take low dose aspirin. Patients could not be taking concomitant warfarin, ticlopidine, clopidrogel or digoxin. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Study funded by industry (Merck Research Laboratories)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NAPROXEN versus PLACEBO

Protocol outcome 1: Pain at >6 weeks
- Actual outcome: Pain, 100mm VAS at 12 weeks ; MD; -9.1 (95%CI -13 to -5.3) Visual Analogue Scale 0-100 Top=High is poor outcome, Units: mm, Comments: Least squares mean of the time weighted average change from baseline over 12 weeks (measured at 2, 4, 8 and 12 weeks);
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - "modified ITT" of all patients taking at least one dose and attending one follow up. Least squares mean of the time weighted average change from baseline over 12 weeks (measured at 2, 4, 8 and 12 weeks); Indirectness of outcome: No indirectness ; Baseline details: VAS pain at baseline not reported; Blinding details: No description of matched placebo but said to be double blind; Group 1 Number missing: 74, Reason: 62 for lack of efficacy, 8 due to clinical AE, 1 due to lab AE, 3 other reasons; Group 2 Number missing: 201, Reason: 176 lack of efficacy, 10 clinical AE, 1 lab AE, 14 other reasons

Protocol outcome 2: Function at >6 weeks
- Actual outcome: HAQ disability score at 12 weeks ; MD; -0.14 (95%CI -0.22 to -0.07) 0-3 Stanford Health Assessment Questionnaire (HAQ) Top=High is poor outcome, Comments: Least squares mean of the time weighted average change from baseline over 12 weeks (measured at 2, 4, 8 and 12 weeks);
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - "modified ITT" of all patients taking at least one dose and attending one follow up. Least squares mean of the time weighted average change from baseline over 12 weeks (measured at 2, 4, 8 and 12 weeks); Indirectness of outcome: No indirectness ; Baseline details: HAQ at

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baseline not reported; Blinding details: No description of matched placebo but said to be double blind; Group 1 Number missing: 74, Reason: 62 for lack of efficacy, 8 due to clinical AE, 1 due to lab AE, 3 other reasons; Group 2 Number missing: 201, Reason: 176 lack of efficacy, 10 clinical AE, 1 lab AE, 14 other reasons

Protocol outcome 3: Adverse events: mortality at Longest time period reported
- Actual outcome: Mortality at 12 weeks ; Group 1: 0/170, Group 2: 0/323
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Functional class differences; Blinding details: No description of matched placebo but said to be double blind; Group 1 Number missing: 0, Reason: Assume zero (all deaths would have been recorded even in those discontinuing); Group 2 Number missing: 0, Reason: Assume zero (all deaths would have been recorded even in those discontinuing)

Protocol outcome 4: Adverse events: gastrointestinal effects at Longest time period reported
- Actual outcome: Perforation, ulcer or bleed at 12 weeks ; Group 1: 1/170, Group 2: 0/323
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: Serious indirectness, Comments: Due to non-slective NSAID utilised without PPI treatment; Blinding details: No description of matched placebo but said to be double blind; Group 1 Number missing: 74, Reason: 62 for lack of efficacy, 8 due to clinical AE, 1 due to lab AE, 3 other reasons; Group 2 Number missing: 201, Reason: 176 lack of efficacy, 10 clinical AE, 1 lab AE, 14 other reasons

Protocol outcome 5: Adverse events: cardiac and vascular events at Longest time period reported
- Actual outcome: Cardiovascular events at 12 weeks ; Group 1: 0/170, Group 2: 0/323
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Blinding details: No description of matched placebo but said to be double blind; Group 1 Number missing: 74, Reason: 62 for lack of efficacy, 8 due to clinical AE, 1 due to lab AE, 3 other reasons; Group 2 Number missing: 201, Reason: 176 lack of efficacy, 10 clinical AE, 1 lab AE, 14 other reasons

Protocol outcome 6: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation: adverse events at 12 weeks ; Group 1: 9/170, Group 2: 11/323
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Blinding details: No description of matched placebo but said to be double blind; Group 1 Number missing: 65, Reason: 62 for lack of efficacy, 3 other reasons; Group 2 Number missing: 190, Reason: 176 lack of efficacy, 14 other reasons
- Actual outcome: Discontinuation: inefficacy at 12 weeks ; Group 1: 62/170, Group 2: 176/323
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Blinding details: No description of matched placebo but said to be double blind; Group 1 Number missing: 12, Reason: 8 due to clinical AE, 1 due to lab AE, 3 other reasons; Group 2 Number missing: 25, Reason: 10 clinical AE, 1 lab AE, 14 other reasons

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ETORICOXIB versus PLACEBO

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Protocol outcome 1: Pain at >6 weeks
- Actual outcome: Pain, 100mm VAS at 12 weeks ; MD; -15.8 (95%CI -19.2 to -12.6) Visual Analogue Scale 0-100 Top=High is poor outcome, Units: mm, Comments: Least squares mean of the time weighted average change from baseline over 12 weeks;
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - "modified ITT" of all patients taking at least one dose and attending one follow up. Least squares mean of the time weighted average change from baseline over 12 weeks (measured at 2, 4, 8 and 12 weeks); Indirectness of outcome: No indirectness ; Baseline details: VAS pain at baseline not reported; Blinding details: No description of matched placebo but said to be double blind; Group 1 Number missing: 93, Reason: 70 for lack of efficacy, 11 due to clinical AE, 1 due to lab AE, 11 other reasons; Group 2 Number missing: 201, Reason: 176 lack of efficacy, 10 clinical AE, 1 lab AE, 14 other reasons

Protocol outcome 2: Function at >6 weeks
- Actual outcome: HAQ disability score at 12 weeks ; MD; -0.26 (95%CI -0.32 to -0.19) Stanford Health Assessment Questionnaire (HAQ) 0-3 Top=High is poor outcome, Comments: Least squares mean of the time weighted average change from baseline over 12 weeks (measured at 2, 4, 8 and 12 weeks);
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - "modified ITT" of all patients taking at least one dose and attending one follow up. Least squares mean of the time weighted average change from baseline over 12 weeks (measured at 2, 4, 8 and 12 weeks); Indirectness of outcome: No indirectness ; Baseline details: HAQ at baseline not reported; Blinding details: No description of matched placebo but said to be double blind; Group 1 Number missing: 93, Reason: 70 for lack of efficacy, 11 due to clinical AE, 1 due to lab AE, 11 other reasons; Group 2 Number missing: 201, Reason: 176 lack of efficacy, 10 clinical AE, 1 lab AE, 14 other reasons

Protocol outcome 3: Adverse events: mortality at Longest time period reported
- Actual outcome: Mortality at 12 weeks ; Group 1: 0/323, Group 2: 0/323
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Functional class differences; Blinding details: No description of matched placebo but said to be double blind; Group 1 Number missing: 0, Reason: Assume zero (all deaths would have been recorded even in those discontinuing); Group 2 Number missing: 0, Reason: Assume zero (all deaths would have been recorded even in those discontinuing)

Protocol outcome 4: Adverse events: gastrointestinal effects at Longest time period reported
- Actual outcome: Perforation, ulcer or bleed at 12 weeks ; Group 1: 0/323, Group 2: 0/323
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Functional class differences; Blinding details: No description of matched placebo but said to be double blind; Group 1 Number missing: 93, Reason: 70 for lack of efficacy, 11 due to clinical AE, 1 due to lab AE, 11 other reasons; Group 2 Number missing: 201, Reason: 176 lack of efficacy, 10 clinical AE, 1 lab AE, 14 other reasons

Protocol outcome 5: Adverse events: cardiac and vascular events at Longest time period reported
- Actual outcome: Cardiovascular events at 12 weeks ; Group 1: 2/323, Group 2: 0/323; Comments: One transient ischemic attack and a non-Q wave MI.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

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Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Blinding details: No description of matched placebo but said to be double blind; Group 1 Number missing: 93, Reason: 70 for lack of efficacy, 11 due to clinical AE, 1 due to lab AE, 11 other reasons; Group 2 Number missing: 201, Reason: 176 lack of efficacy, 10 clinical AE, 1 lab AE, 14 other reasons Protocol outcome 6: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: adverse events at 12 weeks ; Group 1: 12/323, Group 2: 11/323 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Blinding details: No description of matched placebo but said to be double blind; Group 1 Number missing: 81, Reason: 70 for lack of efficacy, 11 other reasons; Group 2 Number missing: 190, Reason: 176 lack of efficacy, 14 other reasons - Actual outcome: Discontinuation: inefficacy at 12 weeks ; Group 1: 70/323, Group 2: 176/323 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Functional class differences; Blinding details: No description of matched placebo but said to be double blind; Group 1 Number missing: 23, Reason: 11 due to clinical AE, 1 due to lab AE, 11 other reasons; Group 2 Number missing: 25, Reason: 10 clinical AE, 1 lab AE, 14 other reasons	
Protocol outcomes not reported by the study	Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at <2 weeks; Adverse events: impaired renal function at Longest time period reported

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Study	Mehta 1992[131]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in India; Setting: All India Institute of Medical Sciences between April 1986 and June 1988.
Line of therapy	Not applicable
Duration of study	Intervention time: 2 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Assessed using American Rheumatology Association criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Rheumatoid arthritis by ARA criteria
Exclusion criteria	Severe cardiovascular, pulmonary or renal disease. Previous documented peptic ulcer, history of previous gastrointestinal haemorrhage requiring blood transfusions, previous gastrointestinal surgery, use of more than 1 anti- inflammatory drug, use of anti-ulcer drugs in past 4 weeks, age under 18 or over 70, presence of endoscopic abnormalities in the upper gastrointestinal tract after stopping anti-inflammatory treatment for 2 weeks.
Recruitment/selection of patients	Consecutive patients with RA
Age, gender and ethnicity	Age - Mean (SD): Naproxen group: 38.4 (9.8), Placebo group: 16.7 (11.9). The age reported for the placebo group could not be correct as people under 18 years old were excluded. . Gender (M:F): 11 male, 49 female. Ethnicity: Not stated
Further population details	1. Age: Not stated / Unclear (Mainly under 65 years of age as people over 70 years of age were excluded.).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: NSAIDs - naproxen . 500mg per day in two doses. Increased to 750mg per day after 2 weeks. Further changes were made to control symptoms. . Duration 2 months. Concurrent medication/care: None detailed. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (2 months). 2. Route of administration: Oral (Identical capsules to other treatments). 3. Within-class differences : Non-selective NSAIDs (Naproxen). (n=30) Intervention 2: Placebo. 0.5ml caster oil. 4 times per day. Dosage was increased for control of symptoms. . Duration 2 months. Concurrent medication/care: None detailed. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) (2 months). 2. Route of administration: Oral (Identical capsules to other treatments). 3. Within-class differences : Not applicable

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	(Placebo).
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NAPROXEN versus PLACEBO Protocol outcome 1: Adverse events: gastrointestinal effects at Longest time period reported - Actual outcome: Dyspeptic symptoms: epigastric pain, retrosternal distress, nausea at Assessment once every 2 weeks for 2 months of treatment; Group 1: 9/30, Group 2: 0/30; Comments: Mean symptom score also available. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Due to non-slective NSAID utilised without PPI treatment; Baseline details: Similar for gender, duration of disease, haemoglobin was slightly higher in the placebo group, age was incorrectly reported for the placebo group. No details of previous RA treatment. Other NSAID treatment discontinued. ; Blinding details: Identical appearing capsules for each treatment. Physician assessing symptoms not aware of treatment or other investigations.; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Ulcer developed: duodenal or gastric at During 2 months of treatment; Group 1: 3/30, Group 2: 0/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Due to non-slective NSAID utilised without PPI treatment; Baseline details: Similar for gender, duration of disease, haemoglobin was slightly higher in the placebo group, age was incorrectly reported for the placebo group. No details of previous RA treatment. Other NSAID treatment discontinued. ; Blinding details: Identical appearing capsules for each treatment. Endoscopist and pathologist blinded to treatment as well as other symptoms.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported; Drug continuation at Longest time period reported

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Study	Sarzi puttini 1988[160]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=28)
Countries and setting	Conducted in Italy; Setting: Out-patients
Line of therapy	Unclear
Duration of study	Intervention + follow up: 7 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Stratified then randomised: Stratified into depressed and not depressed. Only not depressed is extracted
Inclusion criteria	Patients with classical or definite active rheumatoid arthritis, diagnosed according to the ARA criteria. They were required to satisfy at least three of the following criteria: Ritchie's index >15; erythrocyte sedimentation rate >25mmHg; duration of morning stiffness >30 min; and subjective pain index (VAS >50 mm)
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: Mean (SD): 50.2 (2.1). Gender (M:F): 5:25. Ethnicity: Not reported
Further population details	1. Age: ≤65 years
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Tricyclic anti-depressants - Dothiepin. Ibuprofen was given orally at a dose of 600mg three times a day for the whole period of the trail. For week 2-5 (4 weeks) dothiepin given orally as a dose of 75mg once nightly were added to the ibuprofen therapy. At the end of week 5, dothiepin was stopped, while ibuprofen was continued for a further 2 weeks. Duration 4 weeks. Concurrent medication/care: Ibuprofen was given orally at a dose of 600mg three times a day for the whole period of the trail.. Indirectness: No indirectness Further details: 1. Duration of intervention use: Not applicable (4 weeks). 2. Route of administration: Oral 3. Within-class differences : Not stated / Unclear Comments: 30 patients overall, unclear how many in each group (n=15) Intervention 2: Placebo. Ibuprofen was given orally at a dose of 600mg three times a day for the whole period of the trail. For week 2-5 (4 weeks) placebo was added to the ibuprofen therapy. At the end of week 5, dothiepin was stopped, while ibuprofen was continued for a further 2 weeks. Duration 4 weeks. Concurrent medication/care: Ibuprofen was given orally at a dose of 600mg three times a day for the whole period of the trail. Indirectness: No indirectness

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	Further details: 1. Duration of intervention use: Not applicable (4 weeks). 2. Route of administration: Oral 3. Within-class differences : Not stated / Unclear Comments: 30 patients overall, unclear how many in each group
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOTHIEPIN versus PLACEBO Protocol outcome 1: Pain at >6 weeks - Actual outcome: Daytime pain at 7 weeks; Mean; , Comments: Results presented graphically so cannot be extracted; Risk of bias: All domain - ; Indirectness of outcome: No indirectness - Actual outcome: Nighttime pain at 7 weeks; Mean; , Comments: Results presented graphically so cannot be extracted; Risk of bias: All domain - ; Indirectness of outcome: No indirectness - Actual outcome: Spontaneous pain at 7 weeks; Mean; , Comments: Results presented graphically so cannot be extracted; Risk of bias: All domain - ; Indirectness of outcome: No indirectness Protocol outcome 2: Adverse events: gastrointestinal effects at Longest time period reported - Actual outcome: Epigastric pain at 7 weeks; Mean; , Comments: Results not separated for different stratas; Risk of bias: All domain - ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported; Drug continuation at Longest time period reported

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Study	Simon 1998[168]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=330)
Countries and setting	Conducted in USA
Line of therapy	Mixed line
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with RA flare, Steinbrocker functional capacity classification of I-III
Exclusion criteria	Inflammatory condition other than RA, non-inflammatory type of arthritis symptomatic enough to interfere with assessment, recently begun receiving or had a change in regimen of DMARDs, antimalarial agents, glucocorticoids, taken any NSAIDs within 2 days of baseline visit, or taken analgesics within 24 hours of baseline visit, active GI disease, chronic or acute renal or hepatic disorder, significant coagulation defect.
Age, gender and ethnicity	Age - Mean (range): Placebo group: 56.5 (25-82), celecoxib 40mg: 55.6 (28-78), celecoxib 200mg 55.5 (25-86), celecoxib 400mg: 56.7 (21-80). Gender (M:F): Male: 74, Female: 256. Ethnicity: Not stated
Further population details	1. Age: Not applicable (Ages ranged from 18 to 86.).
Indirectness of population	--
Interventions	(n=245) Intervention 1: NSAIDs - celecoxib. Randomised to receive 40mg (n=153), 100mg (n=107), 200mg (=n=187), 400mg (n=87). Twice daily. . Duration 4 weeks. Concurrent medication/care: Not detailed. Further details: 1. Duration of intervention use: Not applicable (4 weeks). 2. Route of administration: Oral (Capsule). 3. Within-class differences : Selective COX-2 inhibitors (n=85) Intervention 2: Placebo. Not detailed. . Duration 4 weeks. Concurrent medication/care: Not detailed. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Not applicable (4 weeks). 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Study funded by industry (Supported by G.D. Searle & Co)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CELECOXIB versus PLACEBO	

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Protocol outcome 1: Drug continuation at Longest time period reported - Actual outcome: Discontinuation due to adverse events at During 4 weeks of treatment; Group 1: 11/245, Group 2: 5/85 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for age, gender, RA duration. Current and previous use of medication not stated. ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study (subsidiary papers)	Simon 1999[169] (Zhao 2000[197])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1149)
Countries and setting	Conducted in Canada, USA; Setting: Outpatient
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1987 ACR criteria
Stratum	Overall:
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women outpatients aged 18 years or older were eligible to participate in the study if they fulfilled the American College of Rheumatology criteria for a diagnosis of RA evident for 3 months or longer and were in a functional class of I, II, or III. Additional selection criteria were based on disease activity. Patients were eligible to participate if the dosages of any glucocorticoids, disease-modifying antirheumatic drugs, or methotrexate had been stable and were expected to remain constant throughout the study.
Exclusion criteria	Patients were excluded from the study if they had active GI tract, renal, hepatic, or coagulation disorders; history of malignancy (unless removed surgically with no recurrence within 5 years); esophageal or gastroduodenal ulceration within the previous 30 days; or a history of gastric or duodenal surgery other than an oversew. In addition, patients were excluded if the upper GI tract endoscopy performed at baseline disclosed an esophageal, gastric, or duodenal ulcer or more than 10 erosions in the stomach or duodenum. Patients were not excluded for a history of peptic ulcer disease.
Recruitment/selection of patients	Recruited from 79 clinical sites.
Age, gender and ethnicity	Age - Mean (range): placebo - 54 (27-79), 100mg celecoxib - 54 (22-85), 200mg celecoxib - 55 (20-90), 400 mg celecoxib - 54 (22-85), 500mg naproxen - 55 (28-81). Gender (M:F): 72-74% female across the groups. Ethnicity: Not detailed
Further population details	1. Age: Not applicable
Extra comments	Duration of disease, mean (SD) years: P - 11 (11), C100 - 11 (10), C200 - 11 (10), C400 - 10 (9), N - 10 (9). Patients global assessment, % poor or very poor: P - 64%, C100 - 63%, C200 - 62%, C400 - 56%, N - 54%. Arthritis pain, VAS (mm), mean (SD): P - 69 (19), C100 - 67 (20), C200 - 68 (20), C400 - 66 (21), N - 67 (18). Duration of morning stiffness (min), mean (SD): P - 267.5 (350.5), C100 - 279.4 (388.5), C200 - 305.3 (209.8), C400 - 310.9 (418.7), N - 312.6 (407.6).
Indirectness of population	No indirectness
Interventions	(n=693) Intervention 1: NSAIDs - celecoxib. 100-400mg bid. Duration 12 weeks. Concurrent

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	medication/care: Stable doses of aspirin no more than 325 mg/d were allowed, and acetaminophen up to 2 g/d for no longer than 3 consecutive days was also allowed except within 48 hours prior to arthritis assessments, during which no analgesics were allowed. NSAIDs, injectable glucocorticoids, and anticoagulants were prohibited. Stable doses of oral glucocorticoids (up to 10 mg of prednisone per day) or disease-modifying antirheumatic drugs (DMARDs) were allowed and antiulcer drugs were prohibited.. Indirectness: No indirectness; Indirectness comment: 400mg above BNF max for RA Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral 3. Within-class differences : Selective COX-2 inhibitors Comments: Combined results of 100mg, 200mg and 400mg groups reported in study (n=225) Intervention 2: NSAIDs - naproxen . 500 mg BID. Duration 12 weeks . Concurrent medication/care: Stable doses of aspirin no more than 325 mg/d were allowed, and acetaminophen up to 2 g/d for no longer than 3 consecutive days was also allowed except within 48 hours prior to arthritis assessments, during which no analgesics were allowed. NSAIDs, injectable glucocorticoids, and anticoagulants were prohibited. Stable doses of oral glucocorticoids (up to 10 mg of prednisone per day) or disease-modifying antirheumatic drugs (DMARDs) were allowed and antiulcer drugs were prohibited.. Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=231) Intervention 3: Placebo. matched placebo. Duration 12 weeks. Concurrent medication/care: Stable doses of aspirin no more than 325 mg/d were allowed, and acetaminophen up to 2 g/d for no longer than 3 consecutive days was also allowed except within 48 hours prior to arthritis assessments, during which no analgesics were allowed. NSAIDs, injectable glucocorticoids, and anticoagulants were prohibited. Stable doses of oral glucocorticoids (up to 10 mg of prednisone per day) or disease-modifying antirheumatic drugs (DMARDs) were allowed and antiulcer drugs were prohibited.. Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	-- ("Supported by" G.D. Searle & Co (Pfizer))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CELECOXIB versus PLACEBO

Protocol outcome 1: Pain at >6 weeks
- Actual outcome: Arthritis pain, VAS (mm) at 12 weeks; Group 1: mean -18.57 mm (SD 28.28); n=693, Group 2: mean -9.3 mm (SD 30.4); n=231; Visual Analogue Scale 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: VAS baseline, mm (SD): P - 69 (19), C (range) - 66-68 (20-21), N - 67 (18); Blinding details: "All treatment regimes were fully masked so that all patients took the same number of capsules, and all regimens were identical in

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appearance and frequency."; Group 1 Number missing: 244, Reason: See discontinuation outcome ; Group 2 Number missing: 130, Reason: See discontinuation outcome

Protocol outcome 2: Stiffness at >6 weeks
- Actual outcome: Duration of morning stiffness, min at 12 weeks; Group 1: mean -125.5 min (SD 443.3); n=693, Group 2: mean 8.9 min (SD 481.8); n=231
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Stiffness, baseline - P - 276 min, C - 298 min with similar variance; Blinding details: "All treatment regimes were fully masked so that all patients took the same number of capsules, and all regimens were identical in appearance and frequency."; Group 1 Number missing: 244, Reason: See discontinuation outcome ; Group 2 Number missing: 130, Reason: See discontinuation outcome

Protocol outcome 3: Function at >6 weeks
- Actual outcome: HAQ total functional disability index at 12 weeks; Group 1: mean -0.2 (SD 0.56); n=693, Group 2: mean -0.1 (SD 0.61); n=231; Standford Health Assessment Questionnaire (HAQ) disability index 0-3 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: HAQ baseline, mean (SD)- P - 1.4 (0.66), C (range) - 1.4-1.5 (0.65-0.73); Blinding details: "All treatment regimes were fully masked so that all patients took the same number of capsules, and all regimens were identical in appearance and frequency."; Group 1 Number missing: 244, Reason: See discontinuation outcome ; Group 2 Number missing: 130, Reason: See discontinuation outcome

Protocol outcome 4: Adverse events: gastrointestinal effects at Longest time period reported
- Actual outcome: Gastroduodenal ulcers at 12 weeks; Group 1: 23/423, Group 2: 4/99
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: No patients had ulcers at baseline. Baseline endoscopic scores were 'not significantly different' between treatment groups. The incidence of H pylori positive serology results at baseline was also not statistically significantly different across the groups. ; Blinding details: "All treatment regimes were fully masked so that all patients took the same number of capsules, and all regimens were identical in appearance and frequency." Endoscoper was stated to be blinded to the treatment allocation. ; Group 1 Number missing: 270, Reason: See discontinuation outcome, plus an additional 26 (presumably marked 'unknown' on endoscopy); Group 2 Number missing: 132, Reason: See discontinuation outcome, plus an additional 2 (presumably marked 'unknown' on endoscopy)

Protocol outcome 5: Adverse events: impaired renal function at Longest time period reported
- Actual outcome: Creatinine, µmol/L at 12 weeks; Group 1: mean 64.28 µmol/L (SD 16.26); n=693, Group 2: mean 66.8 µmol/L (SD 16.9); n=231
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Creatinine, mean: P - 68.5, C - 65.6. ; Blinding details: "All treatment regimes were fully masked so that all patients took the same number of capsules, and all regimens were identical in appearance and frequency."; Group 1 Number missing: 244, Reason: See discontinuation outcome ; Group 2 Number missing: 130, Reason: See discontinuation outcome

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Protocol outcome 6: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation for treatment failure at 12 weeks; Group 1: 176/625, Group 2: 104/205
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See pop details; Blinding details: "All treatment regimes were fully masked so that all patients took the same number of capsules, and all regimens were identical in appearance and frequency." Endoscoper was stated to be blinded to the treatment allocation. ; Group 1 Number missing: 68, Reason: Lost to follow up = 5, disc. due to AEs = 42, other = 21; Group 2 Number missing: 26, Reason: Lost to follow up = 3, disc. due to AEs =11, other = 12
- Actual outcome: Discontinuation for adverse events at 12 weeks; Group 1: 42/491, Group 2: 11/112
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See pop details; Blinding details: "All treatment regimes were fully masked so that all patients took the same number of capsules, and all regimens were identical in appearance and frequency." Endoscoper was stated to be blinded to the treatment allocation. ; Group 1 Number missing: 202, Reason: Lost to follow up = 5, treatment failure = 176, other = 21; Group 2 Number missing: 119, Reason: Lost to follow up = 3, treatment failure = 104, other = 12

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NAPROXEN versus PLACEBO

Protocol outcome 1: Pain at >6 weeks
- Actual outcome: Arthritis pain, VAS (mm) at 12 weeks; Group 1: mean -16.9 mm (SD 27); n=225, Group 2: mean -9.3 mm (SD 30.4); n=231; Visual Analogue Scale 0-100 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: VAS baseline, mm (SD): P - 69 (19), N - 67 (18); Blinding details: "All treatment regimes were fully masked so that all patients took the same number of capsules, and all regimens were identical in appearance and frequency."; Group 1 Number missing: 87, Reason: See discontinuation outcome ; Group 2 Number missing: 130, Reason: See discontinuation outcome

Protocol outcome 2: Stiffness at >6 weeks
- Actual outcome: Duration of morning stiffness, min at 12 weeks; Group 1: mean -90.1 min (SD 424.5); n=225, Group 2: mean 8.9 min (SD 481.8); n=231
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Stiffness, baseline - P - 276 min, N - 312 min with similar variance; Blinding details: "All treatment regimes were fully masked so that all patients took the same number of capsules, and all regimens were identical in appearance and frequency."; Group 1 Number missing: 87, Reason: See discontinuation outcome ; Group 2 Number missing: 130, Reason: See discontinuation outcome

Protocol outcome 3: Function at >6 weeks
- Actual outcome: HAQ total functional disability index at 12 weeks; Group 1: mean -0.2 (SD 0.45); n=225, Group 2: mean -0.1 (SD 0.61); n=231; Standford Health Assessment Questionnaire (HAQ) disability index 0-3 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: HAQ baseline, mean (SD)- P - 1.4 (0.66), N - 1.5 (0.7) (difference equivalent to magnitude of effect); Blinding details: "All treatment regimes were fully masked so that all patients took the same number of capsules, and all regimens

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	were identical in appearance and frequency."; Group 1 Number missing: 87, Reason: See discontinuation outcome ; Group 2 Number missing: 130, Reason: See discontinuation outcome Protocol outcome 4: Adverse events: gastrointestinal effects at Longest time period reported - Actual outcome: Gastroduodenal ulcers at 12 weeks; Group 1: 36/137, Group 2: 4/99 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Due to non-slective NSAID utilised without PPI treatment; Baseline details: No patients had ulcers at baseline. Baseline endoscopic scores were 'not significantly different' between treatment groups. The incidence of H pylori positive serology results at baseline was also not statistically significantly different across the groups. ; Blinding details: "All treatment regimes were fully masked so that all patients took the same number of capsules, and all regimens were identical in appearance and frequency." Endoscoper was stated to be blinded to the treatment allocation. ; Group 1 Number missing: 89, Reason: See discontinuation outcome, plus an additional 2 (presumably marked 'unknown' on endoscopy); Group 2 Number missing: 132, Reason: See discontinuation outcome, plus an additional 2 (presumably marked 'unknown' on endoscopy) Protocol outcome 5: Adverse events: impaired renal function at Longest time period reported - Actual outcome: Creatinine, µmol/L at 12 weeks; Group 1: mean 65.4 µmol/L (SD 16); n=225, Group 2: mean 66.8 µmol/L (SD 16.9); n=231 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Creatinine, mean: P - 68.5, C - 66.4; Blinding details: "All treatment regimes were fully masked so that all patients took the same number of capsules, and all regimens were identical in appearance and frequency."; Group 1 Number missing: 87, Reason: See discontinuation outcome ; Group 2 Number missing: 130, Reason: See discontinuation outcome Protocol outcome 6: Drug continuation at Longest time period reported - Actual outcome: Discontinuation for treatment failure at 12 weeks; Group 1: 65/203, Group 2: 104/205 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See pop details; Blinding details: "All treatment regimes were fully masked so that all patients took the same number of capsules, and all regimens were identical in appearance and frequency." Endoscoper was stated to be blinded to the treatment allocation. ; Group 1 Number missing: 22, Reason: Lost to follow up = 1, disc. due to AEs = 12, other = 9; Group 2 Number missing: 26, Reason: Lost to follow up = 3, disc. due to AEs =11, other = 12 - Actual outcome: Discontinuation for adverse events at 12 weeks; Group 1: 12/150, Group 2: 11/112 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See pop details; Blinding details: "All treatment regimes were fully masked so that all patients took the same number of capsules, and all regimens were identical in appearance and frequency." Endoscoper was stated to be blinded to the treatment allocation. ; Group 1 Number missing: 75, Reason: Lost to follow up = 1, treatment failure = 65, other = 9; Group 2 Number missing: 119, Reason: Lost to follow up = 3, treatment failure = 104, other = 12
Protocol outcomes not reported by the study	Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at <2 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported

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Study	Turner 1987[180]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=46)
Countries and setting	Conducted in USA; Setting: Multicentre.
Line of therapy	Mixed line
Duration of study	Intervention time: 3 weeks
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with definite or classical RA. 20% flare on Articular Index after washout period.
Exclusion criteria	None detailed.
Recruitment/selection of patients	Randomisation stratified by DMARD usage.
Age, gender and ethnicity	Age - Mean (SD): Not stated. Gender (M:F): Not detailed. Ethnicity: Not detailed
Further population details	1. Age: Not stated / Unclear (Age not stated.).
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: NSAIDs - nabumentone. 1000mg taken at bedtime. . Duration 3 weeks. Concurrent medication/care: DMARD treatment continued with same dosage. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Not applicable (3 weeks). 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=23) Intervention 2: Placebo. Not detailed. Duration 3 weeks. Concurrent medication/care: DMARD treatment continued with same dosage. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Not applicable (3 weeks). 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Study funded by industry (Beecham Laboratories)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NABUMENTONE versus PLACEBO

Protocol outcome 1: Stiffness at <2 weeks
- Actual outcome: Morning stiffness at 3 weeks; Group 1: mean 1.3 (SD 2.32); n=15, Group 2: mean -0.2 (SD 1.73); n=12; Unclear Unclear Top=High is good outcome

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Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Stratified by DMARD use, groups stated to be similar for demographic statistics and severity of RA. ; Group 1 Number missing: 8, Reason: Unclear; Group 2 Number missing: 12, Reason: Unclear Protocol outcome 2: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: adverse events at 3 weeks; Group 1: 0/18, Group 2: 0/20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Stratified by DMARD use, groups stated to be similar for demographic statistics and severity of RA. ; Group 1 Number missing: 5, Reason: Unclear; Group 2 Number missing: 3, Reason: Unclear	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Vetter 1982[185]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=24)
Countries and setting	Conducted in Germany
Line of therapy	Mixed line
Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Hospitalised adults with at least 5/11 criteria for RA.Functional class I, II or III or stage 1 or stage 2 of Steinbrocker Progression Scale. Presence of at least 3 of the 4 following criteria: 1) at least 6 painful or tender joints on motion, 2) at least 3 swollen joints, 3) at least 45 minutes of morning stiffness, 4) sedimentation rate of 28mm/h or more.
Exclusion criteria	Pregnant or nursing women. People with significant hepatic, renal, cardiovascular or haematological disorders. People receiving systemic glucocorticoid, d-pencillamine, antimalrials, or investigational drugs within 6 months of beginning of study. People receiving intra-articular glucocorticoids, long-acting NSAIDs within 6 weeks of study. People receiving immunosuppressive therapy at any time.
Age, gender and ethnicity	Age - Mean (SD): Etodolac low: 59 (6), placebo low: 62 (4), etodolac high: 59 (8), placebo high: 59 (4). Gender (M:F): Define. Ethnicity: All Caucasian
Further population details	1. Age: Not applicable (Age range spans 65 year cut off).
Extra comments	Anti-rheumatic treatment stopped and participants instructed to return within 2 weeks after flare for inclusion in trial.
Indirectness of population	Serious indirectness: Participants required to have a history of positive response to previous treatment with on or more NSAIDs
Interventions	(n=16) Intervention 1: NSAIDs - etodolac. 8 participants on low dose: 25gm or 50mg or 100mg twice daily. 8 participants on high dose: 100gm or 200mg or 300mg twice daily. Fixed titration regimen. Dose levels increased after 1st and 2nd week. . Duration 4 weeks. Concurrent medication/care: No concomitant therapy permitted except for acetaminophen for pain. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Not applicable (4 weeks). 2. Route of administration: Oral 3. Within-class differences : Selective COX-2 inhibitors (n=8) Intervention 2: Placebo. No details. Duration 4 weeks. Concurrent medication/care: No concomitant

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	therapy permitted except for acetaminophen for pain. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Not applicable (4 weeks). 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Funding not stated (1 author from Auerbach Klinik and 2 authors from Ayerst Laboratories.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ETODOLAC versus PLACEBO

Protocol outcome 1: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation: adverse events at 4 weeks; Group 1: 0/15, Group 2: 0/2
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, height, weight, gender. Differences in terms of disease duration, Steinbrocker stage, ARA functional class. ; Group 1 Number missing: 1; Group 2 Number missing: 6
- Actual outcome: Discontinuation: inefficacy at 4 weeks; Group 1: 1/16, Group 2: 6/8
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, height, weight, gender. Differences in terms of disease duration, Steinbrocker stage, ARA functional class. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

ISBN: 978-1-4731-3003-6

Study	Weintraub 1977[190]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=19)
Countries and setting	Conducted in USA
Line of therapy	Mixed line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Participants with classical or definite RA. Met criteria for disease activity.
Exclusion criteria	Pregnant women, people with serious renal, hepatic, cardiovascular, neurologic disease. Demonstrable active ulcers.
Age, gender and ethnicity	Age - Mean (SD): Peroxicam 20mg group: 47 (11), peroxicam 30mg group: 50 (10), placebo group: 45 (15). Gender (M:F): Male: 9, Female: 10. Ethnicity: Not detailed
Further population details	1. Age: Not applicable (One participant was over 65 years old.).
Extra comments	. Participants could be taking aspirin, gold salts, or stable doses of glucocorticoids.
Indirectness of population	No indirectness
Interventions	(n=7) Intervention 1: Placebo. Regime matched with piroxicam. Duration 12 weeks. Concurrent medication/care: Continuing other medications. Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral (Tablets). 3. Within-class differences : Not applicable (n=12) Intervention 2: NSAIDs - piroxicam. 20mg or 30mg once per day. Duration 12 weeks. Concurrent medication/care: Continuing other medications. Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral (Tablets). 3. Within-class differences : Non-selective NSAIDs
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PIROXICAM versus PLACEBO

Protocol outcome 1: Adverse events: gastrointestinal effects at Longest time period reported

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- Actual outcome: Adverse events: gastrointestinal ulcers at 12 weeks; Group 1: 3/12, Group 2: 0/6 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Due to non-slective NSAID utilised without PPI treatment; Baseline details: Groups comparable for age, gender, duration of disease, walking speed, painful and swollen joint count, duration of stiffness, ARA class, presence of nodules, prednisone/gold therapy. ; Group 1 Number missing: 0; Group 2 Number missing: 1 Protocol outcome 2: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: adverse events at 12 weeks; Group 1: 4/12, Group 2: 0/6 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups comparable for age, gender, duration of disease, walking speed, painful and swollen joint count, duration of stiffness, ARA class, presence of nodules, prednisone/gold therapy. ; Group 1 Number missing: 0; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Weisman 1986[191]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=182)
Countries and setting	Conducted in USA
Line of therapy	Mixed line
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ARA criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged 21 to 65 years of age, definite or classical RA. Evidence of active disease during washout period. Active disease defined as: 1) at least 1 hour of morning stiffness, 2) at least 7 tender joints, 3) at least 7 swollen joints. Have been on aspirin or other NSAID to control RA symptoms.
Exclusion criteria	People with Significant concomitant disorders such as gastrointestinal, hermatological, metabolic, cardiovascular, renal or hepatic diseases. Those who had undergone a gastronomy or had a history of gastrointestinal bleeding. Pregnant or nursing women. Women of a child bearing age not using an acceptable contraceptive method. People who were hypersensitive to aspirin or other NSAIDs or with a history of noncompliance to drug regimens. People with a serum salicylate level of 10mg/dl or over during placebo/washout period.
Age, gender and ethnicity	Age - Mean (range): Diclofenac group: 51 (26-65), placebo group: 50 (21-65). Gender (M:F): Male: 42, Female: 116. Ethnicity: White: 146, other: 12
Further population details	1. Age: ≤65 years (All under 66 years of age.).
Extra comments	Study begins with 2 day to 4 week washout period under placebo.
Indirectness of population	No indirectness
Interventions	(n=89) Intervention 1: NSAIDs - diclofenac. 50mg 3 times per day. . Duration 6 weeks. Concurrent medication/care: No other anti-inflammatory or analgesic medication permitted. Concomitant use of gold or penicillamine permitted if dose had been stable for 6 months. Use of glucocorticoids permitted if dose had been stable for 3 months and did not exceed equivalent of 7.5mg/day prednisone. Acetaminophen permitted as a rescue analgesic. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (6 weeks). 2. Route of administration: Oral 3. Within-class differences : Non-selective NSAIDs (n=94) Intervention 2: Placebo. Identical appearing placebo tablets on the same regime as diclofenac. .

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	Duration 6 weeks. Concurrent medication/care: No other anti-inflammatory or analgesic medication permitted. Concomitant use of gold or penicillamine permitted if dose had been stable for 6 months. Use of glucocorticoids permitted if dose had been stable for 3 months and did not exceed equivalent of 7.5mg/day prednisone. Acetaminophen permitted as a rescue analgesic. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (6 weeks). 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Academic or government funding (Supported in party by the Arthritis Foundation Clinical Center grant, NIH Rheumatic Diseases Training Grant AM-07062-07, UCSD General Clinical Research Center Grant, NIH/Division of Research Resources grant RR-00827.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DICLOFENAC versus PLACEBO Protocol outcome 1: Drug continuation at Longest time period reported - Actual outcome: Discontinuation: inefficacy at 6 weeks; Group 1: 27/83, Group 2: 38/89 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for gender, age, race, body weight, duration of disease, ARA classification, use of other therapy. ; Group 1 Number missing: 6; Group 2 Number missing: 5 - Actual outcome: Discontinuation: adverse events at 6 weeks; Group 1: 2/58, Group 2: 1/51 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for gender, age, race, body weight, duration of disease, ARA classification, use of other therapy. ; Group 1 Number missing: 31; Group 2 Number missing: 42	
Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported; Adverse events: impaired renal function at Longest time period reported

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Study	Williams 2006[193]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=439)
Countries and setting	Conducted in Brazil, Canada, Mexico, USA; Setting: 131 investigators across 225 study sites.
Line of therapy	Mixed line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1987 ACR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People 18 years old and over with adult onset rheumatoid arthritis. Diagnosed at least 6 months prior to study. Functional capacity between I and III. Stable use of NSAIDs and functional capacity for 1 month. Flare state begun 2 to 7 days after discontinuation of NSAIDs, aspirin, celecoxib or within 4-7 days of discontinuation of oxaprozin and/or piroxicam or within 4 days of discontinuation of rofecoxib. Flare state is fair, poor or very poor on both the patient's and physician's global assessments of disease activity, >/=6 tender/painful joints and an increase of 2 tender/painful joints (or >/=20% increase in the number of swollen joints), >/=3 swollen joints with an increase of >/=2 swollen joints, (or >/=20% increase in number of swollen joints), Patients also required to experience >/=45 minutes of morning stiffness with an increase of >/=15 minutes for flare, or a measurement of >/=40mm on patient assessment of arthritic pain with an increase of 10mm or 20% for flare.
Exclusion criteria	Inflammatory arthritis other than RA, secondary non-inflammatory type of arthritis. Initiation or change of dose regimen for gold salts or antimalarials, within past 4 months, sulfasalazine, azathioprine, penicillamine, methotrexate, etanercept, leflunomide, combination therapies, antibiotics for RA within 12 weeks. Glucosamine/chondroitin within 4 weeks. Oral glucocorticoids within 4 weeks. Glucocorticoid injection within 8 weeks. Exposure to antineoplastic agents for RA within 12 weeks. Use of any non-selective NSAID within 48 hours or any analgesic within 24 hours. Aspirin treatment permitted. Diagnosed or treated for esophageal, gastric, pyloric channel, duodenal ulceration within 30 days. Use of lithium. Abnormal liver function test results, uncontrolled diabetes, hypertension, hypersensitivity of COX-2 inhibitors, lactose or conventional NSAIDs. Pregnant or breast feeding.
Age, gender and ethnicity	Age - Mean (SD): Naproxen group: 55 (13), placebo group: 58 (13). Gender (M:F): Male: 115, Female: 324. Ethnicity: White: 352, Hispanic: 56, Black: 27, Asian: 1, Other: 3
Further population details	1. Age: Not stated / Unclear (Age range not stated but likley to be participants spanning 65 year dividing line).
Indirectness of population	No indirectness

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Interventions	(n=219) Intervention 1: NSAIDs - naproxen . 500mg twice per day . Duration 12 weeks. Concurrent medication/care: NSAIDs or other analgesics discontinued. Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral (Tablets). 3. Within-class differences : Selective COX-2 inhibitors (n=220) Intervention 2: Placebo. 1 placebo tablet twice per day. Duration 12 weeks. Concurrent medication/care: NSAIDs or other analgesics discontinued. Indirectness: No indirectness Further details: 1. Duration of intervention use: Long term use (>6 weeks) (12 weeks). 2. Route of administration: Oral (Tablet). 3. Within-class differences : Not applicable
Funding	Study funded by industry (Study sponsored by Pharmacia Corporation and Pfizer Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NAPROXEN versus PLACEBO

Protocol outcome 1: Function at >6 weeks
- Actual outcome: Patients' assessments of physical function at 12 weeks; Group 1: mean -0.4 (SD 1.33); n=219, Group 2: mean -0.1 (SD 1.33); n=220
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, weight, race, gender, RA duration, medical history, use of other medications. ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Adverse events: mortality at Longest time period reported
- Actual outcome: Adverse events: mortality at 12 weeks; Group 1: 0/219, Group 2: 0/220
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, weight, race, gender, RA duration, medical history, use of other medications. ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Adverse events: cardiac and vascular events at Longest time period reported
- Actual outcome: Adverse events: serious myocardial, endocardial, or pericardial and valve disorders or serious respiratory disorders or serious cerebrovascular disorders at 12 weeks; Group 1: 2/219, Group 2: 3/220
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Groups similar for age, weight, race, gender, RA duration, medical history, use of other medications. ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at <2 weeks; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: impaired renal function at Longest time period reported; Drug continuation at Longest time period reported

ISBN: 978-1-4731-3003-6

Study	Wong 2007[194]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=25)
Countries and setting	Conducted in United Kingdom; Setting: Outpatient clinic
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ACR criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with RA with unchanged DMARD dosage for at least 4 weeks and ceased NSAIDs or COX-2 drugs for at least 2 weeks before screening visit.
Exclusion criteria	Known ischaemic heart disease, cerebrovascular disease, peripheral vascular disease, diabetes mellitus, gastritis, intolerance to anti-inflammatory medications, or taking aspirin, prenisolone, or statins. Surgery of parenteral corticosteriod injections in the preceding 4 weeks.
Recruitment/selection of patients	Consecutive consenting patients recruited from outpatient clinics at Guy's and St Thomas' Hospitals
Age, gender and ethnicity	Age - Mean (SD): Placebo - 52 (10), Indomethacin - 52 (12) (completers). Gender (M:F): 7:16 (completers). Ethnicity: NR
Further population details	1. Age: Not applicable
Extra comments	. Below data based on study completers RF+ : Placebo - 67%, Indomethacin - 82% Disease duration (years): Placebo - 8 (8), Indomethacin - 8 (8) DAS: Placebo - 4.1 (1.1), Indomethacin - 3.6 (1.3) HAQ: Placebo - 0.94 (0.96), Indomethacin - 1.05 (1.15) MTX use: Placebo - 58%, Indomethacin - 82% Leflunomide use: Placebo - 33%, Indomethacin - 0%
Indirectness of population	No indirectness
Interventions	(n=13) Intervention 1: NSAIDs - indomethacin. 75 mg twice daily. Duration 2 weeks. Concurrent medication/care: DMARDs. All other NSAIDs including COX-2, as well as aspirin, prednisolone and statins were prohibited during study. . Indirectness: Serious indirectness; Indirectness comment: No mention of co-prescription with PPI Further details: 1. Duration of intervention use: Short term use (<2 weeks) 2. Route of administration: Oral 3.

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	Within-class differences: Non-selective NSAIDs (n=12) Intervention 2: Placebo. Placebo tablet. Duration 2 weeks. Concurrent medication/care: DMARDs. Use of NSAIDs including COX-2 drugs, as well as aspirin, prednisolone, and statins was prohibited during the study. . Indirectness: No indirectness Further details: 1. Duration of intervention use: Short term use (<2 weeks) 2. Route of administration: Oral 3. Within-class differences : Not applicable
Funding	Academic or government funding (Supported by Arthritis Foundation of Australia and Friends of Guy's Hospital, London, UK)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INDOMETHACIN versus PLACEBO

Protocol outcome 1: Adverse events: impaired renal function at Longest time period reported
- Actual outcome: Creatinine at 2 weeks; Group 1: mean 78 umol/L (SD 7); n=11, Group 2: mean 68 umol/L (SD 5); n=12
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - NB: different creatinine values reported for 'pre-treatment' and 'baseline' (but similar between groups in both instances); Indirectness of outcome: No indirectness ; Baseline details: See pop panel. Differences in % RF+, % smokers. Similar at baseline for outcome (2 umol/L difference); Blinding details: 'Double blind'; Group 1 Number missing: 2, Reason: Withdrawal due to dyspepsia; Group 2 Number missing: 0

Protocol outcome 2: Drug continuation at Longest time period reported
- Actual outcome: Discontinuation: adverse events at 2 weeks; Group 1: 2/13, Group 2: 0/12
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: See pop panel. Differences in % RF+, % smokers. ; Blinding details: 'Double blind'; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Pain at >6 weeks; Pain at <2 weeks; Quality of life at >6 weeks; Quality of life at <2 weeks; Stiffness at >6 weeks; Stiffness at <2 weeks; Function at >6 weeks; Function at <2 weeks; Adverse events: mortality at Longest time period reported; Adverse events: gastrointestinal effects at Longest time period reported; Adverse events: cardiac and vascular events at Longest time period reported

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Appendix E: Forest plots

E.1 Paracetamol plus opioid plus NSAID versus NSAID

Figure 2: Change in pain (VAS) Scale from: 0 to 100.

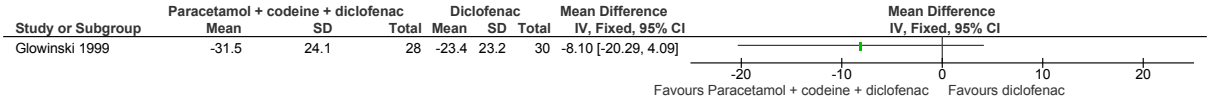


Figure 3: Discontinuation: inefficacy

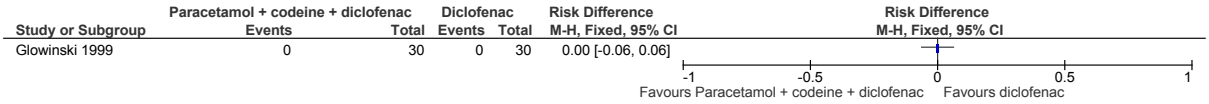
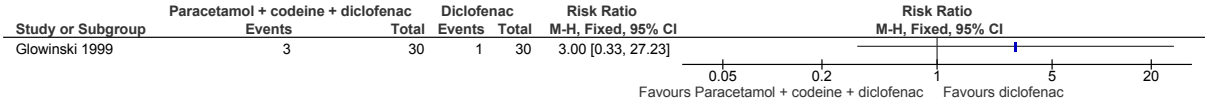


Figure 4: Discontinuation: adverse events



E.2 NSAID versus paracetamol

Figure 5: Change in pain: Patient rated (none=1, mild=2, moderate=3, severe=4, very severe=5). Scale from: 1 to 5.

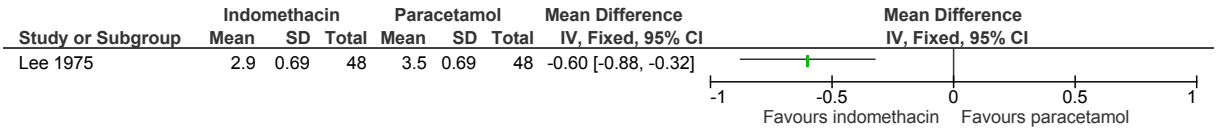


Figure 6: Discontinuation: adverse events

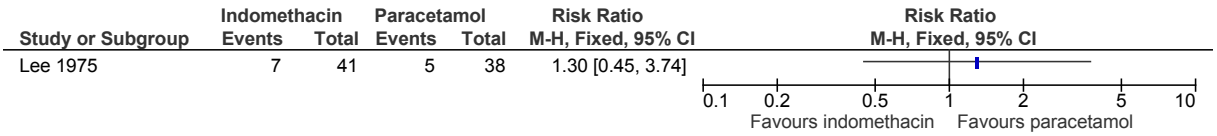
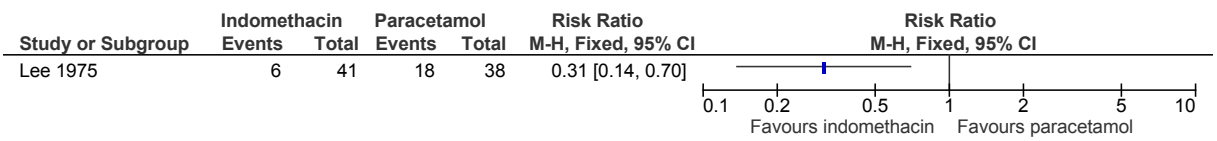


Figure 7: Discontinuation: inefficacy



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E.3 NSAID versus placebo

Figure 8: Pain (change score) (VAS) Scale from: 0 to 100: ≤2 weeks

Study or Subgroup	NSAID Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kawai 2010	-15.7	16	338	-13.2	16.4	338	100.0%	-2.50 [-4.94, -0.06]
Total (95% CI)			**338**			**338**	**100.0%**	**-2.50 [-4.94, -0.06]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.01 (P = 0.04)

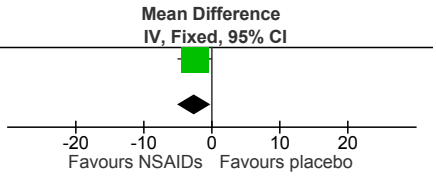

Figure 9: Pain (change or final) (VAS) Scale from: 0 to 100: >2 weeks to ≤ 6 weeks

Study or Subgroup	NSAID Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bickham 2016	-28.25	26.34	818	-20.26	20.95	118	87.3%	-7.99 [-12.18, -3.80]
Hunter 1996	42	21.9	38	56.5	25.7	35	12.7%	-14.50 [-25.50, -3.50]
Total (95% CI)			**856**			**153**	**100.0%**	**-8.81 [-12.73, -4.90]**

Heterogeneity: Chi² = 1.18, df = 1 (P = 0.28); I² = 15%
Test for overall effect: Z = 4.41 (P < 0.0001)

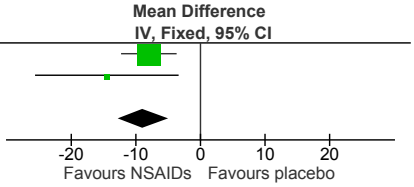

Figure 10: Pain (change score) (VAS) Scale from: 0 to 100: >6 weeks

Study or Subgroup	NSAID Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Furst (diclofenac) 2002	-25.4	28.25	180	-14.4	27.94	87	10.6%	-11.00 [-18.18, -3.82]
Furst (meloxicam) 2002	-23.56	28.13	535	-14.4	27.94	87	12.7%	-9.16 [-15.50, -2.82]
Geusens 2004	-24.1	23.83	279	-18.8	24.71	284	21.6%	-5.30 [-9.31, -1.29]
Gibofsky 2007	-30.8	28.6	166	-14.9	29.12	169	13.1%	-15.90 [-22.08, -9.72]
Greenwald 2011	-23.01	23.36	140	-16.79	23.37	161	16.0%	-6.22 [-11.51, -0.93]
Simon (celecoxib) 1999	-18.57	28.28	693	-9.3	30.4	116	13.9%	-9.27 [-15.19, -3.35]
Simon (naproxen) 1999	-16.9	27	225	-9.3	30.4	116	12.1%	-7.60 [-14.16, -1.04]
Total (95% CI)			**2218**			**1020**	**100.0%**	**-8.76 [-11.48, -6.04]**

Heterogeneity: Tau² = 4.70; Chi² = 9.30, df = 6 (P = 0.16); I² = 36%
Test for overall effect: Z = 6.32 (P < 0.00001)

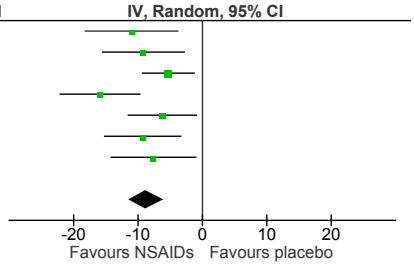

Figure 11: Pain (change or final score): ≤2 weeks: varying scales

Study or Subgroup	NSAID Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Anonymous (ibuprofen) 1980	2.83	0.7	40	3.31	0.7	14	16.0%	-0.68 [-1.30, -0.05]
Anonymous (naproxen) 1980	2.69	0.7	122	3.31	0.7	14	17.1%	-0.88 [-1.44, -0.32]
Anonymous (sulindac) 1980	2.83	0.71	81	3.31	0.7	14	16.9%	-0.67 [-1.25, -0.10]
Ballesteros 1990	0.86	0.44	29	1.86	0.44	29	15.3%	-2.24 [-2.91, -1.58]
Lee (indomethacin) 1978	2.79	0.66	44	3.39	0.64	21	17.4%	-0.91 [-1.45, -0.36]
Lee (naproxen) 1978	2.76	0.65	42	3.39	0.64	21	17.3%	-0.96 [-1.51, -0.41]
Total (95% CI)			**358**			**113**	**100.0%**	**-1.04 [-1.47, -0.61]**

Heterogeneity: Tau² = 0.19; Chi² = 15.95, df = 5 (P = 0.007); I² = 69%
Test for overall effect: Z = 4.78 (P < 0.00001)

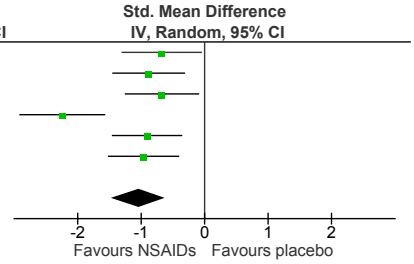

Figure 12: Stiffness (change score) in minutes: ≤ 6 weeks

Study or Subgroup	NSAID Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Lanier 1987	-1.3	1.56	61	-0.4	1.41	50	19.9%	-0.60 [-0.98, -0.22]
Lemmel 1997	-47	84	321	-15	94	147	75.4%	-0.37 [-0.56, -0.17]
Turner 1987	-1.3	2.32	15	0.2	1.73	12	4.7%	-0.70 [-1.48, 0.09]
Total (95% CI)			**397**			**209**	**100.0%**	**-0.43 [-0.60, -0.26]**

Heterogeneity: Chi² = 1.60, df = 2 (P = 0.45); I² = 0%
Test for overall effect: Z = 4.92 (P < 0.00001)

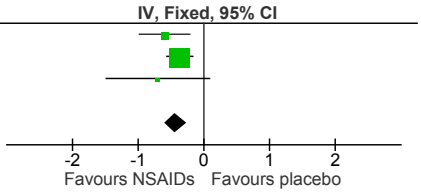

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Figure 13: Stiffness (change score) in minutes: >6 weeks

Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Gibofsky 2007	-4.4	6.44	166	-1	6.37	169	23.4%	-0.53 [-0.75, -0.31]
Greenwald 2011	-44.18	75.44	600	-30	97.11	161	28.4%	-0.18 [-0.35, -0.00]
Simon 1999 (cele)	-125.5	443.3	693	8.9	481.8	116	25.6%	-0.30 [-0.50, -0.10]
Simon 1999 (naprox)	-90.1	424.5	225	8.9	481.8	116	22.7%	-0.22 [-0.45, 0.00]
Total (95% CI)			**1684**			**562**	**100.0%**	**-0.30 [-0.45, -0.15]**

Heterogeneity: Tau² = 0.01; Chi² = 6.65, df = 3 (P = 0.08); I² = 55%
Test for overall effect: Z = 3.91 (P < 0.0001)

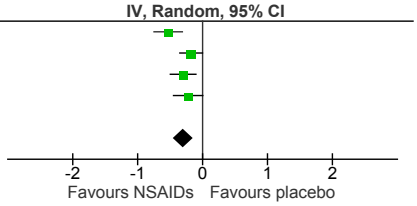

Figure 14: Stiffness (final value) Scale from: 0 to 3: ≤2 weeks

Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Anonymous 1980 (ibupro)	3	0.76	40	3.17	0.76	13	16.2%	-0.22 [-0.85, 0.41]
Anonymous 1980 (naprox)	2.6	0.77	122	3.17	0.76	13	16.8%	-0.74 [-1.32, -0.16]
Anonymous 1980 (sulindac)	2.8	0.77	81	3.17	0.76	13	16.7%	-0.48 [-1.07, 0.11]
Ballesteros 1990	1.17	0.47	29	1.96	0.18	29	15.8%	-2.19 [-2.85, -1.53]
Lee 1978 (indo)	2.62	0.6	44	3.21	0.64	21	17.2%	-0.95 [-1.50, -0.40]
Lee 1978 (naprox)	2.77	0.65	42	3.21	0.64	21	17.3%	-0.67 [-1.21, -0.13]
Total (95% CI)			**358**			**110**	**100.0%**	**-0.86 [-1.37, -0.36]**

Heterogeneity: Tau² = 0.30; Chi² = 21.94, df = 5 (P = 0.0005); I² = 77%
Test for overall effect: Z = 3.37 (P = 0.0007)

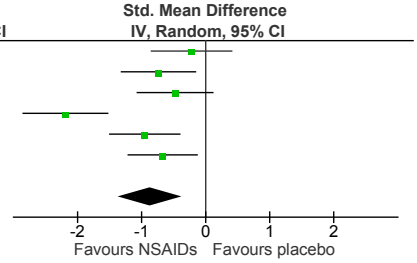

Figure 15: Function (change score) (HAQ) Scale from: 0 to 3: >6 weeks

Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Furst 2002 (diclo)	-0.32	0.54	180	-0.24	0.53	87	8.5%	-0.08 [-0.22, 0.06]
Furst 2002 (melox)	-0.35	0.53	535	-0.24	0.53	87	10.9%	-0.11 [-0.23, 0.01]
Geusens 2004	-0.3	0.58	279	-0.2	0.54	284	18.4%	-0.10 [-0.19, -0.01]
Gibofsky 2007	-0.4	0.52	166	-0.2	0.52	169	12.7%	-0.20 [-0.31, -0.09]
Greenwald 2011	-0.318	0.444	600	-0.14	0.45	161	25.8%	-0.18 [-0.26, -0.10]
Simon 1999 (cele)	-0.2	0.56	693	-0.1	0.61	116	11.2%	-0.10 [-0.22, 0.02]
Simon 1999 (naprox)	-0.2	0.45	225	-0.1	0.61	116	10.0%	-0.10 [-0.23, 0.03]
Williams 2006	-0.4	1.33	219	-0.1	1.33	220	2.5%	-0.30 [-0.55, -0.05]
Total (95% CI)			**2897**			**1240**	**100.0%**	**-0.14 [-0.18, -0.10]**

Heterogeneity: Chi² = 6.12, df = 7 (P = 0.53); I² = 0%
Test for overall effect: Z = 6.78 (P < 0.00001)

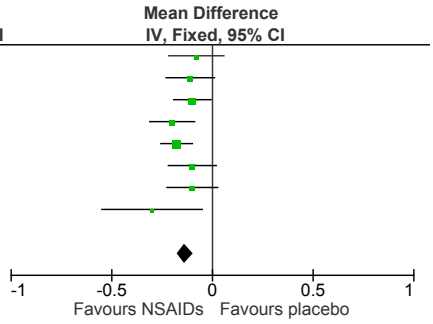

Figure 16: Function (change score): Scale from: 0 to 3: ≤2 weeks

Study or Subgroup	NSAID Mean	NSAID SD	NSAID Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Ballesteros 1990	1.1	0.55	29	1.93	0.37	29		-0.83 [-1.07, -0.59]

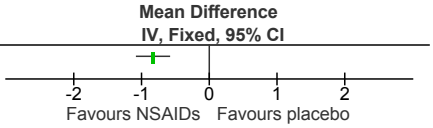

Figure 17: Adverse events: mortality

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Furst 2002 (diclo)	0	181	0	89		Not estimable
Furst 2002 (melox)	0	536	0	89		Not estimable
Geusens 2002	0	142	1	289	47.0%	0.23 [0.00, 14.56]
Gibofsky 2007	0	150	1	163	53.0%	0.15 [0.00, 7.41]
Matsumoto 2002 (etori)	0	323	0	162		Not estimable
Matsumoto 2002 (naprox)	0	170	0	162		Not estimable
Williams 2006	0	219	0	220		Not estimable
Total (95% CI)		**1721**		**1174**	**100.0%**	**0.18 [0.01, 3.12]**
Total events	0		2			

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.18 (P = 0.24)

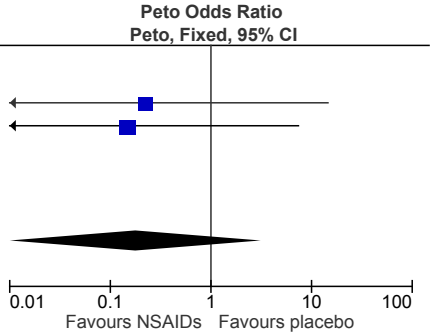

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Figure 18: Adverse events: gastrointestinal effects

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
Collantes 2002 (etori)	1	295	0	121	11.3%	0.00 [-0.01, 0.02]
Collantes 2002 (naprox)	0	151	0	121	11.2%	0.00 [-0.01, 0.01]
Furst 2002 (diclo)	0	181	0	89	10.7%	0.00 [-0.02, 0.02]
Furst 2002 (melox)	4	536	0	88	10.7%	0.01 [-0.01, 0.02]
Geusens 2002	4	135	0	276	8.1%	0.03 [-0.00, 0.06]
Kirchheiner 1976 (diclo)	0	52	0	20	3.2%	0.00 [-0.07, 0.07]
Kirchheiner 1976 (indo)	0	49	0	19	3.0%	0.00 [-0.07, 0.07]
Lemmel 1997	1	321	1	147	11.2%	-0.00 [-0.02, 0.01]
Matsumoto 2002 (etori)	0	323	0	162	12.0%	0.00 [-0.01, 0.01]
Matsumoto 2002 (naprox)	1	170	0	161	10.9%	0.01 [-0.01, 0.02]
Mehta 1992	3	30	0	30	1.3%	0.10 [-0.02, 0.22]
Simon 1999 (cele)	23	423	2	50	4.1%	0.01 [-0.04, 0.07]
Simon 1999 (naprox)	36	137	2	49	2.1%	0.22 [0.13, 0.31]
Weintraub 1977	3	12	0	6	0.2%	0.25 [-0.06, 0.56]
Total (95% CI)		**2815**		**1339**	**100.0%**	**0.01 [-0.00, 0.03]**
Total events	76		5			

Heterogeneity: Tau² = 0.00; Chi² = 66.39, df = 13 (P < 0.00001); I² = 80%
Test for overall effect: Z = 1.47 (P = 0.14)

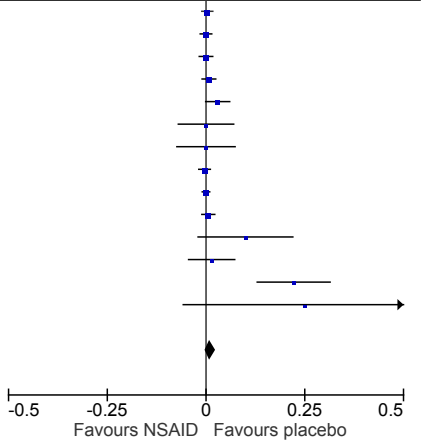

Figure 19: Adverse events: cardiac and vascular events

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bensen 2002	1	226	0	222	9.0%	7.26 [0.14, 365.91]
Bickham 2016	0	1270	0	116		Not estimable
Geusens 2002	0	131	0	276		Not estimable
Lemmel 1997	3	321	1	147	30.7%	1.35 [0.16, 11.22]
Matsumoto 2002 (etori)	2	323	0	162	15.9%	4.50 [0.24, 85.30]
Matsumoto 2002 (naprox)	0	170	0	162		Not estimable
Williams 2006	2	219	3	220	44.4%	0.67 [0.12, 3.90]
Total (95% CI)		**2660**		**1305**	**100.0%**	**1.39 [0.43, 4.51]**
Total events	8		4			

Heterogeneity: Chi² = 1.95, df = 3 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.55 (P = 0.58)

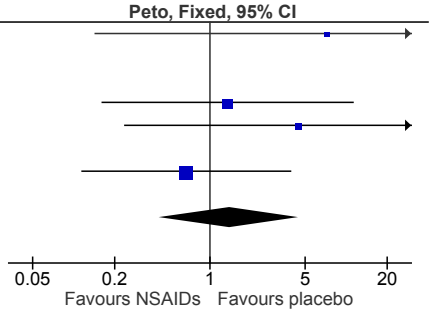

Figure 20: Adverse events: impaired renal function

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Fixed, 95% CI
Geusens 2002	0	131	0	276	100.0%	0.00 [-0.01, 0.01]
Total (95% CI)		**131**		**276**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

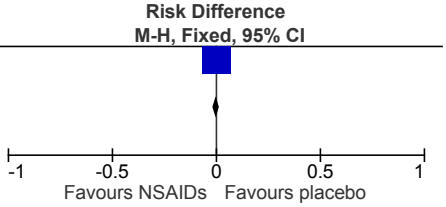

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Figure 21: Discontinuation: adverse events

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anonymous 1967	10	66	7	60	3.6%	1.30 [0.53, 3.20]
Anonymous 1980 (ibupro)	3	40	3	14	2.2%	0.35 [0.08, 1.54]
Anonymous 1980 (naprox)	11	122	2	13	1.8%	0.59 [0.15, 2.36]
Anonymous 1980 (sulindac)	8	81	2	13	1.7%	0.64 [0.15, 2.69]
Bensen 2002	13	226	10	222	4.9%	1.28 [0.57, 2.85]
Bickham 2016	16	1286	2	118	1.8%	0.73 [0.17, 3.15]
Bobrove 1983	10	158	3	45	2.3%	0.95 [0.27, 3.30]
Collantes 2002 (etori)	8	302	5	126	3.5%	0.67 [0.22, 2.00]
Collantes 2002 (naprox)	4	155	5	126	2.7%	0.65 [0.18, 2.37]
Doreen 1978	1	21	1	22	0.5%	1.05 [0.07, 15.69]
Durrigl 1975	0	17	0	17		Not estimable
Edwards 1983	0	5	1	2	1.0%	0.17 [0.01, 2.98]
Furst 2002 (diclo)	20	181	7	88	4.6%	1.39 [0.61, 3.16]
Furst 2002 (melox)	47	536	7	89	5.9%	1.11 [0.52, 2.39]
Geusens 2002	11	142	13	289	4.2%	1.72 [0.79, 3.75]
Geusens 2004	30	222	20	178	10.9%	1.20 [0.71, 2.04]
Gibofsky 2007	16	166	8	170	3.9%	2.05 [0.90, 4.66]
Gordon 1983	0	4	0	2		Not estimable
Greenwald 2011	24	600	4	161	3.1%	1.61 [0.57, 4.57]
Hawkey 2003	22	208	9	204	4.4%	2.40 [1.13, 5.08]
Hunter 1996	3	32	4	23	2.3%	0.54 [0.13, 2.18]
Jacob 1983	5	45	4	38	2.1%	1.06 [0.30, 3.65]
Kawai 2010	9	338	7	338	3.4%	1.29 [0.48, 3.41]
Kirchheiner 1976 (diclo)	5	57	2	22	1.4%	0.96 [0.20, 4.61]
Kirchheiner 1976 (indo)	8	57	2	21	1.4%	1.47 [0.34, 6.39]
Lanier 1987	0	70	0	69		Not estimable
Lavie 1990	0	9	0	10		Not estimable
Lee 1978 (indo)	6	44	1	11	0.8%	1.50 [0.20, 11.21]
Lee 1978 (naprox)	4	39	2	12	1.5%	0.62 [0.13, 2.96]
Lemmel 1997	14	321	7	147	4.7%	0.92 [0.38, 2.22]
Matsumoto 2002 (etori)	12	323	5	161	3.3%	1.20 [0.43, 3.34]
Matsumoto 2002 (naprox)	9	170	6	162	3.0%	1.43 [0.52, 3.93]
Simon 1998	11	245	5	85	3.6%	0.76 [0.27, 2.13]
Simon 1999 (cele)	42	491	6	56	5.3%	0.80 [0.36, 1.79]
Simon 1999 (naprox)	12	150	5	56	3.6%	0.90 [0.33, 2.43]
Turner 1987	0	18	0	20		Not estimable
Vetter 1982	0	15	0	2		Not estimable
Weisman 1986	2	58	1	51	0.5%	1.76 [0.16, 18.83]
Wong 2007	2	13	0	12	0.3%	4.64 [0.25, 87.91]
Total (95% CI)		**7033**		**3255**	**100.0%**	**1.17 [0.98, 1.40]**
Total events	398		166			

Heterogeneity: Chi² = 20.42, df = 32 (P = 0.94); I² = 0%
Test for overall effect: Z = 1.74 (P = 0.08)

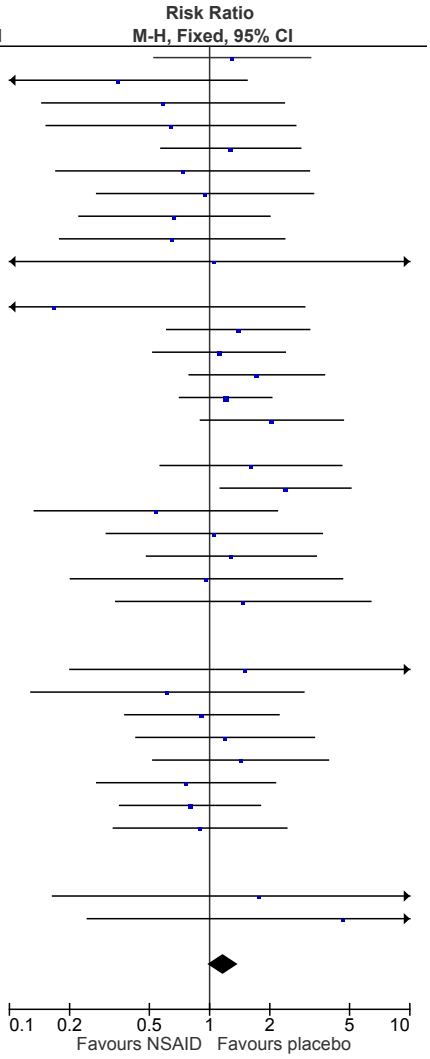

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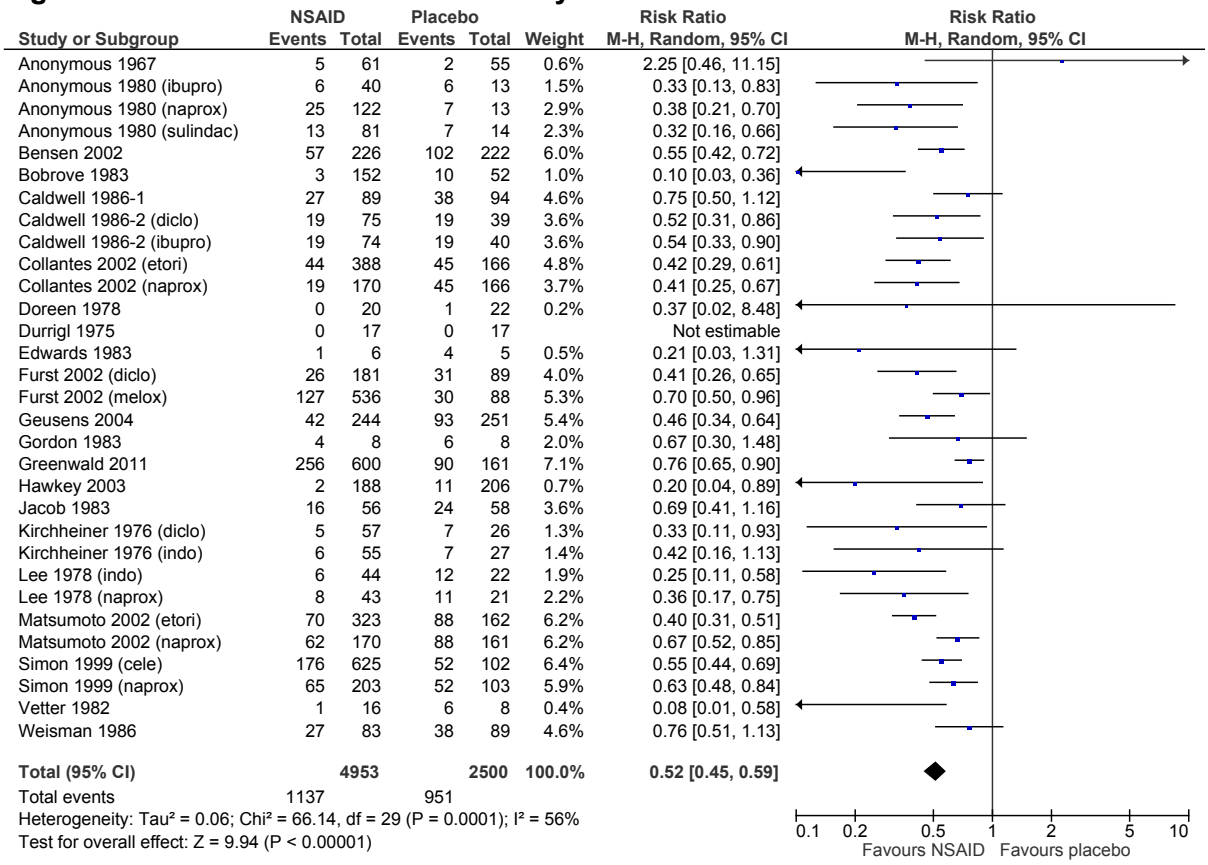
Figure 22: Discontinuation: inefficacy



E.4 Tricyclic antidepressants versus placebo

Figure 23: Discontinuation: adverse events

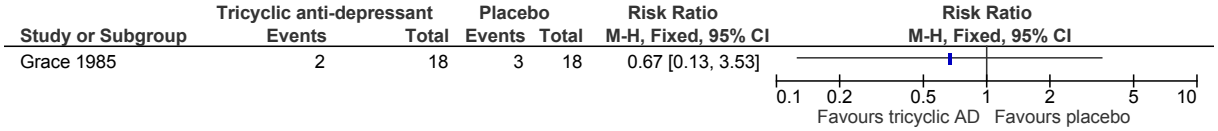
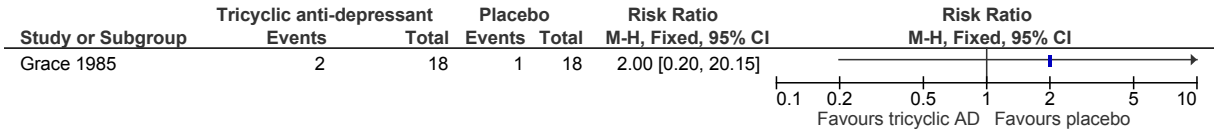


Figure 24: Discontinuation: inefficacy



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E.5 Paracetamol plus opioid versus placebo

Figure 25: Pain (final score) (VAS) Scale from: 0 to 100

Study or Subgroup	Opioid + paracetamol Mean [mm]	SD [mm]	Total	Placebo Mean [mm]	SD [mm]	Total	Mean Difference IV, Fixed, 95% CI [mm]
Lee 2006	47.23	19.96	201	53.81	16.59	66	-6.58 [-11.44, -1.72]

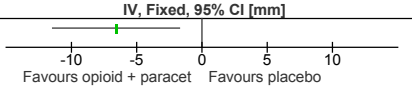


Figure 26: Function via common daily activities score (1 of 8 categories of HAQ disability index) Scale from: 0 to 3

Study or Subgroup	Opioid + paracetamol Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Lee 2006	1.75	0.97	201	1.89	0.94	66	-0.14 [-0.40, 0.12]

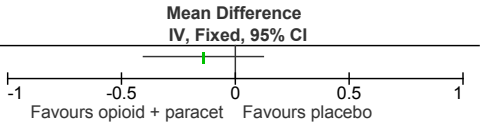


Figure 27: Discontinuation: adverse events

Study or Subgroup	Opioid + paracetamol Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Boureau 1991	2	20	2	20	44.7%	1.00 [0.16, 6.42]
Lee 2006	39	201	2	66	55.3%	6.40 [1.59, 25.80]
Total (95% CI)		**221**		**86**	**100.0%**	**2.79 [0.42, 18.35]**
Total events	41		4			

Heterogeneity: Tau² = 1.16; Chi² = 2.66, df = 1 (P = 0.10); I² = 62%
Test for overall effect: Z = 1.07 (P = 0.29)

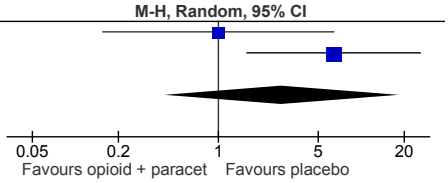
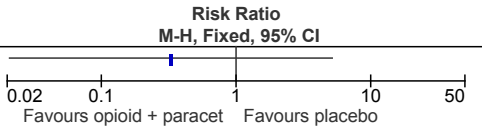


Figure 28: Discontinuation: inefficacy

Study or Subgroup	Opioid + paracetamol Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
Lee 2006	1	201	1	66	0.33 [0.02, 5.18]



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Appendix F:GRADE tables

Table 13: Clinical evidence summary: Paracetamol plus opioid plus NSAID versus NSAID

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol + opioid + NSAID	NSAID	Relative (95% CI)	Absolute		
Change in pain score (measured with: Patient rated on horizontal 100mm VAS; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28	30	-	MD 8.1 lower (20.29 lower to 4.09 higher)	⊕⊕OO LOW	CRITICAL
Discontinuation: inefficacy												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/30 (0%)	0/30 (0%)	See comment[4]	0 fewer per 1000 (from 60 fewer to 60 more)[3]	⊕⊕⊕O MODERATE	IMPORTANT
Discontinuation: adverse events												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/30 (10%)	1/30 (3.3%)	RR 3 (0.33 to 27.23)	67 more per 1000 (from 22 fewer to 874 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

[3] Absolute effect calculated using risk difference

[4] Zero events in both treatment groups and no relative effect could be calculated

Table 14: Clinical evidence summary: NSAID versus paracetamol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAID	Paracetamol	Relative (95% CI)	Absolute		
Pain score (measured with: Patient rated (none=1, mild=2, moderate=3, severe=4, very severe=5); range of scores: 1-5; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48	48	-	MD 0.6 lower (0.88 to 0.32 lower)	⊕OOO VERY	CRITICAL

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											LOW	
Discontinuation: adverse events												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/41 (17.1%)	5/38 (13.2%)	RR 1.3 (0.45 to 3.74)	39 more per 1000 (from 72 fewer to 361 more)	⊕OOO VERY LOW	IMPORTANT
Discontinuation: inefficacy												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/41 (14.6%)	18/38 (47.4%)	RR 0.31 (0.14 to 0.7)	327 fewer per 1000 (from 142 fewer to 407 fewer)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Table 15: Clinical evidence summary: NSAID versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NSAID v placebo**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain : (follow-up 2 weeks; measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	338	338	-	MD 2.5 lower (4.94 to 0.06 lower)	⊕⊕⊕O MODERATE	CRITICAL
Pain: >2 weeks to (follow-up mean 5 weeks; measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	856	153	-	MD 8.81 lower (12.73 to 4.9 lower)	⊕⊕OO LOW	CRITICAL
Pain: >6 weeks (follow-up mean 14 weeks; measured with: VAS; range of scores: 0-100; Better indicated by lower values)												
7	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2218	1020	-	MD 8.76 lower (11.48 to 6.04 lower)	⊕⊕OO LOW	CRITICAL
Pain: (follow-up mean 2 weeks; measured with: Varying scales: Patient Global Assessment of Pain, pain intensity on a 5 point scale by the physician, subjective rating scale converted to 5 point numerical result; Better indicated by lower values)												
6	randomised trials	very serious[1]	serious[4]	no serious indirectness	no serious imprecision	none	358	113	-	SMD 1.04 lower (1.47 to 0.61 lower)	⊕OOO VERY LOW	CRITICAL

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Stiffness (final value): (follow-up mean 2 weeks; range of scores: 0-3; Better indicated by lower values)												
6	randomised trials	very serious[1]	serious[3]	no serious indirectness	serious[2]	none	358	110	-	MD 0.15 lower (0.25 to 0.06 lower)[4]	⊕OOO VERY LOW	IMPORTANT
Stiffness: >2 weeks to (follow-up mean 3 weeks; measured with: Change score in minutes: ; Better indicated by lower values)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	397	209	-	MD 40.42 lower (56.4 to 24.44 lower)	⊕⊕OO LOW	IMPORTANT
Stiffness: >6 weeks (follow-up mean 12 weeks; measured with: Change score in minutes; Better indicated by lower values)												
4	randomised trials	serious[1]	serious[3]	no serious indirectness	no serious imprecision	none	1684	562	-	MD 29.13 lower (43.7 to 14.57 lower)[5]	⊕⊕OO LOW	IMPORTANT
Function: >6 weeks (follow-up mean 12 weeks; measured with: HAQ; range of scores: 0-3; Better indicated by lower values)												
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2897	1240	-	MD 0.14 lower (0.18 to 0.1 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Function: (follow-up 2 weeks; measured with: 0 = normal activity, 1 = normal activity with pain, 2 = limited activity, 3 = disability; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29	29	-	MD 0.83 lower (1.07 to 0.59 lower)	⊕⊕OO LOW	IMPORTANT
Adverse events: mortality (follow-up mean 12 weeks)												
7	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/1721 (0%)	2/1174 (0.17%)	Peto OR 0.18 (0.01 to 3.12)	0 fewer per 1000 (from 10 fewer to 0 more)[7]	⊕OOO VERY LOW	IMPORTANT
Adverse events: gastrointestinal effects (follow-up mean 10 weeks)												
14	randomised trials	very serious[1]	serious[2]	serious[6]	no serious imprecision	none	81/2815 (2.9%)	10/1343 (0.74%)	RR 2.23 (1.31 to 3.79)	9 more per 1000 (from 2 more to 21 more)	⊕OOO VERY LOW	IMPORTANT
Adverse events: cardiac and vascular events (follow-up mean 10 weeks)												
7	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/2660 (0.3%)	4/1305 (0.31%)	Peto OR 1.39 (0.43 to 4.51)	0 more per 1000 (from 0 fewer to 10 more)[7]	⊕OOO VERY LOW	IMPORTANT
Adverse events: impaired renal function (follow-up 12 weeks)												

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1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/131 (0%)	0/276 (0%)	Not estimable[8]	0 fewer per 1000 (from 10 more to 10 more)[7]	⊕⊕OO LOW	IMPORTANT
Discontinuation: adverse events (follow-up mean 10 weeks)												
39	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	398/7033 (5.7%)	166/3255 (5.1%)	RR 1.17 (0.98 to 1.4)	9 more per 1000 (from 1 fewer to 20 more)	⊕OOO VERY LOW	IMPORTANT
Discontinuation: inefficacy (follow-up mean 8 weeks)												
31	randomised trials	serious[1]	serious[3]	no serious indirectness	no serious imprecision	none	1137/4953 (23%)	951/2500 (38%)	RR 0.52 (0.45 to 0.59)	183 fewer per 1000 (from 156 fewer to 209 fewer)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment for heterogeneity. Not explained by subgroup analysis.
[4] Scores estimated using a standardised mean difference of -0.86 (-1.37 to -0.36)
[5] Scores estimated using a standardised mean difference of -0.30 (-0.45 to -0.15)
[6] No requirement for protein pump inhibitor (PPI) treatment in non-selective NSAID studies led to gastrointestinal adverse event outcomes to be considered indirect evidence
[7] Absolute effect calculated using risk difference
[8] Zero events in both groups and relative effect could not be calculated

Table 16: Clinical evidence summary: Tricyclic antidepressants versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Tricyclic anti-depressants**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Discontinuation: adverse events (follow-up 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/18 (11.1%)	3/18 (16.7%)	RR 0.67 (0.13 to 3.53)	55 fewer per 1000 (from 145 fewer to 422 more)	⊕OOO VERY LOW	IMPORTANT
Discontinuation: inefficacy (follow-up 12 weeks)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/18 (11.1%)	1/18 (5.6%)	RR 2 (0.2 to 20.15)	56 more per 1000 (from 44 fewer to 1000 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

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Table 17: Clinical evidence summary: Paracetamol plus opioid versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Opioid + paracetamol	Placebo	Relative (95% CI)	Absolute		
Discontinuation: adverse events (follow-up 1 weeks)												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	41/221 (18.6%)	6.5%	RR 4.25 (1.43 to 12.62)	211 more per 1000 (from 28 more to 755 more)	⊕⊕OO LOW	IMPORTANT
Pain score (follow-up 1 weeks; measured with: 100mm VAS; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	201	66	-	MD 6.58 lower (11.44 to 1.72 lower)	⊕OOO VERY LOW	CRITICAL
Common daily activities score (follow-up 1 weeks; measured with: Health Assessment Questionnaire[4]; range of scores: 0-3; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	201	66	-	MD 0.14 lower (0.4 lower to 0.12 higher)	⊕OOO VERY LOW	IMPORTANT
Discontinuation: inefficacy (follow-up 1 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/201 (0.5%)	1/66 (1.5%)	RR 0.33 (0.02 to 5.18)	10 fewer per 1000 (from 15 fewer to 63 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Heterogeneity, I2=50%, p=0.04, unexplained by subgroup analysis.
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Not the overall HAQ score. Score for common daily activities domain only.

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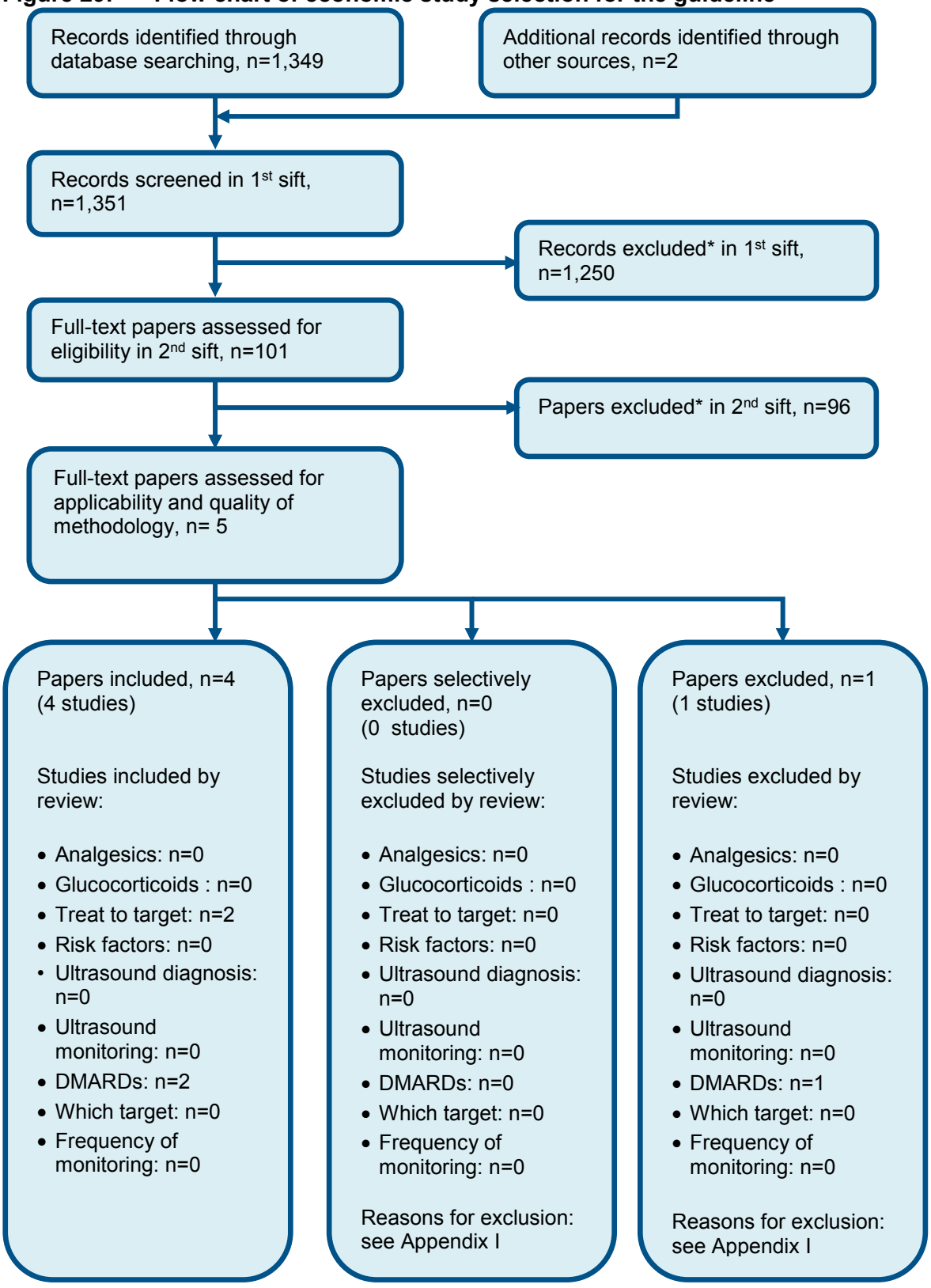
Appendix G: Health economic evidence selection

Figure 29: Flow chart of economic study selection for the guideline



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** Non-relevant population, intervention, comparison, design or setting; non-English language*

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Appendix H: Health economic evidence tables

None.

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Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 18: Studies excluded from the clinical review

Study	Exclusion reason
Aarons 1983[1]	Incorrect study design
Alexander 1975[3]	Crossover study
Al-sharkawi 1984[2]	Mixed population
Alvan 1981[4]	Crossover study
Anderson 1974[5]	Within class comparison
Anonymous 1966[6]	Commentary
Anonymous 1973[8]	Crossover study
Anonymous 1974[10]	Commentary
Anonymous 1974[9]	Commentary
Anonymous 1987[12]	Narrative review
Anonymous 1992[13]	Incorrect interventions
Arendt-nielsen 1994[15]	Incorrect study design
Ash 1999[16]	Incorrect population
Badia flores 1975[18]	No relevant outcomes. Only GI events reported
Badia-flores 1975[17]	Crossover study
Bain 1966[19]	Incorrect interventions
Bayley 1976[22]	Crossover study
Bensen 2000[24]	Mixed population
Berg 1989[25]	Incorrect interventions
Bernhard 1967[26]	Incorrect study design
Berry 1981[28]	Unobtainable
Berry 1982[27]	Crossover study
Berry 1990[29]	Incorrect study design
Boardman 1967[32]	Crossover study
Bolten 1996[34]	Not in English language
Boureau 1994[36]	Not in English
Brooks 1970[37]	Inappropriate comparison
Busson 1986[38]	Incorrect study design
Cahill 1965[39]	Not guideline condition
Camp 1981[41]	Crossover study. Non-comparative
Chalmers 1969[43]	Crossover study. Inappropriate comparison
Chalmers 1971[44]	Not in English language
Chalmers 1972[42]	Crossover study
Chen 2008[45]	Systematic review
Choi 2014[46]	Inappropriate comparison
Ciuffetti 1989[47]	Incorrect interventions
Coats 2004[48]	Not guideline condition
Colebatch 2011[49]	Review - references checked
Curtarelli 1973[51]	Incorrect study design. Mixed population
Delbarre 1979[53]	Not in English

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Study	Exclusion reason
Delbarre 1981[52]	Unobtainable
Dick-smith 1969[54]	Crossover study
Donnelly 1967[55]	Crossover study
Eichler 2005[59]	Mixed population
Ejstrup 1982[60]	Crossover study. Inappropriate comparison
Elmstedt 1985[61]	Mixed population
Emery 1986[62]	Crossover study
Fabule 2014[63]	Review - reference checked
Fancourt 1984[64]	Mixed population
Fernandes 1994[65]	Crossover study
Fiszman 1987[66]	Wrong comparison
Fleischmann 1992[67]	Incorrect study design
Furst 2001[68]	Not in English language
Galeazzi 1993[70]	Not review population
Gentiletti 1987[71]	Incorrect study design. Inappropriate comparison
Godfrey 1975[76]	Inappropriate comparison
Goemaere 1993[77]	Crossover study
Goldie 1974[78]	Crossover study
Goldstein 2004[79]	Incorrect interventions
Gringras 1976[83]	Crossover study. Mixed population
Gross 1987[84]	Incorrect study design
Hazlewood 2012[86]	Review - references checked
Hernandez 1976[87]	Crossover study
Hill 1970[89]	Crossover study
Hill 1974[88]	Crossover study. Inappropriate comparison. Incorrect study design
Hobkirk 1977[90]	Crossover study
Hunt 2003[91]	Mixed population
Hunt 2003[92]	Reports combined results across various populations
Huskisson 1970[96]	Crossover study. Inappropriate comparison
Huskisson 1970[95]	Crossover study
Huskisson 1974[94]	Inappropriate comparison
Jasani 1968[99]	Crossover study. Inappropriate comparison
Kajander 1972[100]	Crossover study
Karim 1999[101]	Crossover study
Katona 1973[102]	Multiple study results presented together
Katona 1975[103]	Unclear study design
Katona 1979[104]	Inappropriate comparison
Katz 1965[105]	Crossover study
Kennedy 1976[107]	Crossover study
Kuntz 1976[109]	Crossover study
Lavalle 1983[112]	Unobtainable
Lee 1976[115]	Inappropriate comparison
Lemmel 1994[119]	Conference abstract
Lipsky 1997[120]	Narrative review
Lisse 1996[121]	Unobtainable

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Study	Exclusion reason
Louly 2009[122]	Not guideline condition. Incorrect interventions
Lussier 1973[124]	Incorrect study design. non responders excluded
Lussier 1973[123]	Crossover study
Macfarlane 1986[125]	Incorrect population
Macneill 1976[126]	Incorrect study design
Martio 1981[127]	Not guideline condition
Mattia 2006[129]	Narrative review
Mccormack 2011[130]	Review - references checked
Messias 1974[132]	Crossover study. Not in English
Meyers 1974[133]	Incorrect study design. Incorrect interventions
Miglioli 1996[134]	Incorrect interventions
Mikulaschek 1974[135]	Review - references checked
Moga 2005[136]	Review - references checked
Morgan 1993[137]	Crossover study. Incorrect interventions. Not review population
Myles 1967[138]	Crossover study. Inappropriate comparison
Nissila 1981[142]	Unobtainable
Nuki 1973[143]	Crossover study
Nyfos 1971[144]	Crossover study
Orozco-alcala 1987[145]	Inappropriate comparison
Palmer 1988[146]	Crossover study
Payne 1965[147]	Incorrect study design
Philip 1982[148]	Crossover study
Pitkeathly 1966[149]	Crossover study. Inappropriate comparison
Pullar 1988[150]	Crossover study
Radermacher 1991[151]	Unclear population
Radner 2012[152]	Review - references checked
Ramiro 2011[153]	Review - references checked
Richards 2011[154]	Review - references checked
Ridolfo 1973[155]	Crossover study
Robinson 1966[156]	Incorrect study design
Rooney 1978[157]	Crossover study
Sugiura yasuo 1974[173]	Unobtainable
Sacks 1974[158]	Crossover study. Incorrect interventions
Saggini 1996[159]	Not guideline condition
Sasaki 1970[161]	Crossover study. Inappropriate comparison
Schnitzer 1999[162]	Incorrect interventions
Scott 1969[163]	Crossover study
Seideman 1993[164]	Crossover study
Seigmund 1981[165]	Unobtainable
Shand 1986[166]	Inappropriate design
Shichikawa 1982[167]	Unobtainable
Slaughter 2002[170]	Incorrect population
Smyth 1970[171]	Commentary
Solomon 1974[172]	Crossover study
Swinson 1988[174]	Crossover study

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Study	Exclusion reason
Tausch 1981[175]	Crossover study. Incorrect study design
Teh 1984[176]	Incorrect interventions
Thorpe 1974[177]	Incorrect interventions. Mixed population
Tilley 1995[178]	Incorrect interventions
Trentham 2000[179]	Incorrect interventions
Tweddell 1981[181]	Incorrect study design
Upasani 1973[182]	Incorrect study design
Vaishnava 1971[183]	Crossover study
Vasanthakumar 1987[184]	Crossover study
Veys 1984[186]	Crossover study
Vojtisek 1975[187]	Incorrect interventions. Inappropriate comparison
Wanka 1964[188]	Crossover study
Wasson 1975[189]	Incorrect study design
Whittle 2011[192]	Review - references checked
Wright 1969[195]	Crossover study
Zayat 2011[196]	Inappropriate comparison

I.2 Excluded health economic studies

None.

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Appendix J: Research recommendations

J.1 Analgesic drugs

Research question: What is the clinical and cost effectiveness of analgesic drugs other than non-steroidal anti-inflammatory drugs (NSAIDs) in adults with rheumatoid arthritis (RA) whose pain or stiffness control is not adequate?

Why this is important:

Analgesics (including NSAIDs, paracetamol, opioids and compound analgesics) are sometimes used in addition to disease-modifying treatments for relief of pain and stiffness in people with rheumatoid arthritis whose symptom control is not adequate. Current practice regarding the choice of analgesic in RA is variable. The evidence base for many of the analgesic drugs in RA (other than NSAIDs) is limited, and thus their relative effectiveness is unknown. Further research in this area may enable the guideline to make recommendations about the use of analgesic drugs other than NSAIDs.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Adults with rheumatoid arthritis whose symptom control is inadequate Intervention(s): Analgesic drugs, for example paracetamol and codeine (excluding NSAIDs) Comparison: NSAIDs / COX II selective inhibitors Outcome(s): Pain, function, stiffness and quality of life
Importance to patients or the population	If unresolved pain can be improved with an acceptable level of side effects, a significant improvement in patient-related outcomes such as function and quality of life would be expected. In addition, many people with RA are currently taking analgesics that are not specifically recommended in the guideline due to a lack of evidence, such as compound analgesics like paracetamol and codeine. Better knowledge of the effectiveness of these drugs would be of benefit to people with RA as it will improve shared decision making on their best treatment options.
Relevance to NICE guidance	Current guidance is to consider NSAIDs for people with RA whose symptom control is inadequate. No recommendations were made on the use of other analgesic drugs, including paracetamol and codeine, due to the paucity of evidence. Further research on these other analgesic drugs may enable recommendations on their use to be included in future updates of the guideline.
Relevance to the NHS	Better management of symptoms in people with RA would likely improve people's quality of life and reduce length of routine appointments. The use of these medications, should they be found to be beneficial, would not have a significant financial impact on the NHS.
National priorities	N/A
Current evidence base	High quality evidence for analgesic medication other than NSAIDs in RA is lacking.
Equality	None
Study design	Randomised controlled trial (double dummy non-inferiority trial) comparing analgesic drugs with NSAIDs in addition to conventional management (e.g. DMARDs). Participants in each arm should have stable RA, in remission (on a stable DMARD regime), with equal concomitant treatment options available to each group.
Feasibility	This has been designed as a head to head trial to improve feasibility as a placebo controlled trial is likely to be difficult to recruit sufficient numbers.

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	Pharmacological funding for a trial such as this is unlikely due to the drugs being generic and widely available, therefore funding could provide a challenge if not available through non-commercial funders.
Other comments	Unresolved pain is an increasingly recognised problem in adults with rheumatoid arthritis. The importance of this issue means it should be on research agendas of multiple funding agencies.
Importance	Moderate: the research is of interest and will fill existing evidence gaps.

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