Health Technology Assessment 2006; Vol. 10: No. 38

Appendices

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A comparison of the cost-effectiveness of five strategies for the prevention of non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling

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October 2006

Health Technology Assessment
NHS R&D HTA Programme

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Appendix 1

Search strategies

These are the corrected search strategies, which now collect the etodolac studies appropriately.

(a) Search strategy developed for EMBASE

On Ovid, run May 2002, period 1980 to date.

1. NSAID$.mp.
2. ((nonsteroid$ or non-steroid$) adj3 (anti-inflam$ or antiinflam$)).mp.
3. ("Cox 1" or Cox-1 or "cyclo-oxygenase 1" or "cyclooxygenase 1" or clyclooxygenase-1 or cyclo-oxygenase-1).mp.
4. exp aceclofenac/ or exp acemetacin/ or exp alminoprofen/ or exp amfenac/ or exp ampiroxicam/ or exp amtolmetin guacil/ or exp benorilate/ or exp butibufen/ or exp clofezone/ or exp dexketoprofen/ or exp diclofenac/ or exp diflunisal/ or exp epirizole/ or exp etodolac/ or exp etofenamate/ or exp fenbufen/ or exp fenoprofen/ or exp fentiazac/ or exp flunoxaprofen/ or exp flurbiprofen/ or exp furaprofen/ or exp glucametacin/ or exp ibuprofen/ or exp ibuproxam/ or exp indometacin/ or exp isonixin/ or exp kebuzone/ or exp ketoprofen/ or exp ketorolac/ or exp ketorolac trometamol/ or exp lonazolac/ or exp lonazolac calcium/ or exp lornoxicam/ or exp loxoprofen/ or exp meclofenamate sodium/ or exp meclofenamic acid/ or exp mefenamic acid/ or exp meloxicam/ or exp mofebutazone/ or exp mofezolac/ or exp morazone/ or exp morniflumate/ or exp nabumetone/ or exp naproxen/ or exp niflumic acid/ or exp oxametacin/ or exp phenylbutazone/ or exp piroxicam/ or exp pranoprofen/ or exp proglumetacin/ or exp proquazone/ or exp sulindac/ or exp tenoxicam/ or exp tiaprofenic acid/ or exp tiaramide/ or exp tolfenamic acid/ or exp tolmetin/ or exp zaltoprofen/
5. (Aceclofenac$ or Preservex or Acemetacin$ or Acetmetacin$ or Emflex or Alminoprofen$ or Amfenac).mp.
6. (Ampiroxicam$ or Amtolmetin$ or Azapropazone$ or Rheumox or Benorylate$ or benorilate$ or benoral or Butibufen$).mp.
7. (Cinmetacin$ or Clofezone$ or Dexketoprofen$ or Keral or Diclofenac$ or Voltarol or Diclomax or Motifene).mp. [
8. (Difenpiramide$ or Diflunisal$ or Dolobid or Epirazole$ or Etodolac$ or Lodine).mp.
9. (Etofenamate$ or Fenbufen$ or Lederfen or Fenoprofen$ or Fenopron or Fentiazac$ or Floctafenine$).mp.
10. (Flunoxaprofen$ or Flurbiprofen$ or Froben or Furprofen$ or Glucametacin$ or Ibuprofen$ or Arthrofen or Lidifen or Ebufac or Rimafen or Motrin or Nurofen or Galprofen or Orbifen or Brufen or Fenbid).mp.
11. (Ibuproxam$ or Indomethacin$ or Indometacin$ or indomax or slo-indo).mp.
12. (Isonixin$ or Kebuzone$ or Ketoprofen$ or Orudis or oruvail or Ketorolac$ or toradol or Lonazolac$ or Lornoxicam$ or Xefo or Loxoprofen$).mp.
13. (Meclofenamate$ or Mefenamic$ or Ponstan or Meloxicam$ or Mobic or Mofebutazone$ or Mofezolac$ or Morazone$ or Morniflumate$ or Nabumetone$ or Relifex or Naproxen$ or Naprosyn or Synflex).mp.
14. (Nifenazone$ or Niflumic$ or Oxametacin$ or Phenylbutazone$ or Butacote or Piroxicam$ or Feldene or Brexidol).mp.
15. (Pranoprofen$ or Proglumetacin$ or Proquazone$ or Ramifenazone$ or Sulindac$ or Clinoril or Tenoxicam$ or Mobiflex or Tiaprofenic$ or Surgam or Tiaramide$ or Tolfenamic$ or Clotam or Tolmetin$ or Zaltoprofen$).mp.
16. exp Misoprostol/
17. exp Proton Pump Inhibitor/
18. exp Histamine H2 Receptor Antagonist/
19. (cytotec or misoprostil or "SC 29333" or "SC 30249").mp.
20. 59122-48-4.rn.
21. "hydrogen potassium adenosine triphosphatase inhib$".mp.
22. "hydrogen potassium ATPase inhib$".mp.
23. (H2 adj3 (antagon$ or block$)).mp.
24. ("histamine 2" adj3 (block$ or antagon$)).mp.
25. (cimetidine$ or famotidine$ or nizatidine$ or ranitidine$).mp.
26. (dyspamet or tagamet or algitec or pepcid or axid or zantac or pylorid).mp.

27. (omeprazole$ or lansoprazole$ or pantoprazole$ or rabeprazole$).mp.
28. (losec or zoton or protium or pariet).mp.
29. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
30. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
31. 29 and 30
32. (arthrotec or napratec).mp. or 31
33. (Cox-2 or Cox-II or "Cox 2" or "Cox II").mp.
34. (cyclooxygenase-2 or "cyclooxygenase 2" or cyclooxygenase-II or "cyclooxygenase II").mp.
35. exp Cyclooxygenase 2 Inhibitor/
36. celecoxib$.mp.
37. flosulide$.mp.
38. meloxicam$.mp.
39. nimesulide$.mp.
40. rofecoxib$.mp.
41. (cyclo-oxygenase-2 or "cyclo-oxygenase 2" or cyclo-oxygenase-II or "cyclo-oxygenase II").mp.
42. (celebrex or vioxx).mp.
43. etodolac$.mp
44. exp Etodolac/
45. 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
46. 32 or 45
47. controlled study/
48. randomized controlled trial/
49. clinical trial/
50. major clinical study/
51. (trial$ or compar$ or control$).tw.
52. study.tw.
53. "follow$ and up".tw.
54. (blind$ or clinic$ or placebo).tw.
55. placebo/
56. clinical article/
57. 47 or 48 or 49 or 50 or 52 or 53 or 54 or 55 or 56
58. exp human/
59. nonhuman/
60. 59 not 58
61. 57 not 60
62. exp Longitudinal Study/
63. exp Prospective Study/
64. (cohort$ or quintile$ or quartile$ or tertile$ or quantile$).mp.
65. (follow-up$ or followup$).mp,tw.
66. longitud$.mp.
67. ((prospectiv$ or observation$) adj5 (research$ or data$ or stud$)).mp.
68. 62 or 63 or 64 or 65 or 66 or 67
69. 68 not 60
70. 69 or 61
71. 46 and 70
72. Child/
73. Adult/
74. 72 and 73
75. 72 not 74
76. 71 not 75
77. exp In Vitro Study/
78. exp In Vivo Study/
79. 77 and 78
80. 77 not 79
81. 76 not 80

(b) Search strategy developed for MEDLINE

On Ovid, run May 2002, period 1966 to date:

1. NSAID$.mp.
2. ((nonsteroid$ or non-steroid$) adj3 (anti-inflam$ or antiinflam$)).mp.
3. ("Cox 1" or Cox-1 or "cyclo-oxygenase 1" or "cyclooxygenase 1" or clyclooxygenase-1 or cyclo-oxygenase-1).mp.
4. (Aceclofenac$ or Preservex or Acemetacin$ or Acetmetacin$ or Emflex or Alminoprofen$ or Amfenac).mp.
5. (Ampiroxicam$ or Amtolmetin$ or Azapropazone$ or Rheumox or Benorylate$ or benorilate$ or benoral or Butibufen$).mp.
6. (Cinmetacin$ or Clofezone$ or Dexketoprofen$ or Keral or Diclofenac$ or Voltarol or Diclomax or Motifene).mp.
7. (Difenpiramide$ or Diflunisal$ or Dolobid or Epirazole$ or Etodolac$ or Lodine).mp.
8. (Etofenamate$ or Fenbufen$ or Lederfen or Fenoprofen$ or Fenopron or Fentiazac$ or Floctafenine$).mp.
9. (Flunoxaprofen$ or Flurbiprofen$ or Froben or Furprofen$ or Glucametacin$ or Ibuprofen$ or Arthrofen or Lidifen or Ebufac or Rimafen or Motrin or Nurofen or Galprofen or Orbifen or Brufen or Fenbid).mp.
10. (Ibuproxam$ or Indomethacin$ or Indometacin$ or indomax or slo-indo).mp.
11. (Isonixin$ or Kebuzone$ or Ketoprofen$ or Orudis or oruvail or Ketorolac$ or toradol or Lonazolac$ or Lornoxicam$ or Xefo or Loxoprofen$).mp.
12. (Meclofenamate$ or Mefenamic$ or Ponstan or Meloxicam$ or Mobic or Mofebutazone$ or Mofezolac$ or Morazone$ or Morniflumate$ or Nabumetone$ or Relifex or Naproxen$ or Naprosyn or Synflex).mp.
13. (Nifenazone$ or Niflumic$ or Oxametacin$ or Phenylbutazone$ or Butacote or Piroxicam$ or Feldene or Brexidol).mp.
14. (Pranoprofen$ or Proglumetacin$ or Proquazone$ or Ramifenazone$ or Sulindac$

or Clinoril or Tenoxicam$ or Mobiflex or Tiaprofenic$ or Surgam or Tiaramide$ or Tolfenamic$ or Clotam or Tolmetin$ or Zaltoprofen$).mp.
15. exp diclofenac/ or exp diflunisal/ or exp epirizole/ or exp etodolac/ or exp fenoprofen/ or exp flufenamic acid/ or exp flurbiprofen/ or exp ibuprofen/ or exp indomethacin/ or exp ketoprofen/ or exp ketorolac/ or exp ketorolac tromethamine/ or exp meclofenamic acid/ or exp mefenamic acid/ or exp naproxen/ or exp niflumic acid/ or exp phenylbutazone/ or exp piroxicam/ or exp sulindac/ or exp tolmetin/
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. (cytotec or misoprostil or "SC 29333" or "SC 30249").mp.
18. "hydrogen potassium adenosine triphosphatase inhib$".mp.
19. "hydrogen potassium ATPase inhib$".mp.
20. (H2 adj3 (antagon$ or block$)).mp.
21. ("histamine 2" adj3 (block$ or antagon$)).mp.
22. (cimetidine$ or famotidine$ or nizatidine$ or ranitidine$).mp.
23. (dyspamet or tagamet or algitec or pepcid or axid or zantac or pylorid).mp.
24. (omeprazole$ or lansoprazole$ or pantoprazole$ or rabeprazole$).mp.
25. (losec or zoton or protium or pariet).mp.
26. exp MISOPROSTOL/
27. exp burimamide/ or exp cimetidine/ or exp famotidine/ or exp metiamide/ or exp Misoprostol/ or exp nizatidine/ or exp omeprazole/ or exp ranitidine/
28. exp Histamine H2 Antagonists/
29. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 16 and 29
31. (arthrotec or napratec).mp. or 30
32. (Cox-2 or Cox-II or "Cox 2" or "Cox II").mp.
33. (cyclooxygenase-2 or "cyclooxygenase 2" or cyclooxygenase-II or "cyclooxygenase II").mp.
34. (celecoxib$ or etodolac$).mp.
35. (flosulide$ or meloxicam$).mp.
36. exp Etodolac/
37. nimesulide$.mp.
38. rofecoxib$.mp.
39. (cyclo-oxygenase-2 or "cyclo-oxygenase 2" or cyclo-oxygenase-II or "cyclo-oxygenase II").mp.
40. (celebrex or vioxx).mp.
41. 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42. 31 or 41
43. randomized controlled trial.pt.
44. controlled clinical trial.pt.
45. Randomized controlled trials/
46. random allocation.sh.
47. double blind method.sh.
48. single-blind method.sh.
49. 43 or 44 or 45 or 46 or 47 or 48
50. (animal not human).sh.
51. 49 not 50
52. clinical trial.pt.
53. exp Clinical trials/
54. (clin$ adj25 trial$).ti,ab.
55. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.
56. placebos.sh.
57. placebo$.ti,ab.
58. random$.ti,ab.
59. research design.sh.
60. comparative study.sh.
61. exp Evaluation studies/
62. follow up studies.sh.
63. prospective studies.sh.
64. (control$ or prospectiv$ or volunteer$).ti,ab.
65. 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64
66. 65 not 50
67. 51 or 66
68. exp Cohort Studies/
69. (cohort$ or quintile$ or quartile$ or quantile$ or tertile$).mp.
70. (follow-up$ or followup$).mp,tw.
71. longitud$.mp.
72. ((prospectiv$ or observation$) adj5 (research$ or data$ or stud$)).mp.
73. 68 or 69 or 70 or 71 or 72
74. 73 not 50
75. 67 or 74
76. 42 and 75
77. Child/
78. Adult/
79. 77 and 78
80. 77 not 79
81. 76 not 80
82. exp in vitro/
83. 81 not 82

(c) Search strategy developed for the Cochrane Library

On CD rom, run on 2002, Issue 2.

1. NSAID*
2. ((NONSTEROID* or NON-STEROID*) near (ANTI-INFLAM* or ANTIINFLAM*))
3. (COX1 or COX-1)
4. COX
5. (CYCLO-OXYGENASE* or CYCLOOXYGENASE*)
6. COX-1

7. COX
8. ((((((ACECLOFENAC* or PRESERVEX) or ACEMETACIN*) or ACETMETACIN*) or EMFLEX) or ALMINOPROFEN*) or AMFENAC)
9. (((((((AMPIROXICAM* or AMTOLMETIN*) or AZAPROPAZONE*) or RHEUMOX) or BENORYLATE*) or BENORILATE*) or BENORAL) or BUTIBUFEN*)
10. (((((((CINMETACIN* or CLOFEZONE*) or DEXKETOPROFEN*) or KERAL) or DICLOFENAC*) or VOLTAROL) or DICLOMAX) or MOTIFENE)
11. (((((DIFENPIRAMIDE* or DIFLUNISAL*) or DOLOBID) or EPIRAZOLE*) or ETODOLAC*) or LODINE)
12. ((((((ETOFENAMATE* or FENBUFEN*) or LEDERFEN) or FENOPROFEN*) or FENOPRON) or FENTIAZAC*) or FLOCTAFENINE*)
13. ((((((((((((((FLUNOXAPROFEN* or FLURBIPROFEN*) or FROBEN) or FURPROFEN*) or GLUCAMETACIN*) or IBUPROFEN*) or ARTHROFEN) or LIDIFEN) or EBUFAC) or RIMAFEN) or MOTRIN) or NUROFEN) or GALPROFEN) or ORBIFEN) or BRUFEN) or FENBID)
14. ((((IBUPROXAM* or INDOMETHACIN*) or INDOMETACIN*) or INDOMAX) or SLO-INDO)
15. ((((((((((ISONIXIN* or KEBUZONE*) or KETOPROFEN*) or ORUDIS) or ORUVAIL) or KETOROLAC*) or TORADOL) or LONAZOLAC*) or LORNOXICAM*) or XEFO) or LOXOPROFEN*)
16. ((((((((((((MECLOFENAMATE* or MEFENAMIC*) or PONSTAN) or MELOXICAM*) or MOBIC) or MOFEBUTAZONE*) or MOFEZOLAC*) or MORAZONE*) or MORNIFLUMATE*) or NABUMETONE*) or RELIFEX) or NAPROXEN*) or NAPROSYN) or SYNFLEX)
17. (((((((NIFENAZONE* or NIFLUMIC*) or OXAMETACIN*) or PHENYLBUTAZONE*) or BUTACOTE) or PIROXICAM*) or FELDENE) or BREXIDOL)
18. ((((((((((((((PRANOPROFEN* or PROGLUMETACIN*) or PROQUAZONE*) or RAMIFENAZONE*) or SULINDAC*) or CLINORIL) or TENOXICAM*) or MOBIFLEX) or TIAPROFENIC*) or SURGAM) or TIARAMIDE*) or TOLFENAMIC*) or CLOTAM) or TOLMETIN*) or ZALTOPROFEN*)
19. DICLOFENAC*:ME
20. DIFLUNISAL*:ME
21. EPIRIZOLE*:ME
22. ETODOLAC*:ME
23. FENOPROFEN*:ME
24. IBUPROFEN*:ME
25. FLUFENAMIC-ACID*:ME
26. FLURBIPROFEN*:ME
27. INDOMETHACIN*:ME
28. KETOPROFEN*:ME
29. MECLOFENAMIC-ACID*:ME
30. MEFENAMIC-ACID*:ME
31. NAPROXEN*:ME
32. NIFLUMIC-ACID*:ME
33. PHENYLBUTAZONE*:ME
34. PIROXICAM*:ME
35. SULINDAC*:ME
36. TOLMETIN*:ME
37. ((((((((((#1 or #2) or #3) or #4) or #5) or #6) or #7) or #8) or #9) or #10) or #11) or #12)
38. ((((((((((#13 or #14) or #15) or #16) or #17) or #18) or #19) or #20) or #21) or #22) or #23) or #24)
39. ((((((((((#25 or #26) or #27) or #28) or #29) or #30) or #31) or #32) or #33) or #34) or #35) or #36)
40. ((#37 or #38) or #39)
41. (CYTOTEC or MISOPROSTIL)
42. (((CYTOTEC or MISOPROSTIL) or 29333) or 30249)
43. (HYDROGEN next (POTASSIUM next (ADENOSINE next (TRIPHOSPHATASE next INHIB*))))
44. (HYDROGEN next (POTASSIUM next (ATPASE next INHIB*)))
45. (HISTAMINE* near (BLOCK* or ANTAGON*))
46. (((CIMETIDINE* or FAMOTIDINE*) or NIZATIDINE*) or RANITIDINE*)
47. ((((((DYSPAMET or TAGAMET) or ALGITEC) or PEPCID) or AXID) or ZANTAC) or PYLORID)
48. (((OMEPRAZOLE* or LANSOPRAZOLE*) or PANTOPRAZOLE*) or RABEPRAZOLE*)
49. (((LOSEC or ZOTON) or PROTIUM) or PARIET)
50. MISOPROSTOL*:ME
51. BURIMAMIDE*:ME
52. CIMETIDINE*:ME
53. FAMOTIDINE*:ME
54. METIAMIDE*:ME
55. NIZATIDINE*:ME
56. OMEPRAZOLE*:ME
57. RANITIDINE*:ME
58. HISTAMINE-H2-ANTAGONISTS*:ME
59. (((((((#42 or #43) or #44) or #45) or #46) or #47) or #48) or #49) or #50)
60. (((((((#51 or #52) or #53) or #54) or #55) or #56) or #57) or #58) or #59)

61. (#60 and #40)
62. (ARTHROTEC or NAPRATEC)
63. (((COX-2 or COX-II) or CYCLOOXYGENASE-2) or CYCLO-OXYGENASE-2)
64. (((((((CELECOXIB* or FLOSULIDE*) or MELOXICAM*) or NIMESULIDE*) or ROFECOXIB*) or CELEBREX) or VIOXX) or ETODOLAC*)
65. ((#62 or #63) or #64)
66. (#61 or #65)
67. CHILD*:ME
68. ADULT*:ME
69. (#67 and #68)
70. (#67 not #69)
71. (#66 not #70)

(d) Search strategy developed for EMBASE to locate CCTs and cohort studies (similar strategy used on MEDLINE)

On Ovid, run May 2002, period 1966 to date.

1. NSAID$.mp.
2. ((nonsteroid$ or non-steroid$) adj3 (anti-inflam$ or antiinflam$)).mp.
3. ("cox 1" or cox-1 or "cyclo-oxygenase 1" or "cyclooxygenase 1" or clyclooxygenase-1 or cyclo-oxygenase-1).mp.
4. exp aceclofenac/ or exp acemetacin/ or exp alminoprofen/ or exp amfenac/ or exp ampiroxicam/ or exp amtolmetin guacil/ or exp benorilate/ or exp butibufen/ or exp clofezone/ or exp dexketoprofen/ or exp diclofenac/ or exp diflunisal/ or exp epirizole/ or exp etodolac/ or exp etofenamate/ or exp fenbufen/ or exp fenoprofen/ or exp fentiazac/ or exp flunoxaprofen/ or exp flurbiprofen/ or exp furaprofen/ or exp glucametacin/ or exp ibuprofen/ or exp ibuproxam/ or exp indometacin/ or exp isonixin/ or exp kebuzone/ or exp ketoprofen/ or exp ketorolac/ or exp ketorolac trometamol/ or exp lonazolac/ or exp lonazolac calcium/ or exp lornoxicam/ or exp loxoprofen/ or exp meclofenamate sodium/ or exp meclofenamic acid/ or exp mefenamic acid/ or exp meloxicam/ or exp mofebutazone/ or exp mofezolac/ or exp morazone/ or exp morniflumate/ or exp nabumetone/ or exp naproxen/ or exp niflumic acid/ or exp oxametacin/ or exp phenylbutazone/ or exp piroxicam/ or exp pranoprofen/ or exp proglumetacin/ or exp proquazone/ or exp sulindac/ or exp tenoxicam/ or exp tiaprofenic acid/ or exp tiaramide/ or exp tolfenamic acid/ or exp tolmetin/ or exp zaltoprofen/
5. (Aceclofenac$ or Preservex or Acemetacin$ or Acetmetacin$ or Emflex or Alminoprofen$ or Amfenac).mp.
6. (Ampiroxicam$ or Amtolmetin$ or Azapropazone$ or Rheumox or Benorylate$ or benorilate$ or benoral or Butibufen$).mp.
7. (Cinmetacin$ or Clofezone$ or Dexketoprofen$ or Keral or Diclofenac$ or Voltarol or Diclomax or Motifene).mp.
8. (Difenpiramide$ or Diflunisal$ or Dolobid or Epirazole$ or Etodolac$ or Lodine).mp.
9. (Etofenamate$ or Fenbufen$ or Lederfen or Fenoprofen$ or Fenopron or Fentiazac$ or Floctafenine$).mp.
10. (Flunoxaprofen$ or Flurbiprofen$ or Froben or Furprofen$ or Glucametacin$ or Ibuprofen$ or Arthrofen or Lidifen or Ebufac or Rimafen or Motrin or Nurofen or Galprofen or Orbifen or Brufen or Fenbid).mp.
11. (Ibuproxam$ or Indomethacin$ or Indometacin$ or indomax or slo-indo).mp.
12. (Isonixin$ or Kebuzone$ or Ketoprofen$ or Orudis or oruvail or Ketorolac$ or toradol or Lonazolac$ or Lornoxicam$ or Xefo or Loxoprofen$).mp.
13. (Meclofenamate$ or Mefenamic$ or Ponstan or Meloxicam$ or Mobic or Mofebutazone$ or Mofezolac$ or Morazone$ or Morniflumate$ or Nabumetone$ or Relifex or Naproxen$ or Naprosyn or Synflex).mp.
14. (Nifenazone$ or Niflumic$ or Oxametacin$ or Phenylbutazone$ or Butacote or Piroxicam$ or Feldene or Brexidol).mp.
15. (Pranoprofen$ or Proglumetacin$ or Proquazone$ or Ramifenazone$ or Sulindac$ or Clinoril or Tenoxicam$ or Mobiflex or Tiaprofenic$ or Surgam or Tiaramide$ or Tolfenamic$ or Clotam or Tolmetin$ or Zaltoprofen$).mp.
16. exp Misoprostol/
17. exp Proton Pump Inhibitor/
18. exp Histamine H2 Receptor Antagonist/
19. (cytotec or misoprostil or "SC 29333" or "SC 30249").mp.
20. 59122-48-4.rn.
21. "hydrogen potassium adenosine triphosphatase inhib$".mp.
22. "hydrogen potassium ATPase inhib$".mp.
23. (H2 adj3 (antagon$ or block$)).mp.
24. ("histamine 2" adj3 (block$ or antagon$)).mp.
25. (cimetidine$ or famotidine$ or nizatidine$ or ranitidine$).mp.

26. (dyspamet or tagamet or algitec or pepcid or axid or zantac or pylorid).mp.
27. (omeprazole$ or lansoprazole$ or pantoprazole$ or rabeprazole$).mp.
28. (losec or zoton or protium or pariet).mp.
29. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
30. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
31. 29 and 30
32. (arthrotec or napratec).mp. or 31
33. (cox-2 or cox-II or "cox 2" or "cox II").mp.
34. (cyclooxygenase-2 or "cyclooxygenase 2" or cyclooxygenase-II or "cyclooxygenase II").mp.
35. exp Cyclooxygenase 2 Inhibitor/
36. celecoxib$.mp.
37. flosulide$.mp.
38. meloxicam$.mp.
39. nimesulide$.mp.
40. rofecoxib$.mp.
41. (cyclo-oxygenase-2 or "cyclo-oxygenase 2" or cyclo-oxygenase-II or "cyclo-oxygenase II").mp.
42. (celebrex or vioxx).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
43. 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44. 32 or 43
45. controlled study/
46. randomized controlled trial/
47. clinical trial/
48. major clinical study/
49. (trial$ or compar$ or control$).tw.
50. study.tw.
51. "follow$ and up".tw.
52. (blind$ or clinic$ or placebo).tw.
53. placebo/
54. clinical article/
55. 45 or 46 or 47 or 48 or 49 or 50 or 52 or 53 or 54
56. exp human/
57. nonhuman/
58. 57 not 56
59. 55 not 58
60. exp Longitudinal Study/
61. exp Prospective Study/
62. (cohort$ or quintile$ or quartile$ or tertile$ or quantile$).mp.
63. (follow-up$ or followup$).mp,tw.
64. longitud$.mp.
65. ((prospectiv$ or observation$) adj5 (research$ or data$ or stud$)).mp.
66. 60 or 61 or 62 or 63 or 64 or 65
67. 66 not 58
68. 67 or 59
69. 44 and 68
70. Child/
71. Adult/
72. 70 and 71
73. 70 not 72
74. 69 not 73
75. exp In Vitro Study/
76. exp In Vivo Study/
77. 75 and 76
78. 75 not 77
79. 74 not 78

(e) Letter sent to all contact authors of included studies

Dear Professor X,

Re. Systematic review with economic modelling comparing the cost-effectiveness of four strategies for the prevention of NSAID-induced gastrointestinal toxicity (UK HTA review).

We would like to include details of your study (*full reference of included study*) in our meta-analysis. In order to represent your study adequately we need additional information and hope you can help us. We would greatly appreciate if you could provide us with some information on the trial.

1. Would you be able to provide us with the number of events in each arm (and the total number of people analysed)?

Please label each intervention arm.

	CONTROL	**Group B**	**Group C**	**Group D**
Total number analysed in this arm				
Death (all-cause, with reasons for death)				
Serious GI complications (pyloric obstruction, haemorrhage, haemorrhagic erosions, recurrent upper GI bleeds, perforation, inc death from any of these)				
Symptomatic ulcers (gastric, duodenal, oesophageal, inc bleeding ulcers)				
Serious cardiovascular or renal illness leading to contact with primary or secondary health care (inc. angina, MI, stroke, TIA, renal failure, or death from any of these)				
Quality of life (details of measure/s used and results)				

2. We would also like information that would allow us to classify the study according to our methodological criteria and identify any missing data or studies:

Who was blinded in the trial (for example, patients, clinicians, outcome assessors)?	
How was randomisation achieved: method (e.g. sealed envelopes, dice toss, central computer) and **personnel involved** (e.g. pharmacist, recruiting clinician or central personnel)?	
Please give details of any other publications that report the results of **this study** (copies of these and of full trial reports would be gratefully received).	
Do you know of any other studies (published, unpublished or ongoing) that meet our inclusion criteria? We attach a list of studies already included.	

Thanking you in anticipation of your help. If you have any further questions regarding our requests, please feel free to contact me.

Yours sincerely,

Tamara Brown BA(Hons), MSc.

Appendix 2

NSAIDs and gastroprotective agents

(a) NSAID proprietary names

International List produced from *Martindale*: *The Complete Drug Reference*, 35th ed. Those NSAIDs in bold are not included in the review owing to toxicity or withdrawal (they are not realistic alternatives). Those NSAIDs in italics are currently available in the UK.

Drug	Brand names
Cox-I type	
Aceclofenac	**Preservex,** Biofenac, Airtal, Falcol, Gerbin, Sanein, Barcan
Acemetacin	Rheutrop, Altren, Peran, Rantudil, Acemix, Solart, Espledol, Oldan, Tilur
Acetmetacin	**Emflex**
Aclofenac (withdrawn)	*Mervan*
Alminoprofen	Minalfene
Amfenac	Fenazox
Amidopyrine (very toxic)	*Farmidone, Ftalazone, Fugantil, Malivan, Piroreumal, Rosetin, Termidon, Tiomidone*
Ampiroxicam	
Amtolmetin guacil	Artromed, Eufans
Azapropazone	**Rheumox**, Prolixan, Tolyprin, Prolixana
Benorylate, benorilate	**Benoral (salicylate)**
Benoxaprofen (withdrawn)	*Opren*
Bromfenac (withdrawn)	*Duract*
Bumadizone calcium (very toxic)	*Rheumatol, Eumotol*
Butibufen	Mijal
Cinmetacin	Cetanovo
Clofezone	Perclusone
Dexketoprofen	**Keral**
Diclofenac	**Voltarol, Diclomax, Motifene,** Algefit, Delodor, Deflamat, Diclobene, Diclomelan, Diclosyl, Fenaren, Magulphen, Naclof, Tratul, Voltaren, Arthrotec, Diclohexal, Fenac, Cataflam, Polyflam, Novo-Difenac, Nu-Diclo, Flector, Voldal, Voltarene, Xenid, Allvoran, Arthrex, Arthrex Duo, Benfofen, Delphinac, Diclac, Diclo, Diclo-Puren, Diclo-Saar, Diclo-Spondyril, Diclo-Tablinen, Diclo-Wolff, Dicloberl, Diclofenbeta, Diclomerk, Diclophlogont, Diclorektal, Dignofenac, Diglo-Diclo, Dolobasan, DoloVisano Diclo, Duravolten, Effekton, Jenafenac, Lexobene, Monoflam, Myogit, Rewodina, Rheumasan D, Sigafenac, Silino, Toryxil, Diclomel, Difene, Vologen, Artrotec, Dealgic, Deflamat, Dicloftil, Dicloreum, Fenadol, Flogofenac, Forgenac, Misofenac, Novapirina, Ribex Flu, Naclof, Panamor, Pharmaflam, Sodiclo, Veltex, Di Retard, Dolotren, Liberalgium, Lause, Voltaren T, diclo-basan, Diclosifar, Ecofenac, Grofenac, Inflamac, Olfen, Primofenac, Rheufenac, Rhumalgan, Vifenac
Difenpiramide	Difenax
Diflunisal	**Dolobid,** Fluniget, Biartac, Diflusal, Dolobis, Adomal, Aflogos, Artrodol, Citidol, Difludol, Diflunil, Diflusan, Dolisal, Fluodonil, Flustar, Nalgisa, Noaldol, Reuflos, Dolocid, Diflonid, Donobid, Ilacen, Unisal
Droxicam (very toxic)	*Dobenam, Droxar, Drogelon, Ferpan, Ombolan, Pensatron*
Epirizole	Mebron

continued

Drug	Brand names
Etofenamate	Rheumon, Traumon, Flexium, Algesalona E, Bayro, Afrolate, Deiron, Flogoprofen, Zenavan, Etofen, Traumalix
Felbinac (very toxic)	*Target, Flexfree, Dolinac, Traxam, Napageln, Dolinac*
Fenbufen	**Lederfen**, Cinopal, Cincopal
Fenoprofen calcium	**Fenopron,** Nalfon, Fepron, Nalgesic, Progesic
Fentiazac	Norvedan, Fentac, Domureuma, Flogene, O-Flam, Dermisone Fentiazaco, Donorest, Riscalon
Feprazone (very toxic)	*Zepelin, Brotazona, Cocresol, Rangozona, Represil, Reuflodol*
Floctafenine	Idarac, Idalon
Flufenamic acid (very toxic)	*Mobilisin, Rheugesal, Algesalona, Flexocutan, Flexilat, Assan, Assan-Thermo*
Flunoxaprofen	Priaxim
Flurbiprofen	**Froben,** Ansaid, Novo-Flurprofen, Cebutid, Fenomel, Transact Lat, Antadys, Neo Artrol, Tulip
Furprofen	Dolex
Glafenine (withdrawn)	*Glifan, Glifanan*
Glucametacin	Teoremac, Euminex
Ibuprofen	**Arthrofen, Lidifen, Ebufac, Rimafen, Motrin, Nurofen, Galprofen, Orbifen, Brufen, Fenbid,** Avallone, Brufen, Dismenol neu, Dolgit, Dolibu, Dolofort, Doloren, Duafen, Ibudol, Ibupron, Iburem, Imbun, Kratalgin, Nurofen, Seractil, Tabcin, Urem, ACT-3, Actiprofen, Rafen, Tri-profen, Bufedon, Dolgit, Dolofin, Exidol, Ibu-Slow, Inabrin, Malafene, Motrin, Advil, Medipren, Novo-profen, Algifene, Analgyl, Ergix, Fenalgic, Gelufene, Nureflex, Oralfene, Tiburon, Aktren, Anco, Cesra, Contraneural, Dentigoa, Dignoflex, Dimidon, Dismenol, Dolgit, Dolo neos, Dolo-Dolgit, Dolo-Puren, Dolormin, dura-Ibu, duraibuprofen, Dysdolen, Esprenit, Exneural, Fibraflex, Gynofug, Ibol, Ibu, ibu-Attritin, Ibu-Vivimed, Ibubest, Ibubeta, Ibuflam, Ibufug, Ibuhexal, Ibumerck, Ibuphlogont, Ibuprof, Ibutad, Imbun, Jenaprofen, Kontagripp Mono, Logomed Schmerz, Mensoton, Mobilat, Novogent, Optalidon, Opturem, Parsal, Pfeil, Schmerz-Dolgit, Seclodin, stadasan, Tabalon, Tempil, Togal N, Trauma-dolgit, Trombufen, Urem, Bufigen, Cunil, Melfen, Proflex, Aciril, Arfen, Artene, Asepsal, Benflogin, Brufort, Dolocyl, Faspic, Flubenil, Focus, Gineflor, Ginenorm, Inabrin, Kos, Moment, Neo-Mindol, Prontalgin, Femapirin, Ibosure, Ibumetin, Nerofen, Zafen, Ibux, Abbifen, Adfen, Antiflam, Betagesic, Betaprofen, Brugesic, Clinofen, Dynofen, Ibopain, Ibufarm, Inza, Magnatex, Ranfen, Rofen, Solufen, Algiasidin, Algisan, Altior, Cusialgil, Dalsy, Doctril, Dolocyl, Dorival, Ediluna, Espidifen, Evasprin, Faspic, Femidol, Ibenon, Incefal, Isdol, Kalma, Leonal, Librofem, Liderfeme, Lisi-budol, Medipren, Neobrufen, Noalgil, Pocyl, Sadefen, Solufena, Spidifen, Todalgil, Duobrus, Algifor, Antalgit, Bufeno, Dismenol, Irfen, Neo-Helvagit, Panax N, Redufen, Serviprofen, Spedifen, Dynafed IB, Excedrin IB, Genpril, Haltran, Ibufon, Ibuprohm, Medipren, Menadol, Midol IB, Nuprin, Trendar
Ibuproxam	Deflogon, Ibudros, Nialen
Indomethacin, indometacin	**(Only available in the UK as a generic; some generic names: Indomax 75, Slo-Indo)**, Flexidin, Gaurit, Indocid, Indocollyre, Indohexal, Indomellan, Indoptol, Liometacen, Luiflex, Ralicid, Arthrexin, Hicin, Indomed, Dolcidium, Indotec, Novo-methacin, Nu-indo, Rhodacine, Ainscrid, Chrono-Indocid, Amuno, Chibro-Amuno, Confortid, durametacin, Elmetacin, Indo-tablinen, Indocontin, Indomet-ratiopharm, Indomisal, Indorektal, Jenatacin, Mobilat, Rheubalmin Indo, Sigadoc, Vonum, Cidomel, Flexin Continus, Idomed, Imbrilon, Indomod, Boutycin, Cidalgon, Imet, Indocollirio, Indom Collirio, Indoxen, Liometacin, Metacen, Peralgon, Infree, Inteban, Dolazol, Dometin, Confortid, Acuflex, Aflamin, Arthrexin, Articulen, Betacin, Dynametcin, Famethacin, Flamaret, Flamecid, Indotal, Mediflex, Methabid, Methamax, Methocaps, Nisaid-25, Restameth-SR, Rumitard, Aliviosin, Artrinovo, Butidil, Flogoter, Inacid, Indo Framan, Indocaf, Indoftol, Indolgina, Indonilo, Mederreumol, Neo-Decabutin, Reumo, Reusin, Indomee, Bonidon, Helvecin, Indo-Mepha, Indophtal, Indoptic, Servimeta, Indochron
Isamfazone (withdrawn)	*Combiflexona, Frenespan*
Isonixin	Nixyn

continued

Drug	Brand names
Kebuzone	Ketazon, Chetopir
Ketoprofen	**Orudis, Oruvail,** Actron, Keprodol, Profenid, Birofenid, Fastum, Rofenid, Toprek, Apo-Keto, Novo-Keto, Orafen, Rhodis, Rhovail, Bi-Profenid, Ketum, Topfena, Toprec, Alrheumun, europan, Gabrilen, Spondylon, Alrheumat, Orugesic, Artrosilene, Dexal, Flexen, Iso-K, Kefenid, Ketalgin, Ketartrium, Keto, Ketodol, Ketofen, Meprofen, Oki, Profenil, Reuprofen, Salient, Sinketol, Zepelindue, Oscorel, Ketoflam, Myproflam, Orucote, Oruject, Arcental, Extraplus, Ketosolan, Reumoquin, Prodon, Profenid, Fenoket, Jomrthid, Ketil, Ketocid, Ketovail, Ketozip, Larafen, Actron
Ketorolac trometamol	**Toradol (only for postoperative pain)**, Aculare, Taradyl, Lixidol, Droal, Tonum,
Lonazolac calcium	Irritren, Argun
Lornoxicam	**Xefo**
Loxoprofen	Loxonin
Meclofenamate	Meclomen, Lenidolor, Meclodol, Movens, Meclodium
Mefenamic acid	**(only available in the UK as a generic, used to be Ponstan, Ponstan forte)**, Parkemed, Mefic, Ponstan, Ponstyl, Ponalar, Mefac, Pinalgesic, Ponalgesic, Ponmel, Lysalgo, Clinstan, Fenamin, Mefalgic, Ponac, Ponstel, Coslan, Ecopan, Mefenacide, Ponstel
Mofebutazone	Diadin M, Mofesal
Mofezolac	No brands
Morazone	Rosimon-neu
Morniflumate	Nifluril, Flomax, Morniflu, Actol, Niflactol
Naproxen	**Naprosyn, Synflex**, Miranax, Naprobene, Nycopren, Proxen, Xenopan, Anaprox, Inza, Naprogesic, Naxen, Synflex, Apranax, Diparene, Naprosyne, Nycopren, Apo-Napro-Na, Naxen, Novo-Naprox, Nu-Naprox, Dysmenalgit, Malexin, Napro-Dorsch, Genoxen, Gerinap, Napmel, Naprex, Alganil, Apredan, Artroxen, Axer, Floginax, Flogogin, Floxalin, Gibinap, Gibixen, Gynestrel, Laser, Leniartril, Naprium, Naprius, Naprodol, Naprorex, Natrioxen, Neo-Eblimon, Nitens, Numidan, Piproxen, Praxenol, Prexan, Primeral, Proxine, Synalgo, Ticoflex, Xenar, Aleve, Femex, Naprocoat, Naprovite, Alpoxen, Ledox, Acusprain, Clinosyn, Nafasol, Napflam, Naprel, Naproscript, Pranoxen, Traumox, Aliviomas, Antalgin, Denaxpren, Ilagagen, Lundiran, Naprokes, Naproval, Rofanten, Pronaxen, Naprolag, Servinaprox, Anaprox, Naprelan
Nifenazone	Nicopyron, Algotrex, Neopiran, Reumatosil, Supermidone, Thylin
Niflumic acid	Actol, Nifluril, Flunir, Niflam
Oxametacin	Restid
Oxaprozin (toxic)	*Deflam, Daypro*
Oxyphenbutazone (very toxic)	*Tanderil, Californit, Phlogont, Otone, Diflamil*
Parsalmide (toxic)	*Sinovial*
Phenylbutazone	**Butacote**, Butazolidin, Novo-butazone, Butazolidine, Ambene, Demoplas, Butazina, Butazolidina, Carudol, Kadol, Ticinil, Butrex, Inflazone, Scriptozone, Butadiona, Butadion, Cotylbutazone
Piroxicam	**Feldene, Brexidol**, Brexen, Felden, Pirocam, Candyl, Fensaid, Mobilis, Pirox, Rosig, Brexine,Novo-Pirocam, Nu-Pirox, Brexin, Cycladol, Geldene, Inflaced, Olcam, Brexidol, durapirox, Fasax, Flexase, Jenapirox, Piro-Phlogont, Piro-Puren, Pirobeta, Piroflam, Rirorheum, Pirorheuma, Pirox, Pirox-Spondyril, Piroximerck, Pra-Brexidol, Rheumitin, Geroxicam, Pericam, Antiflog, Artroxicam, Brexin, Bruxicam, Cicladol, Ciclafast, Clevian, Dexicam, Flodol, Flogobene, Lampoflex, Nirox, Piroftal, Pivaloxicam, Polipirox, Reucam, Reudene, Reumagil, Riacen, Roxene, Roxenil, Roxiden, Roxim, Siartrol, Unicam, Zacam, Zelis, Zen, Zunden, Pirox, Tetram, Brexecam, Pixicam, Pyrocaps, Rheugesic, Roxicam, Xycam, Artragil, Brexinil, Dekamega, Doblexan, Improntal, Salcacam, Sasulen, Vitaxicam, Pirosol
Pranoprofen	Pranox, Niflan, Oftalar
Proglumetacin	Protaxon, Tolindol, Afloxan, Proxil, Prodamox, Protaxil
Proquazone	Biarison
Ramifenazone	Delta-Tomanol

continued

Drug	Brand names
Sulindac	**Clinoril**, Aclin, Clusinol, Saldac, Apo-Sulin, Novo-Sundac, Arthrocine, Aflodac, Algocetil, Citireuma, Clisundac, Lyndac, Reumyl, Sudac, Sulatrene, Sulen, Sulic, Sulinol, Sulreuma, R-Flex
Tenoxicam	**Mobiflex**, Liman, Tilcotil, Dolmen, Rexalgan, Artriunic, Reutenox, Alganex
Tiaprofenic acid	**Surgam, Surgam LA**, Artiflam, Albert Tiafen, Lindotab, Artroreuma, Suralgan, Surgamyl, Tiaprorex, Derilate, Surgamic
Tiaramide	Solantal
Tolfenamic acid	**Clotam (not licensed for RA or OA)**, Rociclyn
Tolmetin	Tolectin, Reutol, Artrocaptin
Zaltoprofen	No brands
Cox-1 type with added gastroprotection	
Diclofenac with added misoprostol	**Arthrotec**
Naproxen with added misoprostol	**Napratec**
Cox-2 coxib type	
Celecoxib	**Celebrex**
Flosulide	(?)
Rofecoxib	**Vioxx**
Cox-2 preferential type	
Etodolac	
Meloxicam	Mobic, Movalis, Mobec, MoviCox, MobiCox, Parocin, UtiCox
Nabumetone	**Relifex,** Relafen, Arthaxan, Artaxan, Nabuser, Mebutan, Relifen, Relisan, Relitone, Dolsinal, Listran, Relif, Balmox
Nimesulide	Mesulid, Aulin, Algolider, Eudolene, Fansidol, Flolid, Laidor, Ledoren, Nide, Nimedex, Nimesulene, Nims, Nisal, Remov, Resulin, Sulide, Teonim, Antifloxil, Guaxan, Nisulid

(B) Non-NSAID gastroprotective agents, proprietary names

Generic	Brand
Gastroprotective agents	
H_2RAs	
Cimetidine	Cimetidine, Dyspamet, Tagamet
Famotidine	Famotidine, Pepcid
Nizatidine	Nizatidine, Axid
Ranitidine	Ranitidine, Zantac
Ranitidine bismuth citrate	Pylorid
Misoprosotol	**Cyctotec**
	With diclofenac (Arthrotec)
	With naproxen (Napratec)
PPIs	
Omeprazole	Losec
Esomeprazole	Nexium
Lansoprazole	Zoton
Pantoprazole	Protium
Rabeprazole sodium	Pariet

(c) BNF[23] recommended doses

Drug	Daily oral dose: range in adults with rheumatic diseases (mg)	Comments	Manufacturer
Older NSAIDs			
Aceclofenac	100–200		UCB Pharma
Acetmetacin	120–180	Usual dose 120 mg daily	Merck
Azapropazone	600–1800	Usual dose 1200 mg daily	Goldshield
Dexketoprofen	50–75		Menarini
Diclofenac	75–150		Alpharma, Ashbourne, Berk, Dexcel Pharma, Eastern, Goldshield, IVAX, Kent, Lagap
Diflunisal	500–1500		MSD
Fenbufen	900		Cox, Generics, Genus, Hillcross, IVAX, Kent, Sterwin
Fenoprofen	900–3000		Typharm
Flurbiprofen	150–300	Usual dose 200 mg daily	Abbott
Ibuprofen	600–2400	In divided doses, usually not more than 1800 mg daily	Alpharma, APS, Ashbourne, Berk, CP, DDSA, IVAX, Kent, Ranbaxy, Pharmacia, Sovereign, Sterwin
Indomethacin, indometacin	50–200	50 mg daily often sufficient	Alpharma, Kent, MSD, Ranbaxy, Ashbourne, Generics, Hillcross, Lagap, Pharmacia
Ketoprofen	100–200		Hawgreen
Lornoxicam	12		CeNeS
Mefenamic acid	1500		
Nabumetone	500–2000	Usually just 1000 mg at night	Alpharma, APS, Generics, SmithKline Beecham
Naproxen	500–1250		Roche, Searle
Phenylbutazone	200–600	Not licensed for anything other than ankylosing spondylitis	Novartis
Piroxicam	10–30		Pfizer
Sulindac	400		MSD
Tenoxicam	20		Roche
Tiaprofenic acid	600		Florizel
Tolfenamic acid			
Cox-2 NSAIDs			
Celecoxib	200–400		Pharmacia
Etodolac	600		Shire
Meloxicam	7.5–15	7.5 mg daily often sufficient	Boehringer Ingelheim
Nimesulide	200	(Internet expert)	
Rofecoxib	12.5–25	Can be increased to 50 mg daily in acute pain	Merck

continued

Drug	Daily oral dose: range in adults with rheumatic diseases (mg)	Comments	Manufacturer
H_2RAs			
Cimetidine	400	Maintenance	
Famotidine	20	Maintenance	
Nizatidine	150	Maintenance	
Ranitidine	150/300	150 for maintenance (following healing) 300 for prophylaxis	
Ranitidine bismuth citrate		Not recommended for maintenance	
PA			
Misoprosotol	40–800 μg	Maintenance	
With diclofenac (Arthrotec)			
With naproxen (Napratec)			
PPIs			
Omeprazole	20	Prophylaxis	
Esomeprazole	20	Maintenance	
Lansoprazole	15–30	Prophylaxis	
Pantoprazole		Healing	
Rabeprazole sodium		Healing	

Appendix 3

Inclusion and exclusion forms

(a) RCT inclusion

NSAID inclusion/exclusion form

Ref ID:

Coder name and date

RCT: Is the paper:

	Yes	No	?
A. An individually randomised controlled trial?			
B. In adults (18 years plus, not healthy volunteers) who have taken NSAIDs for at least 3 weeks (21 days)?			
C. Comparing 1. Older NSAIDs plus H_2RAs compared with older NSAIDs (alone or with placebo gastroprotection) 2. Older NSAIDs plus PPIs compared with older NSAIDs (alone or with placebo gastroprotection) 3. Older NSAIDs plus misoprostol compared with older NSAIDs (alone or with placebo gastroprotection) 4. Cox-2 inhibitors compared with older NSAIDs alone 5. Comparing any of the four gastroprotective strategies above with any other active gastroprotective strategy			
D. Assessing any of the following: Haemorrhage, perforation, pyloric obstruction, symptomatic ulcers, death, endoscopically proven ulcers, gastric symptoms, anaemia, occult bleeding, other adverse events, CV or renal events, drop-outs, quality of life			
E. Are doses at least the minimum recommended daily prescribing dose as per BNF in at least 2 arms? (exclude less than minimum daily dose arms)			

RCT for the SR

In / out

(b) CCT or cohort inclusion/exclusion

CCT or cohort: Is the paper:

	Yes	No	?
A parallel controlled trial or a cohort study?			
In adults (18 years plus) who have taken NSAIDs for at least 3 weeks (21 days)?			
Comparing 1. Older NSAIDs plus H_2RAs compared with older NSAIDs (alone or with placebo gastroprotection) 2. Older NSAIDs plus PPIs compared with older NSAIDs (alone or with placebo gastroprotection) 3. Older NSAIDs plus misoprostol compared with older NSAIDs (alone or with placebo gastroprotection) 4. Cox-2 inhibitors compared with older NSAIDs alone 5. Comparing any of the four gastroprotective strategies above with any other active gastroprotective strategy			
If cohort, includes at least 500 participants at start of study (if not cohort, tick 'yes')			
Assessing mortality			

CCT or Cohort for the SR

In / out

Comments:

(c) Health economics papers to collect

Health economics: Is the paper:

	Yes	No	?
A parallel controlled trial or a cohort study?			
Based on work performed at least partly in the UK?			
In adults (18 years plus) who have taken NSAIDs for at least 3 weeks (21 days)?			
Assessing at least one of the following 1. Older NSAIDs plus H_2RAs 2. Older NSAIDs (alone or with placebo gastroprotection) 3. Older NSAIDs plus PPIs 4. Older NSAIDs plus misoprostol 5. Cox-2 inhibitors			
Assessing any of the following:			
Haemorrhage, perforation, pyloric obstruction, symptomatic ulcers, death, endoscopically proven ulcers, gastric symptoms, anaemia, occult bleeding, other adverse events, drop-outs, quality of life, satisfaction, preferences, chest pain, MI, other acute cardiac events, renal disease, resource use, unit costs, total costs of treatment (of drugs, of monitoring or follow-up, of management of adverse outcomes)			

Economic assessment

In / out

Comments:

Appendix 4

Quality assessment and data extraction

(a) Quality data assessment for RCTs

Selection bias

Randomisation procedure:

Allocation concealment
- ❑ A. Adequate concealment
- ❑ B. Concealment unclear
- ❑ C. Inadequate concealment

Were groups comparable at baseline?
- ❑ Yes
- ❑ Unclear
- ❑ No

Performance bias

Were recipients aware of their assigned treatment?
- ❑ Yes
- ❑ Unclear
- ❑ No

Were providers of care aware of the recipients assigned treatment?
- ❑ Yes
- ❑ Unclear
- ❑ No

Detection bias

Were outcome assessors aware of the recipients assigned treatment?
- ❑ Yes
- ❑ Unclear
- ❑ No

Attrition bias

Does the study state how many fewer people were analysed than randomised?
- ❑ Yes
- ❑ Unclear
- ❑ No

Was an *a priori* sample size conducted?
- ❑ Yes
- ❑ Unclear
- ❑ No

Who funded the study (and which of the arms is their drug)?

Notes on allocation concealment

Adequate methods to ensure allocation concealment include:
- ❑ centralised (e.g. allocation by a central office unaware of subject characteristics) or pharmacy-controlled randomisation
- ❑ pre-numbered or coded identical containers which are administered serially to participants

- ❑ on-site computer system combined with allocations kept in a locked unreadable computer file that can be accessed only after the characteristics of an enrolled participant have been entered
- ❑ sequentially numbered, sealed, opaque envelopes
- ❑ similar approaches along with reassurance that the person who generated the allocation scheme did not administer it.

Inadequate approaches to allocation concealment include:
- ❑ alternation
- ❑ use of case record numbers
- ❑ dates of birth or day of the week
- ❑ any procedure that is entirely transparent before allocation, such as an open list of random numbers.

Unclear concealment approaches include:
- ❑ stating that a list or table was used
- ❑ only specifying that sealed envelopes were used
- ❑ reporting an apparently adequate concealment scheme in combination with other information that leads the reviewer to be suspicious.

(b) Quality data assessment for non-RCTs

Type of study:
- ❑ Pseudo-randomised CT,
- ❑ Non-randomised parallel trial,
- ❑ Cohort study

Allocation concealment
- ❑ C. Inadequate concealment

	Active arm	**Control arm**
No. approached		
No. agreed to participate		
No. assessed		
How were participants approached for inclusion?		
How were participants chosen for inclusion?		
Were participants blinded to the intervention?		yes / no / unsure
Were assessors blinded to the intervention?		yes / no / unsure
Were characteristics of the participants well described?		yes / no / unsure
Potential differences between the two groups		
Were characteristics of the drop-outs well described?		yes / no / unsure
Were the participants in different intervention groups recruited from the same population?		yes / no / unsure
Were the participants in different intervention groups recruited at the same time?		yes / no / unsure
Was there adequate adjustment for confounding in the analysis?		yes / no / unsure
Were participants analysed in the groups to which they were allocated?		yes / no / unsure
Were deaths actively sought and recorded?		yes / no / unsure

(c) Data extraction form for RCTs

Ref ID	
Title	
Author/Year	
Dates of study	
Location/setting	
Method of recruitment	
Participants general description (age, sex, baseline disease status, etc.)	

Inclusion criteria	Exclusion criteria
See Pages:	
Remember to highlight relevant section(s) in paper	

DETAILS OF INTERVENTION	Group A CONTROL	Group B	Group C	Group D
Description of intervention Include actual dose and frequency of NSAID and any gastroprotectors used if reported Any other treatment received Ratio, daily dose/min. to max. range in BNF i.e. 120 mg/90–150 mg				
Details of any participant education regarding use of NSAID (type of advice given re potential side effects, how to respond if side-effects occur, and how such advice was provided)				
Length of active treatment from randomisation				
Maximum length of study from randomisation				
Number and frequency of visits from randomisation				
Aspirin allowed? YES/NO				
Analgesic allowed? YES/NO				
Washout period before randomisation? YES/NO details				

BASELINE CHARACTERISTICS	Group A CONTROL	Group B	Group C	Group D
M/F				
Age (mean, SD)				
Smoking history				
Alcohol history				
H. pylori status + test details				
History of aspirin use				
Type + duration arthritis				
History of 1a perforations				
1b ulcers				
1c bleeds				
1d total				
2 history of H_2RA use				

Concomitant use of 3a anti-coags				
3b corticosteroids				
3c antiplatelets				

BASELINE CHARACTERISTICS	Group A CONTROL	Group B	Group C	Group D
4 Concurrent use >1 NSAID				
Co-morbidities				
5a % CVD				
5b % diabetes (1 and 2)				
5c % hypertensive				
5d % renal/hepatic disease				
5e total % co-morbidities				
Total no. risk factors (1–5)				

PARTICIPANT FLOW	Group A CONTROL	Group B	Group C	Group D	TOTAL
Number eligible					
Number assigned to each group					
Number assessed and timing of short-term assessment (3/52–8/52)					
Number assessed and timing of medium-term assessment (>8/52–52/52)					
Number assessed and timing of long-term assessment (>52/52)					
Number assessed at end of study for total GI symptoms					
Number completed					
Total number of drop-outs at end of study					
Number dead at end of study					
What is the study's main outcome and how were participants analysed for this outcome?	ITT as per protocol (only those receiving set regime) completer (all those finishing)				
Were participants excluded from analysis due to GI changes not including frank ulcers?					

OUTCOMES	(Use a different page for each time of assessment, e.g. short, medium, long-term) Timing =			
DON'T COUNT PT >ONCE IN EACH CATEGORY)	Group A CONTROL	Group B	Group C	Group D
Death (all-cause, GI, non-GI) Include age, sex GIVE DENOMINATOR				
Serious GI complications [including haemorrhage, (haemorrhagic erosions, recurrent upper GI bleeds), perforation, pyloric obstruction, melaena, incl. death from any of these] GIVE DENOMINATOR				
Symptomatic ulcers (gastric, duodenal, oesophageal, incl. bleeding ulcers) GIVE DENOMINATOR				
Serious cardiovascular or renal illness leading to contact with primary or secondary health care (incl. angina, MI, stroke, TIA, renal failure, or death from any of these) GIVE DENOMINATOR				

OUTCOMES	(Use a different page for each time of assessment, e.g. short, medium, long-term) Timing =			
	Group A CONTROL	Group B	Group C	Group D
Quality of life GIVE DENOMINATOR				
GI symptoms (nausea, dyspepsia, vomiting, abdo pain, diarrhoea, etc.). Give details GIVE DENOMINATOR Assume each GI symptom counted once for each participant unless otherwise stated				
Endoscopic ulcers (≥3 mm diameter) GIVE DENOMINATOR				

Anaemia GIVE DENOMINATOR				
Occult bleeding GIVE DENOMINATOR				
Economic (YES/NO)				
Participant satisfaction/preferences				
Number of withdrawals due to GI adverse events				
Pain assessment measures used, with scales (e.g. VAS 0 to 100)				
How were adverse events assessed? (e.g. prespecified list checked at each visit or open question about 'any side-effects' or diary, etc.)				
Compliance (how measured and results) GIVE DENOMINATOR				
Subgroup analyses? YES/NO with details				

Any additional comments

CHECKLIST	YES	NO	DATE COMPLETED
Data extraction 1			
Data extraction 2			
Checked and agreed (use as final copy)			
Refs checked			
Action required			

INTER-RATER RELIABILITY

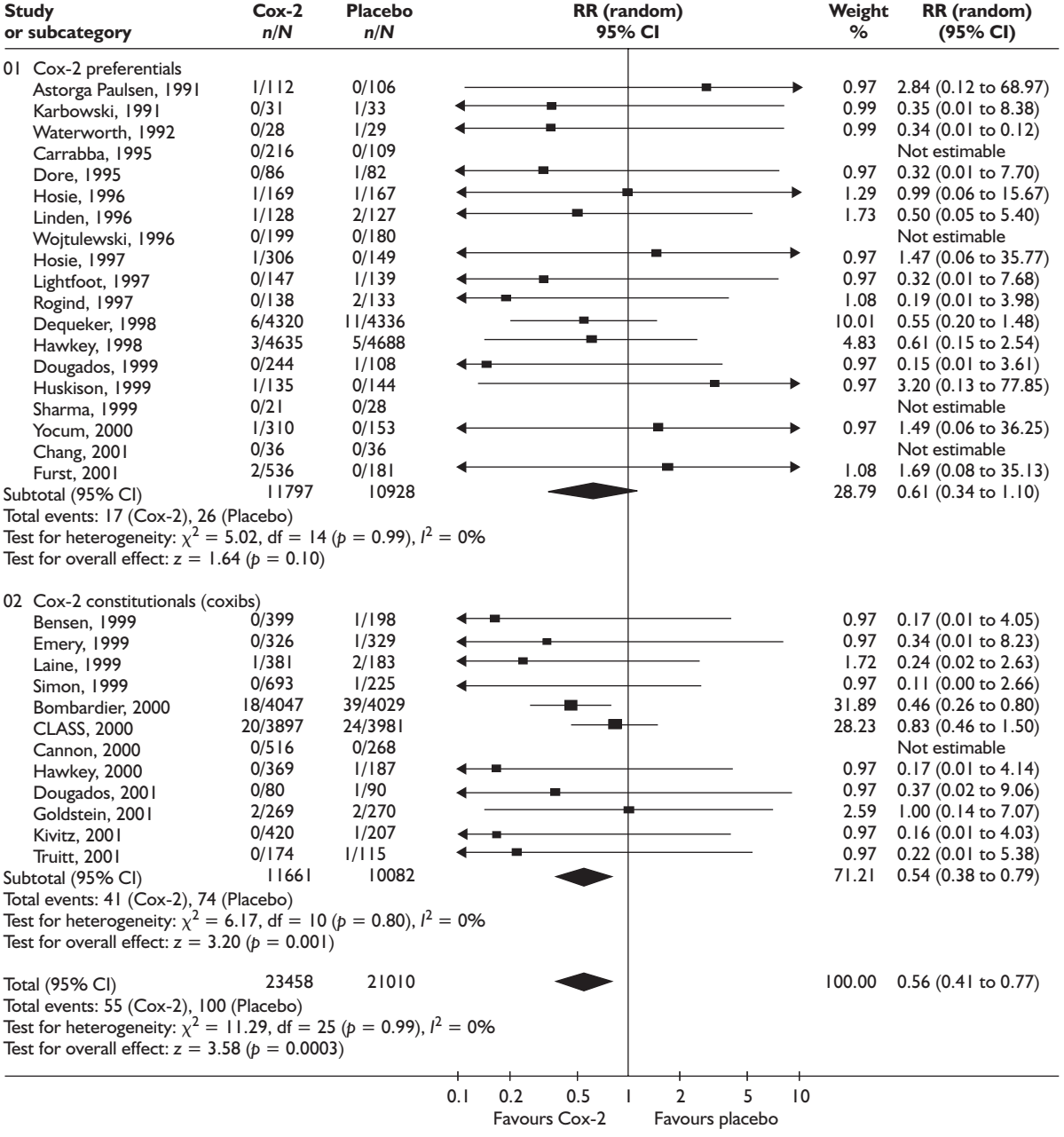
Ref. ID number:	**Agree?**	
	YES	**NO**
Number assessed at end of study		
Total number of drop-outs at end of study		
Total GI symptoms		
Allocation concealment	**TB Y / N**	**LH Y / N**

Appendix 5

Subgrouping the meta-analyses by Cox-2 preferential or Cox-2 constitutional coxib

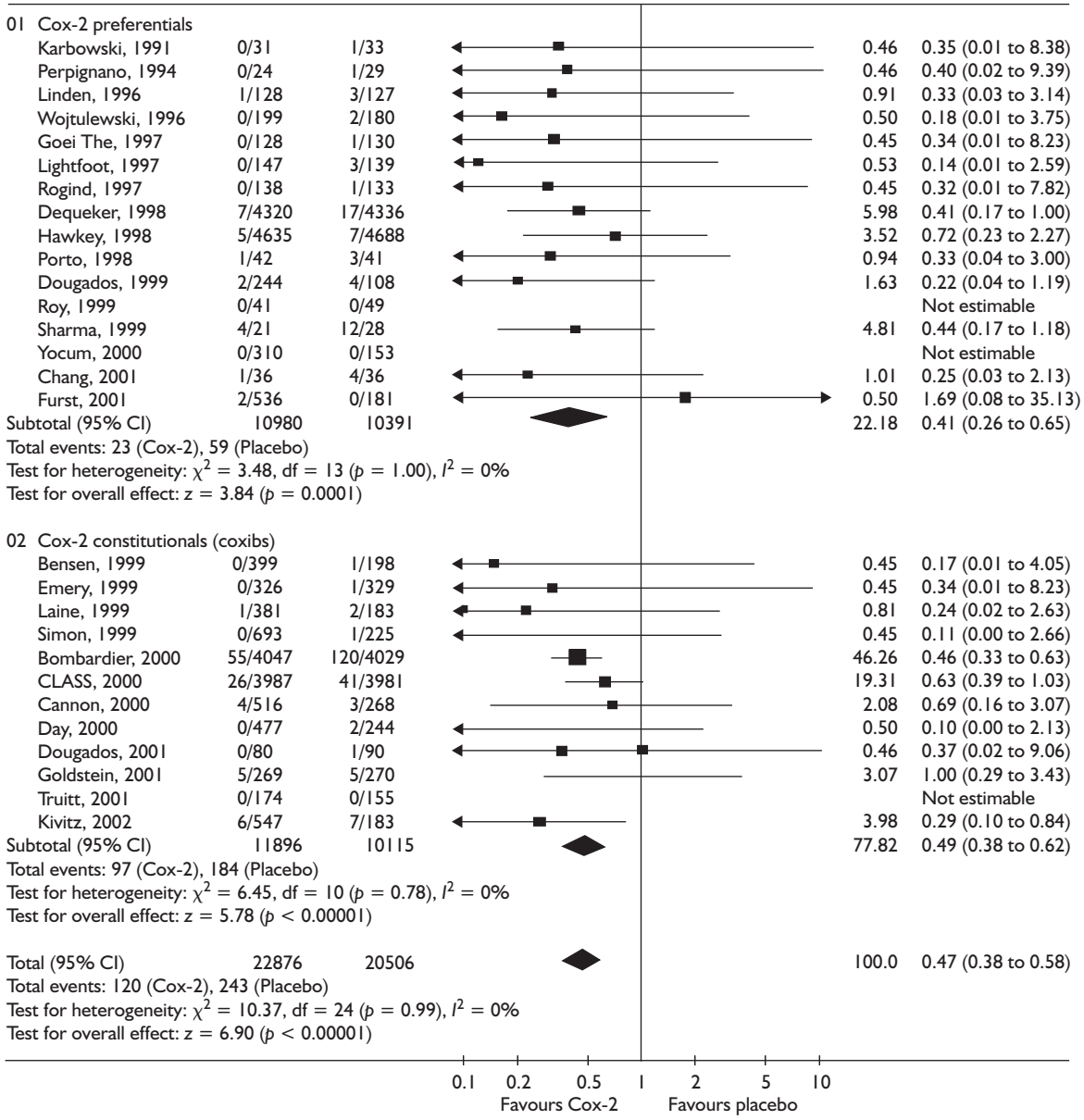
(a) Serious GI complications

Review: NSAID review (subgrouping by Cox-2 preferential)
Comparison: 04 Cox-2 vs Cox-1
Outcome: 12 Serious GI complications, subgrouped by Cox-2 or preferentials



(b) Symptomatic ulcers

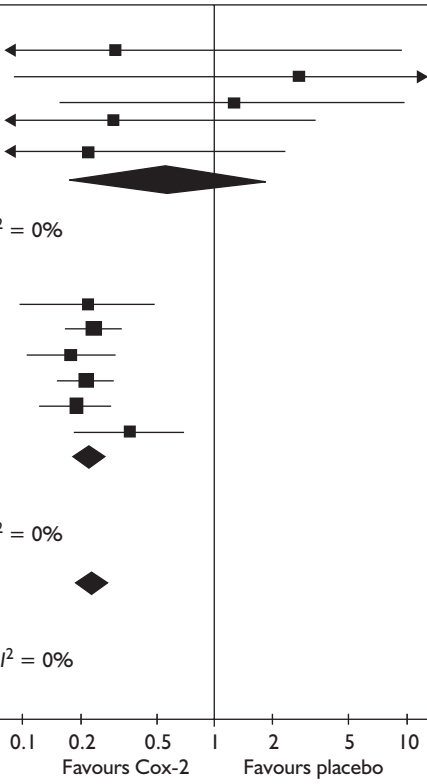
Review: NSAID review (subgrouping by Cox-2 preferentials)
Comparison: 04 Cox-2 vs Cox-1
Outcome: 13 Symptomatic ulcers, subgrouped by Cox-2 or preferentials



(c) Endoscopic ulcers

Review: NSAID review (subgrouping by Cox-2 preferentials)
Comparison: 04 Cox-2 vs Cox-1
Outcome: 14 Endoscopic ulcers, subgrouped by Cox-2 or preferentials

Study or subcategory	Cox-2 *n/N*	Placebo *n/N*	RR (random) 95% CI	Weight %	RR (random) (95% CI)
01 Cox-2 preferentials					
Taha, 1990	0/15	1/15		0.29	0.33 (0.01 to 7.58)
Perpignano, 1991	1/10	0/8		0.30	2.45 (0.11 to 53.25)
Perpignano, 1994	2/24	2/29		0.81	1.21 (0.18 to 7.95)
Porto, 1998	1/42	3/41		0.59	0.33 (0.04 to 3.00)
Chang, 2001	1/36	4/36		0.63	0.25 (0.03 to 2.13)
Subtotal (95% CI)	127	129		2.61	0.58 (0.20 to 1.66)
Total events: 5 (Cox-2), 10 (Placebo)					
Test for heterogeneity: $\chi^2 = 2.41$, df = 4 ($p = 0.06$), $I^2 = 0\%$					
Test for overall effect: $z = 1.01$ ($p = 0.31$)					
02 Cox-2 constitutionals (coxibs)				5.12	0.25 (0.12 to 0.53)
Emery, 1999	8/212	33/218		27.53	0.27 (0.19 to 0.37)
Laine, 1999	44/364	76/167		12.14	0.21 (0.13 to 0.34)
Simon, 1999	23/423	36/137		27.57	0.24 (0.18 to 0.33)
Hawkey, 2000	42/369	88/187		17.23	0.22 (0.15 to 0.33)
Goldstein, 2001	24/269	109/267		7.80	0.39 (0.21 to 0.72)
Kivitz, 2002	21/547	18/183		97.39	0.25 (0.21 to 0.30)
Subtotal (95% CI)	2184	1159			
Total events: 162 (Cox-2), 360 (Placebo)					
Test for heterogeneity: $\chi^2 = 3.25$, df = 5 ($p = 0.66$), $I^2 = 0\%$					
Test for overall effect: $z = 15.82$ ($p < 0.00001$)					
				100.00	0.25 (0.21 to 0.30)
Total (95% CI)	2311	1288			
Total events: 167 (Cox-2), 370 (Placebo)					
Test for heterogeneity: $\chi^2 = 8.09$, df = 10 ($p = 0.62$), $I^2 = 0\%$					
Test for overall effect: $z = 15.82$ ($p < 0.00001$)					



Appendix 6

Full tables of characteristics of included studies

(a) H_2RA plus NSAID versus placebo plus NSAID

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Bianchi Porro, 1987[46] (book chapter) **Location:** one centre, Italy	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** unclear, no details **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** No ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** endoscopy performed and excluded participants without normal gastric mucosa **Baseline NSAID status:** all participants taking one or more NSAIDs **Type and duration of arthritis (years):** rheumatic disease, no further details **Age:** not stated **Sex:** not stated **Inclusion criteria:** patients with rheumatic disease, normal gastric mucosa and treated with one or more NSAIDs **Exclusion criteria:** no details	**Comparison:** ranitidine plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 4 weeks **Interventions:** b, ranitidine tablets 300 mg/150–300 mg (150 mg × 2 daily); a, placebo **NSAIDs:** patients currently prescribed NSAIDs, no further details **Other medication:** no details **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** not stated	**Allocated:** a 127, b 119 **Completed:** a 116, b 110 **Drop-out:** a 11, b 9 **Assessed:** a 127, b 119 **Outcomes reported:** total drop-out **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** No details **FUNDING** **Funded by:** no details **Affiliation of contact author:** L. Sacco Hospital, Milan, Italy **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** unclear
Roth 1987[47] **Location:** one centre, USA	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention to treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** endoscopy performed and excluded participants with ulcer (had to have improvement from grade II or III following 8 weeks of cimetidine or placebo) **Baseline NSAID status:** all participants taking NSAIDs **Type and duration of arthritis (years):** RA or related rheumatic disorders, OA, no further details **Age:** not stated **Sex:** not stated **Inclusion criteria:** 18 years or older, RA or related rheumatic disorders or OA; taking NSAIDs, other concomitant arthritis therapies such as low-dose glucocorticoids (7.5 mg of prednisone	**Comparison:** cimetidine plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 10 months **Interventions:** b, cimetidine tablets 400 mg/400 mg (200 mg ×2 daily); a, matching placebo tablets (×2 daily) **Endoscopy:** 10 months **NSAIDs:** adjusted throughout study without restriction: indomethacin: a 1, b 2 meclofemanate sodium: a 1, b 1 ibuprofin, a 2, b 1 naproxen, a 3, b 1 salsalate, a 2, b 1 aspirin, a 1, b 0	**Allocated:** 36 in total **Completed:** a: 14, b 12 **Drop-out:** 10 in total **Assessed:** a: 14, b 12 **Outcomes reported:** endoscopic ulcers **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** All participants had recent history of grade II or III endoscopy score Concomitant use of anticoagulants (warfarin type): a 0, b 0 **Renal/hepatic disease:** a 0 b 0 **FUNDING** **Funded by:** Smith Kline & French **Affiliation of contact author:** Arthritis Center, Arizona

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
		daily or less) were allowed, as were disease-modifying antirheumatic drugs (methotrexate sodium, penicillamine, aurothioglucose, hydroxychloroquine sulfate) if stabilised for at least 2 months prior to start of study and dosages not increased throughout study; participants had grade II (hyperemic mucosa, friability; and granularity) and grade III (erosions, defined as discontinuation of epithelium without crater formation) and completed an 8-week RCT, (cimetidine 300 mg four times daily vs matching placebo four times daily), participants with an improvement in grade at endoscopy were then eligible for this study **Exclusion criteria:** pregnant or nursing women or those not practising a clinically effective method of birth control; patients receiving warfarin-type anticoagulants, those who had prior gastric surgery or ulcers, defined as a discontinuation of the epithelium with definite ulcer crater present; history of evidence of hepatic, renal or other disease that might interfere with efficacy or safety analysis	other: a 1, b 5 combination: a 3, b 1 **Other medication:** low-dose glucocorticoids and DMARDs allowed, warfarin not allowed, some participants taking salicylates, steroids, gold salt, penicillamine, antineoplastics **Aspirin allowed:** no **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** not stated		Institutes, Phoenix, AZ, USA **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** unclear

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Ehsanullah, 1988[48] **Location:** 18 centres in 5 countries (France, Ireland, Norway, Sweden, UK)	**Method of randomisation:** 'double-blind sequential basis' according to a predetermined randomisation code balanced in blocks of 10 **Allocation concealment:** unclear **Baseline comparability:** no, group b (ranitidine) younger, had arthritis longer **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** High	**Baseline GI status:** baseline endoscopy performed and excluded participants without zero Lanza score **Baseline NSAID status:** a 46/126 and b 60/137 had no previous use of NSAIDs **Type of arthritis:** OA: a 96, b 101 RA: a 28, b 34 Other: a 2, b 2 **Duration of arthritis (years):** a 6 (0–45), b 8 (0–50) **Age:** a 60 (22–87), b 57 (25–85) **Sex:** F/M: 158/105 **Inclusion criteria:** RA or OA, aged over 18 years, requiring treatment with NSAIDs, zero Lanza score on baseline endoscopy, at least 1 week without taking NSAIDs prior to study entry **Exclusion criteria:** patients taking gold, penicillamine azathioprine or chloroquine; concomitant use of ulcerogenic drugs, treatment for peptic ulcers during preceding 30 days (except for low-dose antacids), use of corticosteroids, pregnancy or lactation, GI malignancy, dysphagia, RA of the cervical spine, impairment of liver or kidney function	**Comparison:** ranitidine plus mixed NSAIDs vs placebo plus mixed NSAIDs **Duration:** 4–8 weeks (participants continued after 4-week endoscopy only if little or no gastroduodenal damage) **Interventions:** b, ranitidine 300 mg/150–300 mg (150 mg ×2 daily); a, matching placebo (x2 daily) **Endoscopy:** 4, 8 weeks **NSAIDs:** naproxen ≥750 mg/day: 161 piroxicam ≥20 mg/day: 75 diclofenac ≥100 mg/day: 17 indomathacin ≥100 mg/day: 10 **Other medication:** antacids not permitted, gold, penicillamine, azathioprine, chloroquine, ulcerogenic drugs, corticosteroids excluded **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol **Participant education:** not stated **Washout:** yes, 7 days **Number and frequency of visits:** 3 (0, 4 and 8 weeks, also participants with dyspepsia 'dropped in')	**Allocated:** a 146, b 151 **Completed:** a 126, b 137 **Drop-out:** a: 20, b 14 **Assessed:** a: 126, b 137 **Outcomes reported:** GI symptoms, endoscopic ulcers, serious cardiovascular or renal illness, GI drop-outs **How were adverse events assessed:** participants having unscheduled visit due to dyspepsia were encouraged to have endoscopy **How was compliance assessed:** tablet count at 4 weeks, 75% participants took over 90% of treatment medication	**Risk factors:** history of ulcers, a 11, b 11 history of H_2RA use: a 21, b 20 **Concomitant use of corticosteroids:** a 0, b 0 **Renal/hepatic disease:** a 0, b 0 **FUNDING** **Funded by:** unclear but Glaxo Group Research generated the randomisation sequence **Affiliation of contact author:** Glaxo Group Research, UK **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 3/4 **Other:** participants continued after 4-week endoscopy only if little or no gastroduodenal damage

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Robinson, 1989[49] **Location:** 10 centres in the USA	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and participants without zero endoscopy score excluded **Type and duration of arthritis in (years):** primarily arthritis, no other details **Age:** F/M: a 45.9/43.1, b 50.1/47.0 **Sex:** F/M: 93/51 **Inclusion criteria:** requiring NSAID therapy primarily for arthritis **Exclusion criteria:** baseline stomach or duodenum endoscopy score of >0, previous gastric surgery, Zollinger–Ellison syndrome or other pathological secretory condition, renal impairment (serum creatinine 2 mg/dl or more), elevated SGPT level (3× normal), hypersensitivity to H_2 antagonists, use of NSAIDs within 48 h prior to start of study, consumption of anticholinergics, triclyclic antidepressants, potassium supplements, reserpine, sucralfate or steroids during the week prior to the study, use of >10 mg prednisone or equivalent per day, any unstable medical problem, mental impairment or alcoholism; pregnancy or lactation	**Comparison:** ranitidine plus mixed NSAIDs vs placebo plus mixed NSAIDs **Duration:** 8 weeks **Interventions:** b, ranitidine 300 mg/150–300 mg (150 mg ×2 daily); a, placebo (×2 daily) **Endoscopy:** 1, 4 and 8 weeks **NSAIDs:** a + b, choice of NSAID specified for each participant by referring physician or randomly assigned if physician had no preference ibuprofen ≥ 1600 mg/day: a 17, b 12 naproxen ≥ 750 mg/day: a 25, b 27 sulindac ≥ 300 mg/day: a 17, b 19 indomethacin ≥ 100 mg/day: a 8, b 5 piroxicam ≥ 20 mg/day: a 5, b 7 other: a 0, b 2 **Other medication:** antacid (Maalox) permitted, anticholinergics, tricyclic antidepressants, potassium supplements, reserpine, sucralfate or steroids excluded **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** 48 h for NSAIDs, 1 week for anticholinergics, tricyclic antidepressants, potassium supplements, reserpine, H_2 antagonists, sucralfate, steroids **Number and frequency of visits:** 4 (0, 1, 4 and 8 weeks)	**Allocated:** a 72, b 72 **Completed:** unclear **Drop-out:** unclear **Assessed:** a 50, b 60 **Outcomes reported:** endoscopic ulcers **How were adverse events assessed:** not stated **How was compliance assessed:** tablet count, result not reported	**Risk factors:** no details **FUNDING** **Funded by:** Glaxo **Affiliation of contact author:** Oklahoma City Clinic, Oklahoma City, OK, USA **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 1/7? **Other:** participants withdrawn if clinically significant bleeding on endoscopy

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Swift, 1989,[50] **Location:** University of Wales, rheumatology clinics at Cardiff and Singleton Hospital, UK	**Method of randomisation:** 'randomly allocated by pharmacist' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed: 4 participants had ulcers (2 had oesophageal ulcers, 1 had oesophageal ulcer and duodenal ulcer, 1 had gastric ulcer), 19 had erosions of other types and 1 had normal endoscopy **Baseline NSAID status:** all participants had been taking NSAIDs for at least 3 months **Type and duration of arthritis (years):** rheumatoid disease $n = 20$, OA $n = 3$, cervical spondylosis $n = 1$, no other details **Age:** 56.5 (32–70) **Sex:** F/M: 13/11 **Inclusion criteria:** patients attending rheumatology clinics, taking regular daily doses of an NSAID for 3 months or more **Exclusion criteria:** no details	**Comparison:** ranitidine plus mixed NSAIDs vs placebo plus mixed NSAIDs **Duration:** 14 weeks (2 × 7 week treatment periods) **Interventions:** c, ranitidine 600 mg/150–300 (300 mg ×2 daily) for 7 weeks then 300 mg/150–300 μg (150 mg ×2 daily) for next 7 weeks; b, ranitidine 300 mg/150–300 μg (150 mg ×2 daily) for 7 weeks then 600 mg/150–300 μg (300 mg ×2 daily) for next 7 weeks; a, placebo (number of tablets given corresponded with groups b and c) **Endoscopy:** 1, 8 and 15 weeks **NSAIDs:** no details **Other medication:** other second-line therapy allowed to continue **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** yes, 1 week **Number and frequency of visits:** 4 (0, 1, 8 and 15 weeks)	**Allocated:** a 8, b 8, c 8 **Completed:** a 8, b 8, c 8 **Drop-out:** a 0, b 0, c 0 **Assessed:** a 8, b 8, c 8 **Outcomes reported:** mortality, endoscopic ulcers, GI drop-outs, total drop-outs **How were adverse events assessed:** daily diary cards to record symptoms on scale 0–3 and average daily scores for each 7-week period were calculated **How was compliance assessed:** not stated	**Risk factors:** 4 participants had ulcers (2 had oesophageal ulcers, 1 had oesophageal ulcer and duodenal ulcer, 1 participant had gastric ulcer) **FUNDING** **Funded by:** unclear, but Glaxo provided placebo **Affiliation of contact author:** University Hospital of Wales, UK **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 0/6 **Other:** 2 placebo groups analysed together; 2 participants in group b and 1 in group c were taking less than minimum recommended dose of NSAIDs; participants with baseline ulcer excluded from analyses of endoscopic data; participants with baseline ulcer cannot be excluded from other outcome data by reviewers

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Simon, 1990[51,157,158] **Location:** 5 different centres including Heidelburg and Hamburg, Germany	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and excluded participants with frank ulcers (but not haemorrhages and/or erosions) **Baseline NSAID status:** participants had to have been taking NSAIDs for at least 3 months **Type and duration of arthritis (years):** AS, RA, OA, no other details **Age:** a 52, b 50 **Sex:** F/M: 21/25 **Inclusion criteria:** AS, RA, OA; mean pre-trial durations of NSAID (diclofenac, indomethacin, piroxicam) use at least 3 months, presence of epigastric distress, endoscopically proven morphological changes in gastric and duodenal mucosa **Exclusion criteria:** history of gastric ulcers and/or ulcer complications; pregnancy, lactation, severe concomitant disease, participants taking corticosteroids or gold preparations	**Comparison:** ranitidine plus mixed NSAIDs vs placebo plus mixed NSAIDs **Duration:** 4–8 weeks (treatment continued after 4 weeks if erosions not healed) **Interventions:** b, ranitidine 300 mg/150–300 (150 mg ×2 daily); a, placebo (×2 daily) **Endoscopy:** 4, 8 weeks **NSAIDs:** a + b: at pre-trial dosage levels diclofenac 100–300 mg/day: a 13, b 13 piroxicam 20–30 mg/day: a 5, b 6 indomethacin 50–300 mg/day: a 5, b 4 **Other medication:** antacids not allowed, corticosteroids and gold preparations were excluded **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 3 (0, 4 and 8 weeks)	**Allocated:** 48 in total **Completed:** unclear **Drop-out:** unclear **Assessed:** a 23, b 23 **Outcomes reported:** endoscopic ulcers **How were adverse events assessed:** diary cards, 45% group a (placebo) vs 80% group b (ranitidine) = symptom free but most participants did not complete diary cards **How was compliance assessed:** tablet count, result not reported	**Risk factors:** history of PUBs: a 0, b 0 Concomitant use of corticosteroids: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** Krankenhaus Schwetzingen, Schwetzingen **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 0/4 **Other:** treatment continued after 4 weeks if erosions not healed

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Yanagawa, 1991[52] **Location:** 13 institutions in Japan	**Method of randomisation:** 'envelope method' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** yes **Intention-to-treat:** no ***A priori* sample size:** Unclear **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and excluded participants with more than erosion and haemorrhage at more than 2 sites and more than one area of the stomach; more than erosion and haemorrhage at 1 or 2 sites of the duodenum **Baseline NSAID status:** some participants were not taking NSAIDs prior to study, some were, numbers unclear **Type and duration of arthritis (years):** RA: a 11, b 17 Spondylosis deformans, a 2, b 3 Lumbago, a 9, b 6 Degenerative gonarhtrosis, a 1, b 3 Scapulohumeral periarthritis, a 2, b 1 Carvico-omo-brachial syndrome, a 0, b 2 Others, a 8, b 7 No further details **Age:** a 52.9, b 53.4 **Sex:** F/M: 43/29 **Inclusion criteria:** participants with rheumatic disease or those with lumbago and cervico-omobrachial syndrome who required treatment with NSAIDs, patients receiving previous treatment with NSAIDs in whom a 1-week washout period was possible or those who were not under treatment with NSAIDs at the start of the trial, patients who had did not have endoscopically determined lesions (Lanza score of 2 or more) in the stomach or duodenum **Exclusion criteria:** pregnancy, nursing mothers, or patients judged by attending physician as unsuitable	**Comparison:** ranitidine plus mixed NSAIDs vs placebo plus mixed NSAIDs **Duration:** 8 weeks **Interventions:** b, ranitidine 300 mg/150–300 μg (150 mg ×2 daily); a, placebo (×2 daily) placebo similar to ranitidine in appearance, taste and odour **Endoscopy:** 2, 4 and 8 weeks (adjusted with appearance of subjective or objective symptoms) **NSAIDs:** a + b: indomethacin: a 1, b 3 diclofenac: a 12, b 16 mefanamic acid: a 4, b 6 piroxicam: a 12, b 10 others: a 4, b 4 **Other medication:** concomitant use of drugs for gastritis, antiulcer drugs, anticholinergics and antacids was prohibited **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** yes, 1 week **Number and frequency of visits:** 4 (0, 2, 4 and 8 weeks)	**Allocated:** a 37, b 43 **Completed:** a 7, b 7 **Drop-out:** a 30, b 36 **Assessed:** a 7, b 7 **Outcomes reported:** GI symptoms, endoscopic ulcers, total drop-out **How were adverse events assessed:** subjective and objective symptoms were assessed on scale of 1–4 (severe, moderate, slight, none), severity, duration, extra treatment required and clinical course recorded and relation to NSAID investigated **How was compliance assessed:** not stated	**Risk factors:** CVD (including hypertension): a 10, b 12 Hepatic disease: a 4, b 6 history of gastroduodenal disease: a 5, b 7 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** St Marianna University School of Medicine, Japan **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 0/5 **Other:** participants with lesser lesions were removed from trial when lesions were seen on endoscopy

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Levine, 1993[45] **Location:** multiple sites in USA	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes (participants not returning are classed as treatment failures) ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and excluded participants with acute ulcer **Baseline use of NSAIDs:** all on daily NSAIDs **Type and duration of arthritis:** OA, no other details **Age:** a 57.5 b 56.9 **Sex:** F/M: 325/171 **Inclusion criteria:** OA, daily therapy expected to continue with an NSAID (piroxicam, ibuprofen, naproxen, diclofenac sodium) and complaints of NSAID associated symptoms **Exclusion criteria:** endoscopy disclosing active peptic ulceration 3mm or larger; treatment with another acid-lowering agent; history of a definitive acid-lowering operation; previous esophageal or gastric surgery; pyloric stenosis; concurrent serious systemic disorders; any condition associated with poor patient compliance; admission laboratory values outside the normal range; women of childbearing potential not using an approved method of contraception, pregnant or lactating women	**Comparison:** nizatidine plus mixed NSAIDs vs placebo plus mixed NSAIDs **Duration:** 3 months **Interventions:** b, nizatidine 300 mg/150 μg (150 mg ×2 daily); a, placebo (×2 daily) **Endoscopy:** 1, 2 and 3 months **NSAIDs:** a + b piroxicam, ibuprofen, naproxen, diclofenac, all within label medication dose for OA **Other medication:** liquid antacid prescribed for moderate to severe abdominal pain, other acid-lowering drugs, prokinetic agents and misoprostol not allowed **Aspirin allowed:** yes, no more than 5 g daily for cardiac prophylaxis **Analgesic allowed:** yes acetaminophen, codeine, propaxyphene for non-GI pain relief **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 4 (0, 1, 2 and 3 months)	**Allocated:** a 248, b 248 **Completed:** a 171, b 185 **Drop-out:** a 77, b 63 (but includes participants with ulcers at last visit endoscopy) **Assessed:** a 248, b 248 **Outcomes reported:** mortality, serious GI complications, serious cardiovascular or renal illness, GI symptoms, endoscopic ulcers, anaemia, GI drop-outs, total drop-outs **How were adverse events assessed:** solicited reports of adverse events at each visit **How was compliance assessed:** cross-checking patient daily logs with number of pills remaining for study drug and NSAIDs	**Risk factors:** history of ulcers, a 45, b 43 **FUNDING** **Risk factors:** no details **Funded by:** Eli Lilly **Affiliation of contact author:** Lilly Research Laboratories, Eli Lilly, USA **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 3/3

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Rugstad, 1994[53] **Location:** Norway, multicentre	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** unclear, imbalance at baseline regarding previous **GI discomfort:** a 19%, b 23% **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no endoscopy performed, some participants had GI symptoms **Baseline NSAID status:** 73/259 (group a) and 71/253 (group b) had not previously taken NSAIDs **Type of arthritis (years):** OA (newly diagnosed): a 73, b 71 **Age:** M/F: over 70 years: a 90/29, b 89/22 **Sex:** F/M: 357/155 **Inclusion criteria:** patients 18 years or older with OA knee and/or hip, confirmed with X-ray and with symptoms of a degree that required an NSAID **Exclusion criteria:** pregnant or breastfeeding females, history of GI bleeding or bleeding disorders; peptic ulcer or serious dyspeptic symptoms during the last 12 months; known idiosyncrasy to NSAID, aspirin or cimetidine; history of asthma, concomitant treatment with oral anticoagulants, phenytoine, theophylline, glucocorticoids and antacids	**Comparison:** cimetidine plus mixed NSAIDs vs placebo plus mixed NSAIDs **Duration:** 4 weeks **Interventions:** b, cimetidine 800 mg/400 mg (400mg ×2 daily); a, matching placebo (twice daily) **NSAIDs:** a + b: either started or continued NSAID, choice and dose left to physician responsible **Other medication:** concomitant treatment with oral anticoagulants, phenytoin, theophylline, glucocorticoids and antacids excluded **Aspirin allowed:** yes **Analgesic allowed:** yes **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 3 (0, 2 and 4 weeks)	**Allocated:** a 285, b 285 **Completed:** not stated **Drop-out:** not stated **Assessed:** a 259, b 253 **Outcomes reported:** GI symptoms **How were adverse events assessed:** "Have you experienced any side-effects?" if yes "Have you experienced any GI side-effects?" if yes asked regarding abdominal pain, epigastrial pain, heartburn, belching, nausea, vomiting, diarrhoea **How was compliance assessed:** tablet count, 92% took 70% or more medication in group a (placebo) and 94% took 70% or more medication in group b (cimetidine), but participants with missing values were assumed compliant	**Risk factors:** history of ulcer (previous 12/12): a 0, b 0 **History of bleeds:** a 0 b 0 **Concomitant use of anticoagulants:** a 0, b 0 **Cardiovascular drug use:** a 165, b 153 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** Department of Clinical Pharmacology, Rikshospitalet, Oslo, Norway **Affiliation of statistician:** Life Insurance Companies Institute of Medical Statistics, Oslo, Norway **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 0/4

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Simon, 1994[54] (abstract) **Location:** multicentre, USA	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and excluded participants with ulcers **Type and duration of arthritis (years):** OA, no further details **Age:** 59.4 (23–86) in total **Sex:** F/M: no details **Inclusion criteria:** patients who required NSAIDs to treat OA, absence of gastric ulceration **Exclusion criteria:** gastric ulceration on endoscopy (mucosal break of 3 mm or more)	**Comparison:** famotidine plus NSAIDs vs placebo plus NSAIDs **Duration:** 12 weeks **Interventions:** c, famotidine 80 mg/20 mg (40 mg ×2 daily); b, famotidine 40 mg/20 mg (20 mg ×2 daily); a, matching placebo (×2 daily) **Endoscopy:** 4, 8 and 12 weeks **NSAIDs:** a + b: NSAIDs, no further details **Other medication:** no details **Aspirin allowed:** yes **Analgesic allowed:** yes **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 3 (0, 2 and 4 weeks)	**Allocated:** a 102, b 100, c 103 **Completed:** not stated **Drop-out:** not stated **Assessed:** a 102, b 100, c 103 **Outcomes reported:** Serious GI complications, endoscopic ulcers **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** no details **FUNDING** **Funded by:** not stated **Affiliation of contact author:** Merck Research Laboratories **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** ?/5

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Taha, 1996[55,159] **Location:** Glasgow and Nottingham, UK	**Method of randomisation:** 'randomly assigned with the use of a computer-generated schedule', stratified by type of arthritis **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and excluded participants with ulcer **Baseline use of NSAIDs:** all participants taking NSAIDs for at least 1 month **Type of arthritis:** RA/OA; a 76/17, b 80/15 **Duration of arthritis (years):** a 9.6 (0–50), b 12.2 (0–44), c 10.1 (0–47) **Age:** a 53.4 (22–78), b 57.2 (18–88), c 55 (22–83) **Sex:** F/M: 208/77 **Inclusion criteria:** 18 years or more, RA or OA, standard doses of NSAID for at least 1 month and likely to continue for next 6 months **Exclusion criteria:** taking antiulcer drugs other than antacids within 7 days before enrolment, 7.5 mg/day or more of prednisolone (or the equivalent with another corticosteroids), methotrexate or antineoplastic; lactation, childbearing potential in absence of contraception, renal failure, insulin-dependent diabetes mellitus, clinically important abnormal laboratory tests, ulcers on baseline endoscopy	**Comparison:** famotidine plus mixed NSAIDs vs placebo plus mixed NSAIDs **Duration:** 24 weeks **Interventions:** c, famotidine 80 mg/20 μg (40 mg ×2 daily); b, famotidine 40 mg/20 mg (20 mg x2 daily); a placebo (×2 daily) **Endoscopy:** 4, 12 and 24 weeks **NSAIDs:** a + b: diclofenac, a 24, b 26, c 22 indomethacin, a 19, b 15, c 19 naproxen, a 19, b 13, c 18 ibuprofen, a 9, b 10, c 11 ketoprofen, a 5, b 5, c 5 fenbrufen, a 4, b 6, c 6 other, a 14, b 23, c 20 **Other medication:** antacid (Maalox) prescribed for relief of dyspepsia, DMARDs allowed including sulfasalazine, gold, penicillamine, prednisolone, hydroxychloroquine **Aspirin allowed:** yes, not full dose **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 4 (0, 4, 12 and 24 weeks)	**Allocated:** a 93, b 95, c 97 **Completed:** a 80, b 81, c 81 **Drop-out:** a: 13, b 14, c 16 **Assessed:** a 93, b 95, c 97 **Outcomes reported:** symptomatic ulcer, serious cardiovascular or renal illness, GI symptoms, endoscopic ulcers, GI drop-outs, total drop-outs **How were adverse events assessed:** participants asked to record abdominal symptoms on diary cards, abdominal pain assessed on a 3-point scale (1 = mild, 2 = moderate, 3 = severe), participants questioned about adverse events at each visit **How was compliance assessed:** recorded tablet count a 12, b 11, c 14 had poor compliance with study drugs or NSAIDs	**Risk factors:** history of ulcers: 9, b 15, c 13 **FUNDING** **Funded by:** Merck **Affiliation of contact author:** Glasgow Royal Infirmary, UK **Affiliation of statistician:** Applied Statistics **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 3/10

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Ten Wolde, 1996[56] **Location:** rheumatology outpatients, The Netherlands	**Method of randomisation:** 'consecutive patients randomly assigned', predetermined randomisation list balanced in blocks of 10 **Allocation concealment:** inadequate **Baseline comparability:** no **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** baseline endoscopy performed and excluded participants with active ulcer (or included after ulcer healing with ranitidine 300 mg ×2 daily for 4 weeks) **Baseline use of NSAIDs:** all on NSAIDs **Type and duration of arthritis (years):** RA, a 13, b 22 **Age:** a 58, b 67 **Sex:** F/M: 10/10 **Inclusion criteria:** RA who needed chronic NSAID medication (4 days per week or more) had a history of PUD as established by endoscopy or barium meal radiography, but had no active ulcer as established by endoscopy at entry to study (if PUD found at baseline then patient was treated with ranitidine 300 mg twice daily for 4 weeks and only after ulcer healing was established by endoscopy was the patient considered eligible for the study) **Exclusion criteria:** severe concomitant disease or a recent GI haemorrhage	**Comparison:** ranitidine plus mixed NSAIDs vs placebo plus mixed NSAIDs **Duration:** 12 months **Interventions:** b, ranitidine, 600 mg/150–300 mg (300 mg ×2 daily); a, placebo (×2 daily) **Endoscopy:** 6 and 12 months **Other medication:** Participants taking DMARDs and prednisone allowed to continue **NSAIDs:** a + b: participants encouraged to use NSAIDs in daily doses as stable as possible **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 6 (0, 3, 6, 9 and 12 months)	**Allocated:** a 15, b 15 **Completed:** unclear **Drop-out:** unclear **Assessed:** a 10, b 10 **Outcomes reported:** mortality, endoscopic ulcers, GI drop-out **How were adverse events assessed:** participants asked about gastric symptoms every 3 months **How was compliance assessed:** not stated	**Risk factors:** history of ulcers: all participants **FUNDING** **Funded by:** Glaxo, all medications packed and provided by Glaxo **Affiliation of contact author:** University Hospital Leiden, the Netherlands **Affiliation of statistician:** University Hospital Leiden, The Netherlands **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 0/3

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Van Groenendael, 1996[57] **Location:** rheumatology clinics, Rotterdam, The Netherlands	**Method of randomisation:** 'predetermined randomisation list balanced in blocks of 6' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and participants excluded if more than zero Lanza score (non-erosive) in Study 1 and if not 1–3 Lanza score (erosive but without peptic ulcer disease) in Study 2; all participants had to present with dyspeptic complaints **Baseline use of NSAIDs:** all participants taking NSAIDs prior to study **Type of arthritis:** OA/RA Study 1: a 18/11, b 19/10 Study 2: a 12/5, b 7/10 **Duration of arthritis (years):** Study 1: a 6 (2–30), b 5 (0.5–18) Study 2: a 5 (1–31), b 6 (2–33) **Age:** Study 1: a 52, b 53 Study 2: a 60, b 62 **Sex:** Study 1: F/M: 45/13 Study 2: F/M: 26/ 9 **Inclusion criteria:** RA or OA, with nausea, heartburn, epigastric pain, eructation and/or vomiting **Exclusion criteria:** taking antipeptic medication in the 4 weeks preceding the study, dyspeptic complaints not related to NSAID use according to the investigator, history of peptic ulcer disease documented with X-ray and/or endoscopy	**Comparison:** ranitidine plus mixed NSAIDs vs placebo plus mixed NSAIDs **Duration:** 4 weeks **Interventions:** b, ranitidine 300 mg/150–300 mg (150 mg ×2 daily); a, placebo (×2 daily) **NSAIDs:** Study 1 and 2: a + b: daily stable doses of NSAIDs (ketoprofen 200, indomethacin 150, naproxen 1000, piroxicam 20, salicylates 3600 mg/day) **Endoscopy:** at 4 weeks **Other medication:** antacids obtained from hospital pharmacy, DMARD use allowed **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** twice (0 and 4 weeks)	**Allocated:** Study 1: a 29, b 29 Study 2: a 18, b 18 **Completed:** Study 1: a 29, b 29 Study 2: a 18, b 17 **Drop-out:** Study 1: a 0, b 0 Study 2: a 0, b 1 **Assessed:** Study 1: a 29, b 29 Study 2: a 18, b 17 **Outcomes reported:** Study 1: mortality, serious GI complications, symptomatic ulcers, GI symptoms, GI drop-outs, total drop-outs Study 2: mortality, serious GI complications, GI symptoms, endoscopic ulcers, GI drop-outs, total drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** tablet count, results not reported	**Risk factors:** history of ulcers: a 0, b 0 **FUNDING** **Funded by:** Glaxo **Affiliation of contact author:** Dr Daniel den Hoed Kliniek, The Netherlands **Affiliation of statistician:** Erasmus University of Rotterdam, The Netherlands **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 0/4 **Other:** salicylates used as NSAID treatment by 10 participants in total (Studies 1 and 2 combined = 10/94)

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Hudson, 1997[58] **Location:** Nottingham and Glasgow, UK	**Method of randomisation:** 'randomised' Allocation concealment: unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and participants *only included* with healed ulcers following healing study or in the 4 weeks following, (patients without ulceration prior to the healing study entered a prophylaxis study, see Taha *et al.*[55]) **Baseline use of NSAIDs:** all participants had been taking NSAIDs for at least 1 month, but NSAIDs withdrawn to heal ulcers over the previous 4–12 weeks **Type and duration of arthritis:** RA: a 33, b 34; OA: a 6, b 5; no other details **Age:** median: a 55 (35–89), b 58 (32–79) **Sex:** F/M: 52/26 **Inclusion criteria:** 18 years or more, RA or OA, had been receiving an NSAID within the range of standard recommended dosage for at least 1 month before endoscopy, healed ulcers during healing study or following 4 weeks and wished to continue NSAID therapy **Exclusion criteria:** taking antiulcer drugs other than antacids for less than 7 days before study entry or were taking steroids at a dosage equivalent to 7.5 mg prednisolone daily or more, methotrexate or antineoplastic drugs, lactation, child-bearing potential, renal failure, diabetes or clinically significant pre-study laboratory abnormalities	**Comparison:** famotidine plus mixed NSAIDs vs placebo plus mixed NSAIDs **Duration:** 24 weeks **Interventions:** b, famotidine 80 mg/20 mg (40 mg ×2 daily); a, placebo (×2 daily) **Endoscopy:** 4, 12 and 24 weeks **NSAIDs:** a + b: naproxen: a 11, b 14 indomathacin: a 9, b 3 diclofenac: a 4, b 6 other: a 15, b 16 **Other medication:** antiulcer drugs other than antacids, steroids at a dosage equivalent to 7.5 mg prednisolone daily or more, methotrexate or antineoplastic drugs were excluded **Aspirin allowed:** yes **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** no **Number and frequency of visits:** 4 (0, 4, 12, 24 weeks)	**Allocated:** a: 39, b 39 **Completed:** unclear **Drop-out:** unclear **Assessed:** a: 39, b 38 for endoscopy **Outcomes reported:** deaths, endoscopic ulcers **How were adverse events assessed:** abdominal symptoms recorded daily on specific diary cards, open questioning at each visit **How was compliance assessed:** tablet count, result not reported	**Risk factors:** history of ulcers: all participants Diabetes: a: 0, b 0 **FUNDING** **Funded by:** Merck **Affiliation of contact author:** University Hospital of Nottingham, UK **Affiliation of statistician:** Applied Statistics **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 3/9 **Other:** 'data for 24-week endoscopy confounded by selective drop-out of ulcer patients'

(b) PPI plus NSAID versus placebo plus NSAID

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Ekstrom, 1996[59] **Location:** 18 hospitals in Finland, Norway and Sweden	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** no, more participants with RA in omeprazole arm (b) **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** high	**Baseline GI status:** no baseline endoscopy performed but excluded participants without history of previous dyspepsia or uncomplicated peptic ulcer disease **Baseline NSAID status:** receiving continuous NSAID treatment **Type of arthritis:** OA: a 54, b 49; RA: a 8, b 14; other: a 28. b 22. No other details **Age:** a 59 (30-78), b 58 (25–80) **Sex:** M/F: a 23/67, b 31/54 **Inclusion criteria:** 25–78 years, requiring continuous NSAID treatment for at least 3 months because of OA, RA, spondylarthritis, AS or any other condition requiring continuous NSAID therapy and with a history of dyspepsia or uncomplicated peptic ulcer disease **Exclusion criteria:** patients who had taken more than half the recommended minimum dose of NSAIDs during the 4 weeks prior to randomisation, had recent ulcer bleeding or previous major bleeding or perforation, more than mild dyspeptic symptoms at inclusion, history of gastric surgery, or verified gastro-oesophageal reflux disease, were pregnant or breast-feeding, needed systemic medication with prednisolone in doses of more than 10 mg daily or equivalent doses of other steroids were contraindicated for study drugs or had clinically significant abnormalities in baseline laboratory screen	**Comparison:** omeprazole plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 3 months **Interventions:** b, omeprazole 20 mg/20 mg (20 mg once daily); a, identical placebo (once daily) **NSAIDs:** open NSAID treatment at least minimum recommended dose, combinations and changes in type and dose were permitted, included (descending order with most common first) naproxen, diclofenac, tenoxicam, ibuprofen, ketoprofen, sulinda and others **Endoscopy:** 1 and 3 months Other medication: no details **Aspirin allowed:** not stated **Analgesic allowed:** not stated Participant education: not stated **Washout:** not stated **Number and frequency of visits:** 3 (0, 1 and 3 months)	**Allocated:** a 91, b 86 **Completed:** unclear **Drop-out:** unclear **Assessed:** a 90, b 85 **Outcomes reported:** serious GI complications, symptomatic ulcers, GI symptoms, endoscopic ulcers, GI drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** history of ulcers, a 21, b 23 **FUNDING** **Funded by:** Astra, Sweden **Affiliation of contact author:** Sandvikens Hospital, Sweden **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** unclear **Other:** participants were withdrawn if ≥ 10 erosions, or more than mild dyspeptic symptoms

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Bianchi Porro, 1998[60] **Location:** rheumatology unit, L. Sacco University Hospital, Milan, Italy	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and excluded participants without normal UGI endoscopy **Type of arthritis:** OA: a 53, b 50; no other details **Age:** a 51.6 b 53.1 **Sex:** M/F: a 11/42, b 5/45 **Inclusion criteria:** OA requiring at least 3 weeks of NSAID treatment, normal UGI endoscopy on screening, women of child-bearing potential had adequate contraception **Exclusion criteria:** cardiovascular, GI, renal, metabolic, neurological and haematological disease, psychiatric disorders, previous GI surgery, alcoholism or drug dependency	**Comparison:** Omeprazole plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 3 weeks **Interventions:** b, omeprazole 20 mg/20 mg (20 mg once daily); a, identical placebo (once daily) **NSAIDs:** open treatment with: indomethacin 100 mg daily: a 20, b 16 ketoprofen 150 mg daily: a 14, b 17 diclofenac 150 mg daily: a 19, b 17 **Endoscopy:** 3 weeks **Other medication:** none were receiving antisecretory drugs or any mucosal protective drug at time of study **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** at least 7 days for previous NSAIDs **Number and frequency of visits:** 2 (0 and 3 weeks)	**Allocated:** a 57, b 57 **Completed:** a 53, b 50 **Drop-out:** a 4, b 7 **Assessed:** a 53, b 50 **Outcomes reported:** serious GI complications, GI symptoms, endoscopic ulcers, total drop-out **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** CVD: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** Sacco University Hospital, Italy **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** unclear

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Cullen, 1998[61] **Location:** 19 centres in Ireland, Hungary, France, UK, USA	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and excluded participants who were not free of ulcers and with 10 or fewer gastric erosions and 10 or fewer duodenal erosions **Type of arthritis:** OA: a 41, b 38; RA: a 31, b 33; no other details **Age:** a 56, b 55 **Sex:** M/F: a 30/55, b 26/57 **Inclusion criteria:** patients 18–85 years who were already taking and needed to continue NSAIDs (with more than a minimum daily dose) and who had no more than mild dyspeptic symptoms (epigastric or abdominal pain or empty feeling, heartburn, nausea or bloating), free of ulcers and with 10 or fewer gastric erosions and 10 or fewer duodenal erosions on baseline endoscopy **Exclusion criteria:** use of anti-ulcer medication or steroids in excess of a prednisolone dosage equivalent to 10 mg daily, erosive gastro-oesophageal reflux disease, clinically important bleeding or pyloric stenosis, history of ulcer perforation or surgery, severe concurrent disease or neck instability rendering endoscopy dangerous	**Comparison:** omeprazole plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 6 weeks **Interventions:** b, omeprazole 20 mg/20 mg (20 mg once daily); a, placebo (once daily) **Endoscopy:** at 0, 1, 3 and 6 months **NSAIDs:** with minimum daily dose stated: diclofenac 50 mg: a 22, b 31 naproxen 500 mg: a 17, b 17 indomethacin 50 mg: a 10, b 8 nabumetone 500 mg: a 7, b 8 piroxicam 10 mg: a 8, b 6 other: a 21, b 13 **Other medication:** no other **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 4 (0, 1, 3 and 6 months)	**Allocated:** a 86, b 83 **Completed:** unclear **Drop-out:** unclear **Assessed:** a 85, b 83 **Outcomes reported:** symptomatic ulcers, GI symptoms, endoscopic ulcers **How were adverse events assessed**: not stated **How was compliance assessed:** tablet count, 97.4–99.4% of participants took at least 75% of medication	**Risk factors:** history of ulcers: a 21, b 27 **FUNDING** **Funded by:** Astra Pharmaceuticals **Affiliation of contact author:** Nottingham GI Trials Service **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 2 of 7 worked for Astra **Other:** Minimum allowed daily dose of diclofenac below recommended minimum daily dose in BNF

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Hawkey, 1998[62,65,209–213] OMNIUM **Location:** 93 centres in 14 countries including UK and USA	**Method of randomisation:** 'randomly assigned', randomisation phase not formally balanced according to treatment assignment in the healing phase **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** endoscopy performed and excluded participants without treatment success following 4–8 weeks healing phase (omeprazole 20 mg/day vs omeprazole 40 mg/day vs misoprostol 200 μg/day); treatment success defined as absence of ulcers in the stomach or duodenum and the presence of fewer than five gastric erosions, fewer than five duodenal erosions, and not more than mild symptoms of dyspepsia (corresponded to a 2-point reduction in Lanza scale from grade 4 to grade 2) **Type of arthritis:** OA: a 70, b 129, c 142; RA: a 56, b 107, c 118 other: a 25, b 33, c: 30 combination: a 5, b 5, c 6 **Age:** a 57 (20–80), b 58 (23–79), c 58 (23–85) **Sex:** M/F: a 48/107, b 101/173, c 118/178 **Inclusion criteria:** 18–85 years of age and who had any condition requiring continuous treatment with oral or rectal NSAIDs above a predetermined minimal dose (no maximal dose); treatment success defined as absence of ulcers in the stomach or duodenum and the presence of fewer than five gastric erosions, fewer than five duodenal erosions and not more than mild symptoms of dyspepsia (corresponded to a 2-point reduction in Lanza scale from grade 4 to grade 2) **Exclusion criteria:** concurrent reflux oesophagitis at stage 3 or 4 according to the Savary–Miller classification, clinically important GI bleeding, pyloric stenosis, history of gastric surgery, or GI disorders that might impair the absorption of the study drugs	**Comparison:** misoprostol plus mixed NSAIDs (c) vs omeprazole plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 6 months **Interventions:** c, misoprostol 400 μg /400–800 μg/day, (200 μg ×2 daily; b, omeprazole 20 mg/20 mg (20 mg ×1 daily); a, identical placebo **Endoscopy:** 1, 3 and 6 months **NSAIDs:** (minimum and mean dose) diclofenac (50 mg, 129 mg/day) 23% total participants ketoprofen (100 mg, 137 mg) 16% total participants naproxen (500 mg, 844 mg) 22% total participants **Other medication:** patients could enter the study if they were taking glucocorticoids at a dose ≤10 mg of prednisolone (or its equivalent) **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 4 (0, 1, 3 and 6 months)	**Allocated:** a 155, b 274, c 296 (7 participants unaccounted for) **Completed:** a 139, b 242, c 247 **Drop-out:** a 16, b 33, c 50 **Assessed:** a 155, b 275, c 297 **Outcomes reported:** serious GI complications, quality of life, endoscopic ulcers, total drop-out **How were adverse events assessed:** participants asked if had specific dyspeptic symptoms during the last 7 days and to describe any UGI symptoms on that day, symptoms graded, also symptom diary card used during initial 4 weeks **How was compliance assessed:** tablet count, result not reported	**Risk factors:** 63–64% of participants in each group had recent history of ulcers (remaining participants had recent history of more than 10 gastric or duodenal erosions **FUNDING** **Funded by:** Astra Hassle, Sweden **Affiliation of contact author:** Nottingham Gastrointestinal Trials Service, University Hospital Nottingham, UK **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** One author serves as a consultant for Searle, Australia **Other:** participants were discontinued and excluded from analysis if developed more than 10 erosions or more than moderate dyspepsia or adverse events

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Bianchi Porro, 2000[63] **Location:** Outpatients, L. Sacco University Hospital, Milan, Italy	**Method of randomisation:** 'computer-generated randomisation list' **Allocation concealment:** unclear **Baseline comparability:** no, 43% pantoprazole arm (b) had dyspeptic symptoms vs 18% placebo arm (a) **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** high	**Baseline GI status:** baseline endoscopy performed and excluded participants without lesions grade 0, 1 or 2 **Type and duration of arthritis (years):** OA: a 15, b 24; RA: a 19, b 46; a 5.1 years, b 4.4 years **Age:** a 59, b 58 **Sex:** M/F: a 6/28, b 12/58 **Inclusion criteria:** outpatients over 18 years of age and affected by RA or OA, treated with effective and constant doses of NSAIDs (diclofenac, ketoprofen or indomethacin) for at least 8 weeks prior to the start of the study, Lanza grade 0, 1 or 2 on endoscopy, females who were post-menopausal, surgically sterilised or using adequate contraception **Exclusion criteria:** gastric surgery, recent upper GI bleeding, GI malignancy, inflammatory bowel disease, chronic or acute renal or hepatic disorders, endoscopic evidence of oesophagitis grade 2, 3 or 4 (Savary–Miller classification), pyloric or duodenal stenosis, history of Zollinger–Ellison syndrome, regular intake of drugs with pH-dependent absorption (such as ketoconazole) or severe cardiac or pulmonary impairment, patients needing antisecretory, cytoprotective or corticosteroid drugs, pregnant or lactating females	**Comparison:** pantoprazole plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 12 weeks **Interventions:** b, pantoprazole 40 mg/20 mg (40 mg ×1 daily); a, identical placebo (x1 daily) **Endoscopy:** 0, 4 and 12 weeks, unscheduled endoscopy if dyspeptic symptoms for at least 48 h **NSAIDs:** diclofenac: a 13, b 24 ketoprofen: a 9, b 26 indomethacin: a 12, b 24 **Other medication:** antacids allowed, maximum 3 tablets per day for no more than 48 consecutive hours, any additional medication for GI not permitted **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 3 (0, 4 and 12 weeks)	**Allocated:** a 34, b 70 **Completed:** unclear **Drop-out:** unclear **Assessed:** a 30, b 65 **Outcomes reported:** serious GI complications, endoscopic ulcers, GI drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** tablet count, participants required to take at least 70% NSAIDs and study medication, 4 participants in each group were censored by week 4 for non-compliance	**Risk factors:** concomitant use of corticosteroids: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** Sacco University Hospital, Italy **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 1 of 5 worked for Byk Gulden Italia, Milan, Italy

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Graham, 2002[64,214] **Location:** 63 centres in North America	**Method of randomisation:** 'randomly assigned in blocks of 4', 'randomisation schedule was generated by a statistical specialist who was not involved in the trial design, the randomisation was coded and stored in sealed envelopes' **Allocation concealment:** adequate **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** yes (the statistician), endoscopist also blinded **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** low	**Baseline GI status:** baseline endoscopy performed, patients had to be without *H. pylori*, have history of endoscopically documented gastric ulcer with or without co-existing duodenal ulcer or GI bleeding (2/3 participants had previously completed participation in a healing trial for NSAID-associated gastric ulcer); excluded patients with gastric or duodenal ulcer crater at least 5 mm in diameter or more than 25 erosions or erosive reflux oesophagitis **Baseline NSAID status:** treatment with stable full therapeutic doses of an NSAID for at least the previous month (except nabumetone or aspirin at 1300 mg/day or more) **Type and duration of arthritis (years):** no details **Age:** a 60.5, b 59.4, c 61.6, d 60.2 **Sex:** M/F: a 46/87, b 43/91, c 50/86, d 48/84 **Inclusion criteria:** 18 years or older, history of endoscopically documented gastric ulcer with or without duodenal ulcer or gastrointestinal bleeding, treatment with stable full therapeutic doses of an NSAID (with the exception of nabumetone or aspirin at 1300 mg/day or more; low-dose aspirin for cardiovascular protection was permitted) for at least the previous month **Exclusion criteria:** positive for *H. Pylori*, gastric or duodenal ulcer crater of 5mm or more or severe erosions defined as more than 25 erosions, erosive reflux oesophagitis, use of PPI, misoprostol or H_2RAs within 24 h of start of study	**Comparison:** lansoprazole (c, d) plus mixed NSAIDs vs misoprostol (b) plus mixed NSAIDs vs mixed NSAIDs (a) **Duration:** 12 weeks **Interventions:** d, lansoprazole 30 mg/15–30 mg (30 mg ×1 daily); c, lansoprazole 15 mg/15–30 mg (15 mg ×1 daily); b, misoprostol 800 μg /400–800 μg (200 μg ×4 daily); a, placebo **NSAID use:** ibuprofen: 40% naproxen: 35% diclofenac: 32% aspirin or aspirin combinations: 22% piroxicam: 17% **Other NSAIDs:** 34% Patients could have taken more than one NSAID **Endoscopy:** 1, 2 and 3 months **Other medication:** antacid provided for use as needed for symptom relief, instructed to avoid antiulcer medication other than study medication, ulcerogenic medication and agents that alter haemostasis **Aspirin allowed:** yes **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** ?4 (0, 4, 8 and 12 weeks)	**Allocated:** a 134, b 134, c 136, d 133 **Completed:** a 111, b 111, c 122, d 114 **Drop-out:** a 23, b 23, c 14, d 19 **Assessed:** a 133, b 134, c 136, d 132 **Outcomes reported:** mortality, serious GI complications, serious cardiovascular or renal illness (extra data) endoscopic ulcers, total drop-outs **How were adverse events assessed:** participants kept diary of daily symptoms and asked direct questions at each visit **How was compliance assessed:** tablet count, 90% in groups a, c and d were compliant compared with 73% in group b (misoprostol)	**Risk factors:** history of ulcers: all participants **FUNDING** **Funded by:** TAP Pharmaceutical Products **Affiliation of contact author:** Veterans Affairs Medical Centre, Texas, USA **Affiliation of statistician:** Abbott Laboratories; statistician was also the outcome assessor **Affiliation of study administrator:** TAP Pharmaceutical Products **No. of authors employed by sponsor:** 2 of 7

(c) Misoprostol plus NSAID versus placebo plus NSAID

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Graham, 1988[66,214,215] **Location:** multi-centred, USA	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and excluded patients with endoscopic ulcers (or joined after 4–8 weeks of treatment with misoprostol or placebo with a healed ulcer); participants had abdominal pain thought related to NSAIDS **Baseline NSAID status:** all used NSAIDs for 1 year **Type and duration of arthritis (years):** OA = all, mean 8 years **Age:** total: 58.9 (22–90) **Sex:** M/F total: 147/274 **Inclusion criteria:** OA and currently receiving ibuprofen, piroxicam or naproxen for their arthritic disorder, estimated to require at least 3 months continued NSAID treatment, had abdominal pain, at or above minimum age of consent, only women without childbearing potential (postmenopausal, surgically sterilised, or practising an acceptable method of birth control) **Exclusion criteria:** history or presence of proven recurrent gastric ulcer disease, active bleeding ulcer, malignant disorder or metastasis to the UGI tract, pyloric or duodenal obstruction, acute hepatitis, pancreatitis, inflammatory bowel disease, bleeding diathesis or severe renal impairment, patients taking antineoplastic drugs, anticoagulants or anti-ulcer drugs (other than antacids)	**Comparison:** misoprostol plus mixed NSAIDs (b, c) vs placebo plus mixed NSAIDs (a) **Duration:** 12 weeks **Interventions:** c, misoprostol 800 μg/400–800 μg (4× 200 μg daily); b, misoprostol 400 μg/400–800 μg (4× 100 μg daily); a, matching placebo (4× daily) (medication taken with meals and at bedtime) **NSAIDs:** ibuprofen: 36% total piroxicam: 28% total naproxen: 36% total endoscopy: 0, 4, 8 and 12 weeks **Other medication**: antacid (amphojel) no more than 4 per day for initial week for pain relief, antineoplastic drugs, anticoagulants or anti-ulcer drugs excluded **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** Not stated **Number and frequency of visits:** 4 (0, 4, 8 and 12 weeks)	**Allocated:** a 138, b 143, c 140 **Completed:** a 96, b 98, c 99 **Drop-out:** a 42, b 45, c 41 **Assessed for GI symptoms:** a 138, b 143, c 140 **Outcomes reported:** mortality, serious cardiovascular or renal illness, GI symptoms, endoscopic ulcers, total drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** history of ulcers: 55/421, 22/421 (just received healing treatment for ulcers) **FUNDING** **Funded by:** GD Searle **Affiliation of contact author:** Veteran's Affairs Medical Center, Houston, TX, USA **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** unclear

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Bolten, 1989[67] **Location:** 9 centres in Germany	**Method of randomisation:** 'randomisieerungsliste' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and patients excluded with peptic ulcer but included patients with lesion and upper abdominal complaints **Type and duration of arthritis (years):** RA: all participants, no further details **Age:** no details **Sex:** M/F: 32/35 in total **Inclusion criteria:** 18–83 years, ambulatory with chronic polyarthritis and being treated with NSAIDs for upper abdominal complaints **Exclusion criteria:** pregnancy, non-NSAID-related gastric or duodenal illness and peptic ulcers	**Comparison:** misoprostol plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 4 weeks **Interventions:** b, misoprostol 800 μg/400-800 μg (400 μg ×2 daily); a, placebo **Endoscopy:** 2 and 4 weeks **NSAIDs:** diclofenac: 33% ketoprofen: 16% piroxicam: 4.5% indomethacin: 22.5% ibuprofen: 12% other: 12% **Other medication:** no details **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated Washout: not stated **Number and frequency of visits:** 3 (0, 2 and 4 weeks)	**Allocated:** a 36, b 31 **Completed:** unclear **Drop-out:** unclear **Assessed for GI symptoms:** a 36, b 31 **Outcomes reported:** serious GI complications, GI symptoms, GI drop-outs **How were adverse events assessed:** no details **How was compliance assessed:** not stated	**Risk factors:** not stated **FUNDING** **Funded by:** not stated **Affiliation of contact author:** Rheumaklinik Bad Rappenau, Germany **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 0/1

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Chandrasekaran, 1991[68] **Location:** India	**Method of randomisation:** 'randomly allotted' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** normal endoscopy **Type and duration of arthritis (years):** OA: a 15, b 15; RA: a 15, b 15; seronegative spondarthropathy: a 15, b 15 (no other details) **Age:** a 38.2 b 39.9 **Sex:** M/F: a 24/21, b 21/24 **Inclusion criteria:** OA, RA or seronegative spondarthropathy, patients above 18 years of age, free of UGI symptoms, normal pre-trial UGI endoscopy, not taking NSAIDs in preceding month **Exclusion criteria:** pregnancy, renal, hepatic or cardiovascular disease, inflammatory bowel disease, malignancy of any type, history of previous surgery on the stomach or duodenum, history of alcoholism and known sensitivity to prostaglandins	**Comparison:** misoprostol plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 4 weeks **Interventions:** b, misoprostol 600 μg/400–800 μg (3× 200 μg daily); a, matching placebo (3× daily) **Endoscopy:** baseline then at 4 weeks **NSAIDs:** diclofenac sodium 150 mg/75–150 mg (to 15 OA participants in each group daily) indomethacin 75 mg/50–200 mg (to 15 seronegative spondarthropathy participants in each group daily) ibuprofen 1200 mg/600–2400 mg (to 20 RA participants daily, no other details) aspirin 2700 mg/?? (to 10 RA participants daily, no other details) (given 3× daily in equal divided doses with meals) **Other medication:** no antacids administered **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 5 (0, 1, 2, 3, 4 and 5 weeks)	**Allocated:** a 45, b 45 **Completed:** a 45, b 45 **Drop-out:** a 0, b 0 **Assessed for GI symptoms:** a 45, b 45 **Outcomes reported:** serious GI complications, GI symptoms, endoscopic ulcers, GI drop-outs **How were adverse events assessed:** assessed by physician weekly for symptoms of nausea, heartburn, epigastric pain/distress, improvement of arthritic symptoms and side-effects if any **How was compliance assessed:** not stated	**Risk factors:** no CVD: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** unclear **Affiliation of contact author:** unclear **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 1 of 7 authors is Director of Medical Affairs for Searle India **Other:** unclear how many participants in each group had aspirin

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Geis, 1991[69] **Location:** 14 countries (no further details)	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no more than 3 erosions and/or 10 petechial haemorrhages at baseline endoscopy (some had >10 erosions, oozing or intra-luminal blood or ulceration originally but had undergone treatment with misoprostol to improve GI status) **Type and duration of arthritis:** RA or OA, no further details **Age:** not stated **Sex:** not stated **Inclusion criteria:** OA or RA and had used NSAIDs continuously for 6 months, required chronic NSAID treatment but could not tolerate continuous use owing to GI disturbance or had received NSAIDs for at least 1 month and presented with significant lesions. On endoscopy those with >10 erosions, oozing or intra-luminal blood or ulceration were given 6 weeks of misoprostol and re-endoscoped. Those with no more than 3 erosions and/or 10 petechial haemorrhages at initial or follow-up endoscopy were eligible for this study **Exclusion criteria:** none mentioned	**Comparison:** misoprostol plus diclofenac (b) vs placebo plus diclofenac (a) **Duration:** 52 weeks **Interventions:** b, misoprostol 400–600 μg/400–800 μg (2–3 x 200 μg) daily; a, matching placebo (2–3× daily) (misoprostol or placebo taken with each dose of diclofenac) **NSAIDs:** a and b: diclofenac 100–150 mg/75–150 mg: (2–3 × 50 mg daily) **Endoscopy:** (0, 12, 24, 52 weeks) **Other medication:** no details **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 7 (0, 6, 12, 18, 24, 36, 52 weeks)	**Allocated:** a 99, b 96 **Completed:** not stated (data only supplied to 24 weeks: a 60, b 54) **Drop-out:** for 24 weeks: a 39, b 42 **Assessed for GI symptoms:** not stated **Outcomes reported:** endoscopic ulcers **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** no details (some participants had history of ulceration) **FUNDING** **Funded by:** Searle **Affiliation of contact author:** Searle Research and Development **Affiliation of statistician:** Searle **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 4/4 employed by Searle

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Saggioro, 1991[70] **Location:** Italy	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no more than 3 erosions or petechaie at baseline endoscopy, no GI symptoms **Type and duration of arthritis:** RA: a 14. b 10; OA: a 70, b 72; a 4.7 years, b 4.9 years **Age:** a 54.9, b 56.1 **Sex:** M/F: a 34/50, b 34/48 **Inclusion criteria:** OA or RA, over 18 years of age, female patients of childbearing age who were neither pregnant or lactating and were employing suitable contraception, were estimated to require at least 1 month of continued NSAID therapy, were free of upper GI symptoms, were to be free of significant gastroduodenal lesions (endoscopic score of 1 or less) **Exclusion criteria:** history of surgery on stomach and duodenum or had a significant GI disease, cardiovascular or renal dysfunction or required anti-arthritic therapy with steroids, gold or methotrexate, patients who had received NSAIDs in last 30 days before study admission	**Comparison:** misoprostol plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 4 weeks (±4 days) **Interventions:** b, misoprostol 800 μg/400–800 μg (4× 200 μg daily); a, matching placebo (4× daily) **NSAIDs:** (mean daily doses) piroxicam (20 mg/10–30 mg) a 28, b 30 diclofenac (150 mg/75–150 mg): a 30, b 22 naproxen (750 mg/500–1250 mg): a 19, b 24 ibuprofen (1000 mg/600–2400 mg): a 7, b 6 **Endoscopy:** (0, 4 weeks) **Other medication:** steroids, gold or methotrexate excluded **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated Washout: patients who had received NSAIDs in last 30 days before study admission were excluded **Number and frequency of visits:** 2 (0, 4 weeks)	**Allocated:** a 84, b 82 **Completed:** a 80, b 73 **Drop-out:** a 4, b 9 **Assessed for GI symptoms:** a 80, b 78 **Outcomes reported:** GI symptoms, endoscopy, GI drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** concomitant anti-coagulants a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** address is Searle, Italy **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 0/6

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Bolten, 1992[71] **Location:** Australia, Belgium, Canada, France, Germany, Greece, Luxembourg, Mexico, Portugal, UK, Venezuela	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no more than 10 erosions on baseline endoscopy **Type and duration of arthritis (years):** OA: <1year: a 11, b 7; 1–10 years: a 109, b 119; >10 years: a 63, b 52 **Age:** a 61.3 (37–87), b 59.2 (31–91) **Sex:** M/F: a 54/129, b 43/125 **Inclusion criteria:** patients of both sexes of the legal age of consent, confirmed diagnosis of OA hip and/or knee of at least 3 months duration, requiring continuous NSAID therapy for duration of the study and to have a functional capacity classification I–III, females required to have negative pregnancy test and to use adequate contraception **Exclusion criteria:** arthritis other than OA, any other rheumatic disease, psoriasis, acute joint trauma at the OA site, any musculoskeletal disorder of the lumbsacral area, syphilitic neuropathy, ochronosis or metabolic bone disease, more than 10 erosions in the stomach or duodenum, oesophageal, gastric, pyloric channel or duodenal ulcer, any active GI disease, renal or hepatic disorders, or malignancy, use of DMARDs, corticosteroids in preceding 30 days, use of analgesics or NSAIDs (including aspirin) in a chronic way	**Comparison:** diclofenac–misoprostol fixed combination (b) vs diclofenac–placebo fixed combination (a) **Duration:** 4 weeks **Interventions:** b, misoprostol 400–600 μg/400–800 μg (2–3× 200 μg daily) plus diclofenac 100–150 mg/75–150 mg (2–3× 50 mg daily) fixed combination: a placebo (2–3× daily) plus diclofenac 100–150 mg/75–150 mg (2–3× 50 mg daily) fixed combination **Endoscopy:** at 0 and 4 weeks **Other medication:** DMARDs and corticosteroids excluded **Aspirin allowed:** no **Analgesic allowed:** no **Participant education:** not stated **Washout:** no **Number and frequency of visits:** 3 (0, 2 and 4 weeks)	**Allocated:** a 183, b 178 **Completed:** a 166, b 159 **Drop-out:** a 17, b 19 **Assessed for GI symptoms:** a 183, b 178 **Outcomes reported:** GI symptoms, endoscopic ulcers, GI drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** method not reported, but 'mean compliance was in excess of 90% regardless of group or dosage'	**Risk factors:** concomitant anti-coagulants: a 0, b 0 >1 NSAID: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** GD Searle **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 2/4 worked for GD Searle **Other:** 2 participants with gastroduodenal ulcers at baseline were incorrectly enrolled in group b, both healed at end-point endoscopy and excluded from analysis by reviewers

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Doherty, 1992[72] **Location:** 43 physicians in 9 countries	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** those with active GI disease were excluded (no baseline endoscopy) **Type and duration of arthritis (years):** OA: all <0.5 years: a 7, b 9 5.0–9.9 years: a 46, b 52 15 years or more: a 22, b 21 **Age:** a 62.2 (20–85), b 62.3 (20–86) **Sex:** M/F: a 87/140, b 81/147 **Inclusion criteria:** diagnosis of primary OA of the hip, knee or both (3 historical criteria and 1 radiographic finding required for diagnosis) for at least 3 months before the study and a Steinbrocker functional capacity of Class I, II or III **Exclusion criteria:** the presence of any other type of arthritic condition, any active GI disease, or a scheduled hospitalisation for bed rest or joint replacement surgery because of arthritis, pregnancy or breast-feeding. Also ineligible if any of the following had been used in the 30 days before the study – antineoplastic agents, corticosteroids (including intra-articular injections), gold salts, penicillamine, colchicines, chronic analgesic agents, or continuous NSAIDs (including aspirin)	**Comparison:** Arthrotec (b) vs diclofenac (a) **Duration:** 4 weeks **Interventions:** (identical tablets given at mealtimes) b, misoprostol 400–600 μg/ 400–800 μg (2–3× 200 μg daily) plus diclofenac 100–150 mg/ 75–150 mg (2–3× 50 mg daily) Arthrotec, fixed combination; a, placebo (2–3× daily) plus diclofenac 100–150 mg/75–150 mg (203× 50 mg daily) fixed combination 2× daily: a 151, b 157 3× daily: a 76, b 73 (16% changed dose during study) **Endoscopy:** none **Other medication:** antineoplastic agents, corticosteroids (including intra-articular injections), gold salts, penicillamine and colchicines were excluded **Aspirin allowed:** not stated **Analgesic allowed:** not stated but chronic analgesic use in previous 30 days was an exclusion criterion **Participant education:** not stated **Washout:** Not stated but patients on continuous NSAIDs were excluded **Number and frequency of visits:** 3 (0, 2, 4 weeks)	**Allocated:** a 227, b 228 **Completed:** unclear **Drop-out:** unclear **Assessed for GI symptoms:** not assessed **Outcomes reported:** serious adverse events, efficacy **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** no details **FUNDING** **Funded by:** not stated **Affiliation of contact author:** City Hospital, Nottingham, UK **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** unclear

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Melo Gomes, 1992[73] **Location:** multi-centre, Portugal	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** yes re RA Study 1, no re OA Study 2 **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** Study 1 moderate, Study 2 high	**Baseline GI status:** no more than 10 erosions or any ulcers at baseline endoscopy, 61% diclofenac group and 62% of arthrotec group in Study 1 (RA) had normal mucosa on baseline, 57% diclofenac and 65% arthrotec group in Study 2 (OA) had normal mucosa **Type and duration of arthritis (years):** Study 1: RA: all; <0.5 years: a 4, b 3; 5.0–9.9 years: a 48, b 45; ≥ 15 years: a 31, b 26 Study 2: OA: all; <0.5 years: a 4, b 0; 5.0–9.9 years: a 42, b 51; ≥ 15 years: a 27, b 22 **Age:** Study 1: a 53.4 (19–86), b 53.2 (22–83) Study 2: a 61.3 (37–87), b 59.2 (31–91) **Sex:** M/F Study 1: a 38/137, b 41/123 Study 2: a 54/129, b 43/135 **Inclusion criteria:** free of significant UGI damage and requiring continuous NSAID therapy for duration of the study Study 1: RA, corticosteroids, gold salts, penicillamine, methotrexate, colchicine or antimalarials were permitted if started more than 30 days before start of the study and no change in dose during those 30 days Study 2: patients with OA were required to have involvement of the hip and/or knee for at least 3 months and a functional capacity classification of I–III **Exclusion criteria:** any significant UGI mucosal damage, active GI disease, other serious illnesses Study 2: if any antineoplastics, antimalarials, chronic analgesics, colchicine, corticosteroids, continuous NSAIDs, gold salts or penicillamine were used within 30 days of the start of the study	**Comparison:** Arthrotec (b) vs diclofenac (a) **Duration:** Study 1 = 12 weeks Study 2 = 4 weeks **Interventions:** (identical tablets given at mealtimes) b: misoprostol 400–600 μg/ 400–800 μg (2–3 × 200 μg daily) plus diclofenac 100–150 mg/ 75–150 mg (2–3× 50 mg daily) Arthrotec, fixed combination a: placebo (2–3× daily) plus diclofenac 100–150 mg/75–150 mg daily) fixed combination 2× daily Study 1: a 75, b 81 Study 2: a 132, b 129 3× daily: Study 1: a 100, b 83 Study 2: a 51, b 49 Endoscopy: Study 1: 0 and 12 weeks Study 2: 0 and 4 weeks **Other medication:** Study 1: corticosteroids, gold salts, penicillamine, methotrexate, colchicine or antimalarials were permitted if started more than 30 days before start of the study and no change in dose during those 30 days **Aspirin allowed:** not stated **Analgesic allowed:** no **Participant education:** not stated **Washout:** No **Number and frequency of visits:** Study 1: 4× (0, 4, 8 and 12 weeks) Study 2: 3× (0, 2 and 4 weeks)	**Allocated:** Study 1: a 175, b 164 Study 2: a 183, b 178 **Completed:** unclear **Drop-out:** unclear **Assessed for GI symptoms:** Study 1: a 153, b 137 Study 2: a 167, b 162 **Outcomes reported:** endoscopic ulcers **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** no details **FUNDING** **Funded by:** not stated **Affiliation of contact author:** unclear **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** unclear **Other:** 2 participants in Arthrotec group of study 2 (OA) had ulcers at baseline which were healed at 4-week endoscopy – excluded from analyses by reviewer

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Verdickt, 1992[74] **Location:** Belgium, UK, Germany, Mexico	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no more than 10 erosions in stomach and/or 10 erosions in duodenum, oesophageal, gastric, pyloric channel, no duodenal ulcer at baseline endoscopy Normal mucosa: a 107, b 101 No more than 10 erosions: a 68, b 63 **Type and duration of arthritis:** RA: all participants <1.0 years: a 10, b 8; 5.0–9.9 years: a 48; b 45; ≥10 years: a 65, b 71 **Age:** a 53.4 (19–86), b 53.2 (22–83) **Sex:** M/F: a 38/137, b 41/123 **Inclusion criteria:** legal age of consent, confirmed diagnosis of RA, required continuous NSAID therapy for duration of study, women of childbearing potential were required to use adequate contraception and to have a negative pregnancy test within 72 h of receiving first dose of study medication **Exclusion criteria:** the presence of arthritis other than adult RAs, any other rheumatic disease or psoriasis; chronic or acute renal or hepatic disorders, malignancy of any type, the presence of significant UGI mucosal damage (>10 erosions in the stomach, >10 erosions in the duodenum, oesophageal, gastric, pyloric channel or duodenal ulcer at baseline endoscopy), any active GI disease, history of substance abuse, use of antineoplastics (other than methotrexate as antiarthritic therapy) during the 30 days preceding the study, initiation or dose alteration of any DMARD during the 30 days preceding the study, corticosteroid doses greater than the equivalent of 10 mg prednisone per day, patients who had used	**Comparison:** misoprostol/diclofenac fixed combination (b) vs placebo/diclofenac fixed combination (a) **Duration:** 12 weeks **Interventions:** b, misoprostol 400–600 μg/400–800 μg (2–3× 200 μg daily)) plus diclofenac 100–150 mg/75–150 mg (2–3× 50 mgdaily); a, placebo (2–3× daily) plus diclofenac 100–150 mg/ 75–150 mg (2–3× 50 mg daily) **Endoscopy:** 0 and at 12 weeks **Other medication:** other NSAIDs and antiulcer drugs prohibited, antineoplastics (other than methotrexate as antiarthritic therapy) during the 30 days preceding the study, initiation or dose alteration of any DMARD during the 30 days preceding the study, corticosteroid doses greater than the equivalent of 10 mg prednisone per day were exclusion criteria **Aspirin allowed:** not stated **Analgesic allowed:** no **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 4 (0, 4, 8 and 12 weeks)	**Allocated:** a 175, b 164 **Completed:** a 144, b 132 **Drop-out:** a 31, b 32 **Assessed for GI symptoms:** a 175, b 164 **Outcomes reported:** GI symptoms, endoscopy **How were adverse events assessed:** not stated **How was compliance assessed:** not stated, >90% compliance for both groups	**Risk factors:** renal/hepatic disease: a 0, b 0 >1 NSAID a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** address is Searle, Skokie, IL, USA **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 2/6 employed by Searle Research & Development

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
		an investigative drug during the 30 days prior to study enrolment, known hypersensitivity to diclofenac sodium or other NSAIDs, or misoprostol or other prostaglandins			
Graham, 1993[75] **Location:** Private Veterans Affairs, health maintenance and academic practices in USA	**Method of randomisation:** 'randomised and balanced within each centre' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** yes **Intention-to-treat:** yes ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no ulcer or erosions of 3 mm or more at baseline endoscopy **Type and duration of arthritis (years):** OA: 75% of total **Age (median):** a 61, b 59 **Sex::** M/F: a 163/160, b 169/151 **Inclusion criteria:** RA, OA, psoriatic arthritis, AS or the Reiter syndrome, expected to require at least 3 additional months of daily NSAID treatment with either ibuprofen, piroxicam, naproxen, sulindac, tolmetin, indomethacin or diclofenac, women were required to be postmenopausal, surgically sterilised or practising adequate contraception **Exclusion criteria:** history of peptic ulcer disease requiring treatment in the 30 days immediately before entry, UGI malignancy, pyloric obstruction, acute hepatitis, pancreatitis, bleeding diathesis, UGI surgery within 30 days or severe renal impairment, participants taking antineoplastics, anticoagulants, anti-ulcer drugs other than the study drug, or prednisone at doses of more than 7.5 mg/day	**Comparison:** misoprostol plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 12 weeks **Interventions:** b, misoprostol 800 μg /400–800 μg (4× 200 μg daily with meals and at bedtime with food); a, matching placebo (4× daily with meals and at bedtime with food) **Endoscopy:** baseline then at 4, 8 and 12 weeks **NSAIDs:** (at same dosage as prior to start of study) ibuprofen, piroxicam, naproxen, sulindac, tolmetin, indomethacin or diclofenac **Other medication:** antacid (amphogel 600 mg) 3 tablets or less per day for first 2 weeks for relief of UGI pain, antineoplastics, antiocoagulants, anti-ulcer drugs other than the study drug, or prednisone at doses of more than 7.5 mg/day were not allowed **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** Not stated **Number and frequency of visits:** 4 (0, 4, 8 and 12 weeks)	**Allocated:** a 323, b 320 **Completed:** a 240, b 215 **Drop-out:** a 83, b 105 **Assessed for GI symptoms:** a 319, b 319 **Outcomes reported:** Mortality, GI symptoms, endoscopic ulcers **How were adverse events assessed:** not stated **How was compliance assessed:** non-compliance defined as failure to take at least 60% prescribed medication, determined by pill count at 4, 8 and 12 weeks: a 14%, b 24% = non-compliant	**Risk factors:** history of ulcers: a 84, b 80 anticoagulants: a 0, b 0 >1 NSAID: a 0 b 0 **FUNDING** **Funded by:** GD Searle **Affiliation of contact author:** Veteran's Affairs Medical Center, Houston, TX, USA **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 1/10 for Lederle Laboratories

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Henriksson, 1993[76] **Location:** Karolinska Hospital, Stockholm, Sweden	**Method of randomisation:** 'randomly allocated' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and excluded patients with symptomatic ulcer or treatment for peptic ulcer in last 30 days (1 of 20 in placebo group had frank asymptomatic ulcer and 5 of 20 in placebo group had erosions, 5 of 19 in misoprostol group had erosions, 15 of 39 had haemorrhagic lesions and 13 of 39 had normal mucosa) **Type and duration of arthritis (months):** RA: a 38, b 36 **Age:** a 54 (47–64), b 60 (52–66) **Sex:** M/F: a 7/13, b 3/16 **Inclusion criteria:** RA and continuously treated with NSAIDs **Exclusion criteria:** taking DMARDs in last 3 months, female patients of childbearing age without contraception, patients with clinical or biochemical evidence of severe cardiac, hepatic or renal disease, patients treated for ulcers in preceding 30 days or with symptomatic ulcers	**Comparison:** misoprostol plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 4 weeks **Interventions:** b, misoprostol 800 μg/400–800 μg (3× 200 μg daily immediately after food); a, matching placebo (3× daily immediately after food) **Endoscopy:** baseline and at 4 weeks **NSAIDs:** (median daily dose when used as single drug): ketoprofen (200 mg/100–200 mg) diclofenac (150 mg/75–150 mg) naproxen (1000 mg/500–1250 mg) ibuprofen (1200 mg/600–2400 mg) piroxicam (20 mg/10–30 mg) indomethacin (150 mg/50–200 mg) ASA (3000 mg/?) sodium salicylate (4000mg/ ?) **Other medication:** DMARDs not allowed **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol *ad libitum* and in severe cases intrarticular steroids (1 in each group at day 10) **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 2 (0 and 4 weeks)	**Allocated:** a: 20, b 20 **Completed:** a 20, b 19 **Drop-out:** a 0, b 1 **Assessed for GI symptoms:** a 20, b 19 **Outcomes reported:** GI symptoms, endoscopic ulcers **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** CVD, a 0, b 0 **Renal/hepatic disease:** a 0, b 0 **FUNDING** **Funded by:** Swedish Society Against Rheumatism, King Gustav V 80-years Foundation, U and G af Ugglas Foundation, S and R Sunds Foundation, Nanna Svartz and Ruth and Richard Julin Foundations, Swedish Society of Medicine, Swedish Medical Research Council and Searle **Affiliation of contact author:** Karolinska Hospital, Stockholm, Sweden **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 0/4

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Melo Gomes, 1993[77,217] **Location:** 13 countries	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** no, statistically significant difference in OA severity between groups **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** No ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** no more than 10 erosions in the stomach or 10 erosions in the duodenum, or oesophageal, gastric, pyloric channel, no duodenal ulcer at baseline endoscopy **Type and duration of arthritis (years):** OA: all <0.5 years: a 1, b 6, c 4; 5.0–9.9 years: a 59, b 44, c 69; ≥15 years: a 32, b 30, c 23 **Age:** a: 59.5 (33–85), b 58.7 (26–89) c 60.7 (30–84) **Sex:** M/F: a 48/162, b 55/162, c 52/164 **Inclusion criteria:** legal age of consent, documented radiographic evidence and symptomatic evidence of OA of the hip and/or knee of at least 3 months duration, functional capacity classification of I–III, had physician and patient global assessments of arthritis that were rated no better than 'fair', were experiencing joint pain, and required continuous NSAID therapy for duration of study **Exclusion criteria:** any acute joint trauma at the site of OA, chronic or acute renal or hepatic disorders, significant UGI damage, any active GI disease, use of any NSAID during the 10 days or any analgesic (other than paracetamol) during the 2 days before the baseline arthritis assessments, known hypersensitivity to any NSAIDs or any prostaglandin	**Comparison:** diclofenac sodium/misoprostol (c) vs piroxicam (b) vs naproxen (a) **Duration:** 4 weeks **Interventions:** c, misoprostol 400 μg/400–800 μg (2× 200 μg daily) plus diclofenac sodium 100 mg (2× 50mg daily) fixed combination; b, piroxicam 20mg/10–30 mg (2× 10 mg daily); a naproxen 75 mg/500–1250 mg (2× 375 mg daily) (identical matching placebo, all participants took 1 tablet and 1 capsule with morning meal and again with evening meal) **Endoscopy:** baseline and 4 weeks **Other medication:** not stated **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol **Participant education:** not stated **Washout:** yes, 10 days for NSAIDs, 2 days for analgesics **Number and frequency of visits:** 3 (0, 2 and 4 weeks)	**Allocated:** a 210, b 217, c 216 **Completed:** a 185, b 200, c 193 **Drop-out:** a 25, b 17, c 23 **Assessed for GI symptoms:** a 210, b 217, c 216 **Outcomes reported:** serious GI complications, GI symptoms, endoscopic ulcers, GI drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** tablet count, participants asked if missed medication on 2 or more consecutive days, at least 95% in all 3 groups were compliant at 4 weeks	**Risk factors:** renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by**: not stated **Affiliation of contact author:** GD Searle **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 6/6 authors employed by GD Searle

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Roth, 1993[78] **Location:** 6 centres in the USA	**Method of randomisation:** 'randomised', participants assigned a treatment number that corresponded with treatment medication **Allocation concealment:** unclear **Baseline comparability:** No, misoprostol group contained younger participants and more with normal endoscopies **Participant blinding:** unclear **Assessor blinding:** yes **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** no more than 3 erosions at baseline endoscopy normal endoscopy: a 17, b 18, c 27 hyperemia: a 24, b 20, c 17 erosions: a 17, b 15, c 13 **Type and duration of arthritis:** OA: all participants, no other details **Age:** 60–64: a 15, b 17, c 22; 65–74: a 34, b 32, c 35; ≥75: a 9, b, 4 c 3 **Sex:** F/M: a 19/39, b 12/41, c 11/49 **Inclusion criteria:** OA aged 60 years or older, ACR functional class II or III, used an NSAID for at least 3 months before enrolment and expected to continue the use of this class of medication for at least 3 months **Exclusion criteria:** history of hypersensitivity reaction to any of the study drugs, inefficacy or intolerance to ibuprofen, history of MI within last 6 months, congestive heart failure, medically uncontrolled hypertension or arrhythmias, history of an ulcer or GI tract bleeding within 1 year of study entry, history of gastroduodenal or eosophageal surgery, significant lower bowel disease (including regional enteritis, ulcerative colitis, intestinal bypass surgery, frequently bleeding haemorrhoids), OA which required treatment with multiple NSAIDs within 3 months of enrolment, patients considered to be candidates for joint replacement during time of the study, patients who had received intra-articular steroid injections or oral steroids within 1 month of enrolment	**Comparison:** misoprostol plus ibuprofen (c) vs ibuprofen (b) vs nabumetone (a) **Duration:** 12 weeks **Interventions:** c, misoprostol 800 μg /400–800 μg (4× 200 μg daily) **NSAIDs:** c, ibuprofen 2400 mg/ 600–2400 mg (4× 600 mg daily, administered concurrently with misoprostol); b, ibuprofen 2400 mg/ 600–2400 mg (4× 600 mg daily); a, nabumetone 1000 mg/ 500–2000 mg daily (no other details) **Endoscopy:** 0, 2, 6, 12 weeks and at early withdrawal **Other medication:** concomitant medication was allowed with the exception of anticoagulants, other anti-inflammatories, corticosteroids, immunosuppressant therapy, ulcer therapy (H_2RAs, sucralfate, long-term antacid therapy) **Aspirin allowed:** not stated **Analgesic allowed:** paracetamol max 12× 325 mg tablets in 24 hours **Participant education:** not stated **Washout:** yes, 3–10 days during which administered placebo 3× daily **Number and frequency of visits:** 7 (0, 2, 4, 6, 8, 10 and 12 weeks)	**Allocated:** a, 58, b 53, c 60 **Completed:** a 46, b 25, c 45 **Drop-out:** a 12, b 28, c 15 **Assessed for GI symptoms:** a 58, b 53, c 60 **Outcomes reported:** GI symptoms, endoscopic ulcers, anaemia, GI drop-outs **How were adverse events assessed:** participants asked if there had been any problems since last visit **How was compliance assessed:** tablet count	**Risk factors:** history of ulcers (1 year or more ago) a 10, b 14, c 14; all participants aged 60 years or more CVD a 0, b 0 **FUNDING** **Funded by:** SmithKline Beecham Pharmaceuticals **Affiliation of contact author:** Arthritis Center, Phoenix, AZ, USA **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** unclear

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Delmas, 1994[79,218] **Location:** France, multicentre	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** 0–3 erosions at baseline endoscopy **Type and duration of arthritis (years):** OA: total 77, inflammatory joint disease, total 123, other total 56 **Age:** whole group: 54 **Sex:** M/F: whole group: 151/105 **Inclusion criteria:** patients with rheumatic disease (degenerative OA, inflammatory joint disease, other), requiring continuous NSAID treatment for at least 28 days and if they had no patent gastroduodenal mucosal lesions (0–3 erosions or subepithelial haemorrhages) upon endoscopy **Exclusion criteria:** pregnant or lactating women and women of childbearing age not using effective contraception, active peptic ulcer disease, gastric hypersecretion, use of NSAIDs within 10 days before inclusion, contraindications to NSAIDs (acute hepatitis, inflammatory bowel disease, severe renal dysfunction)	**Comparison:** misoprostol plus mixed NSAIDs (b, c) vs placebo plus mixed NSAIDs (a) **Duration:** 4 weeks **Interventions:** b, misoprostol 400 μg/400–800 μg (2× 200 μg daily after meals) c, misoprostol 800 μg/400–800 μg (2x 400 μg daily after meals); a, identical placebo (2× daily) **Endoscopy:** baseline then at day 28 **NSAIDs:** (minimum daily dose) diclofenac (100 mg/75–150 mg) naproxen (500 mg/ 500–1250 mg) piroxicam (20 mg/10–30 mg) ibuprofen (1000 mg/600–2400 mg) indomethacin (100 mg/ 50–200 mg) ketoprofen (150 mg/100–200 mg) tiaprofenic acid (300 mg/600 mg) **Other medication:** not stated **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol for additional pain relief **Participant education:** not stated **Washout:** 10 days for NSAIDs **Number and frequency of visits:** 2 (0 and day 28)	**Allocated:** a 103, b 73, c 80 **Completed:** a 87, b 59, c 49 **Drop-out:** a 16, b 14, c 31 **Assessed for GI symptoms:** a 103, b 73, c 80 **Outcomes reported:** mortality, serious GI complications, GI symptoms, endoscopic ulcers, **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** history of ulcers in 4% of participants renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** unclear **Affiliation of contact author:** Hôpital Edouard-Herriot, Lyon, France **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 1/3 (Searle Laboratories, France) **Dosage:** tiaprofenic acid less than minimum recommended dose in BNF

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Elliott, 1994[80] **Location:** Arthritis clinics of 2 hospitals in Melbourne, Australia	**Method of randomisation:** 'randomised', stratification according to presence or absence of ulcer at screening endoscopy and whether smoker or non-smoker **Allocation concealment:** unclear **Baseline comparability:** no, baseline endoscopy worse in placebo group, more with RA, on gold, **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** baseline ulcer did not show frank ulcer or, if ulcer present treated with 3 months ranitidine and no ulcer present on repeat endoscopy (in total 12 had healed ulcers) **Type and duration of arthritis (years):** OA: a 14, b 22; RA: a 22. b 15 other: a 7, b 3 **Age:** a 66, b 65 **Sex:** M/F: a 21/22, b 25/15 **Inclusion criteria:** patients over 18 years of age, on stable oral NSAID therapy, who were attending arthritis clinics in the 2 study hospitals, chronic rheumatic disorders and had been on NSAID therapy (including aspirin and its enteric-coated preparations, but excluding enteric-coated preparations of any other NSAIDs) for at least 3 months, females were required to have a negative pregnancy test at entry and at each follow-up visit **Exclusion criteria:** overt UGI haemorrhage within 1 month prior to entry, previous gastric surgery for peptic ulcer, inflammatory bowel disease or chronic diarrhoea, malignancy of any type, administration of other anti-ulcer drugs	**Comparison:** misoprostol plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 12 months **Interventions:** b, misoprostol 600–800 μg/400–800 μg (3–4 x 200 μg daily) 28 participants took 600 μg/daily and 4 participants 800 μg daily; a, placebo (3–4× daily) (dosage regime tailored to frequency of NSAID dosing, NSAIDs continued at dose determined by patients rheumatologist) **Endoscopy:** baseline then at 3, 6 and 12 months **NSAIDs:** piroxicam: a 7, b 5 sulindac: a 10, b 11 naproxen: a 9, b 6 indomethacin: a 6, b 5 ibuprofen: a 3, b 0 diflunisal: a 5, b 3 aspirin: a 1, b 6 ketoprofen: a 0, b 2 doxiprin: a 2, b 2 **Other medication:** antacid (mylanta) provided and allowed up to 3 tablets per day, DMARDs allowed **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 6 (0, 1, 3, 6, 9 and 12 months)	**Allocated:** a: 43, b 40 **Completed:** unclear **Drop-out:** unclear **Assessed for GI symptoms:** a 43, b 40 **Outcomes reported:** serious GI complications, symptomatic ulcers, GI symptoms, endoscopic ulcers, GI drop-outs **How were adverse events assessed:** assessed diary card in which symptoms were recorded **How was compliance assessed:** tablet count, assessed diary card in which all medications taken were recorded	**Risk factors:** participants who had just completed treatment for ulcer healing: a 6, b 6 history of ulcers: a 12, b 11 Concomitant use of steroids: a 9, b 7 **FUNDING** **Funded by:** GD Searle **Affiliation of contact author:** University of Melbourne **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** unclear **Other:** 7/83 participants took aspirin as NSAID

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Viana de Queiroz, 1994[81] **Location:** 8 countries including Portugal, Canada, Germany, USA	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** excluded participants with active GI disease (including peptic ulcer), but no baseline endoscopy **Type and duration of arthritis:** RA: all participants, no other details **Age:** a 56.0, b 56.8 **Sex:** M/F: a 42/127, b 48/129 **Inclusion criteria:** legal age RA for at least 6 months, active RA and a functional capacity classification of I–III at time of enrolment, had their disease adequately controlled by a stable regimen of diclofenac sodium 50 mg 2–3 times daily for at least 30 days prior to entering study, females of childbearing potential were required to use adequate contraception and have a negative pregnancy test within 72 h prior to receiving first dose of study medication **Exclusion criteria:** arthritis other than RA, any other rheumatic disease, psoriasis, active GI disease (e.g. peptic ulcer or inflammatory bowel disease) chronic or acute renal or hepatic disorders, or malignancies of any type, used any drugs which would confound the understanding of the study (antineoplastics and DMARDs)	**Comparison:** misoprostol/diclofenac fixed combination (b) vs placebo/diclofenac fixed combination (a) **Duration:** 12 weeks **Interventions:** b, misoprostol 400–600 μg/400–800 μg (2–3× 200 μg daily) plus diclofenac 100–150 mg/75–150 mg (2–3× 50 mg daily) fixed combination; a, placebo plus diclofenac 100–150 mg/75–150 mg (2–3× 50 mg daily) fixed combination (with meals, not chewed or swallowed whole???) **Endoscopy:** not performed **Other medication:** not stated **Aspirin allowed:** not stated **Analgesic allowed:** no **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 4 (0, 4, 8 and 12 weeks)	**Allocated:** a 169?, b 177? **Completed:** a 133, b 139 **Drop-out:** a 36, b 38 **Assessed for GI symptoms:** a 169, b 177 **Outcomes reported:** GI symptoms **How were adverse events assessed:** diary cards **How was compliance assessed:** tablet count, mean compliance 91–99% in both groups	**Risk factors:** renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** no contact author stated **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 3/6 employed by Searle Research & Development

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Agrawal, 1995[82] **Location:** hospitals, universities and private institutions in USA and Belgium	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** unclear **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** <3 erosions following open label treatment with misoprostol (for >10 erosions or ulcer or visible vessel or oozing or intraluminal blood) **Type and duration of arthritis (years):** OA: a 92 (9.0 years), b 99 (10.3 years); RA: a 99 (12.1 years), b 93 (10.0 years); one participant had neither OA nor RA **Age:** a 57.5, b 57.3 **Sex:** M/F: a 58/133, b 65/128 **Inclusion criteria:** legal age of consent, with RA and/or OA requiring chronic NSAID treatment, females of childbearing potential had to have had a negative pregnancy test 72 h prior to first dose of study medication, required to have completed the screening and treatment phases and have an endoscopy score of 3 or less on endoscopy after treatment Exclusion criteria: changes in doses of second-line antiarthritic therapies (e.g. gold, methotrexate or penicillamine) during the 3 months prior to entering the study, esophageal varices or ulceration, gastrinoma, Zollinger–Ellison syndrome, ulcerated hiatus hernia, a history of gastric or duodenal surgery, inflammatory bowel disease, malignancy, hepatic or renal dysfunction, alcoholism	**Comparison:** misoprostol plus diclofenac (b) vs placebo plus diclofenac (a) **Duration:** 52 weeks **Interventions:** b, misoprostol 400–600 μg/400–800 μg (2–3× 200 μg dailya: placebo (2–3× daily) **NSAIDs:** a + b: diclofenac 100–150 mg/75–150 mg (2–3× 50 mg daily) Misoprostol and diclofenac were co-administered, diclofenac dose increased or decreased as necessary **Other medication:** Maalox tablets provided to use if necessary for dyspepsia **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 7 (0, 6, 12, 18, 24, 36 and 52 weeks) **Endoscopy:** 0, 12, 24 and 52 weeks	**Allocated:** a 191, b 193 **Completed:** unclear **Drop-out:** unclear **Assessed for GI symptoms:** a 191, b 193 **Outcomes reported:** GI symptoms, endoscopic ulcers, GI drop-outs **How were adverse events assessed:** participants provided assessments of specific GI symptoms (abdominal pain, heartburn, nausea, vomiting, eructation, constipation, diarrhoea) **How was compliance assessed:** tablet count, less than 60% of the 2 tablet daily regimen were not evaluated	**Risk factors:** history of gastric ulcers: a 82, b 84 history of duodenal ulcers: a 73, b 64 history of bleeds: a 18, b 25 **FUNDING** **Funded by:** GD Searle **Affiliation of contact author:** GD Searle **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 1 or 2/4 **Other:** participants were withdrawn if scored ≥ 10 erosions, oozing or intraluminal blood on endoscopy

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Raskin, 1995[43] **Location:** 135 centres in the USA	**Method of randomisation:** centralised computer-generated randomisation schedule, each centre was assigned to 1 or more randomisation blocks of 7 in sealed envelopes, patients then assigned sequentially to treatment **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** no **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and excluded patients without UGI symptoms (but excluded endoscopic evidence of gastric or duodenal ulcers, any oesophageal erosions,a mucosal defect of any size with perceptible depth, a gastric or duodenal mucosal defect 0.3 cm or more) **Type and duration of arthritis**: OA: a 341, b 347, c 356, d 180 RA: a 73, b 69, c 71, d 25 Other: a 32, b 42, c 43, d 21 **Age:** median: a 58 (21–83), b 58 (18–89) c 58 (23–85), d 58 (28–81) **Sex:** F/M: a 186/268, b 203/259 c 190/284, d 91/137 **Inclusion criteria:** clinical diagnosis of OA, RA, psoriatic arthritis, ankylosing spondylitis or Reiter syndrome and were receiving NSAID therapy that was expected to continue uninterrupted for at least 3 additional months at a fixed dose, patients had to be having UGI symptoms such as cramp, pain, bloating or heartburn **Exclusion criteria:** patients with a gastric or duodenal mucosal defect of 0.3 cm or more, a mucosal defect of any size with perceptible depth, any oesophageal erosions or ulcers, UGI surgery within 30 days of anticipated entry into the study, UGI malignancy, pyloric obstruction, acute hepatitis, pancreatitis, inflammatory bowel disease or a bleeding diathesis	**Comparison:** misoprostol plus mixed NSAIDs (b, c, d) vs placebo plus mixed NSAIDs (a) **Duration:** 12 weeks **Interventions:** b, misoprostol 400 μg /400–800 μg (2× 200 μg daily) plus identical placebo (2× daily); c, misoprostol 600 μg/ 400–800 μg (3× 200 μg daily) plus identical placebo (1× daily); d, misoprostol 800 μg/400–800 μg (4× 200 μg daily); a, identical placebo (4× daily) (doses taken at breakfast, lunch, dinner and bedtime, for the initial 3 days all participants took half of 1 tablet 4× daily) **NSAIDs** (minimum daily doses) (%): naproxen 750 mg/500–1250 mg: a 21, b 24, c 25, d 22 ibuprofen 1200 mg/600–2400 mg: a 26, b 24, c 24, d 29 piroxicam 20 mg/10–30 mg: a 17, b 16, c 19, d 17 sulindac 200 mg/400 mg: a 7, b 7, c 6, d 5 other: a 29 b 29, c 26, d 27 **Other medication:** antacid tablets provided, 4 tablets per day or less for upper abdominal symptoms in the initial 3 weeks only **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 4 (0, 4, 8 and 12 weeks)	**Allocated:** unclear **Completed:** unclear **Drop-out:** a: 95, b 90, c 110, d 62 **Assessed for GI symptoms:** a 454, b 462, c 474, d 228 **Outcomes reported:** mortality, GI symptoms, endoscopic ulcers, GI drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** tablet count to ensure 60% compliance **Non-compliance:** a 12/454, b 5/462, c 9/474, d 5/228 **Were participants excluded from analyses pre-ulcer?** unclear	**Risk factors**: history of GI disease: a 2, b 2 **FUNDING** **Funded by:** GD Searle **Affiliation of contact author:** Veterans Affairs Medical Center, Miami, FR, USA **Affiliation of statistician:** W Archanbault, GD Searle **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** unclear, JG Fort helped prepare the manuscript (?medical director at Searle) **Other:** 1 participant in misoprostol group c had peptic ulcer at baseline; these participants were excluded from analyses % data for type of arthritis does not add up to total number of participants in each arm, number of drop-outs does not add up

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Silverstein, 1995[6] MUCOSA **Location:** 661 practices in USA, 3 in Canada	**Method of randomisation:** 'randomly assigned in blocks of four' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** yes **Intention-to-treat:** unclear ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** without active peptic ulcer disease in last 30 days (no baseline endoscopy) **Type and duration of arthritis:** RA: all participants a 12.7 years (1–73), b 13.1 years (1–70) **Age:** a 67.6, b 67.6 **Sex:** M/F: a 1299/3136, b 1271/3130 **Inclusion criteria:** ambulatory patients at least 52 years of age who had chronic RA and were expected to be taking 1 of 10 specified NSAIDs at predefined minimum doses for 6 months **Exclusion criteria:** active peptic ulcer disease within 30 days of study enrolment, were taking or expected to need anti-ulcer medication (HH_2RA, sucrafate, omeprazole), or any experimental medication during the study, Zollinger–Ellison syndrome, pyloric or duodenal obstruction, previous gastric resection or vagotomy, gastroesophageal reflux disease, varices or cirrhosis, history of inflammatory bowel disease, UGI tract malignancies, hepatitis, alcoholism or bleeding diathesis, were estimated to have a life expectancy of less than 8 months or had do-not-resuscitate status, women of childbearing potential, could not tolerate misoprostol or any prostaglandin	**Comparison:** misoprostol plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 6 months **Interventions:** b, misoprostol 400–800 μg/400–800 μg (2–4× 200 μg daily); a placebo (2–4x daily); (with meals and at bedtime) [started taking half tablet (100 μg or placebo) 4× daily for 10 days then if tolerated increased up to full tablet (200 μg or placebo) 4μ daily] Full dose, 800 μg (or placebo) daily: a 3524, b 2974 Half dose, 400 μg (or placebo) daily: a: 690, b 1230 Not stated: a 207, b 200 **NSAIDs:** (minimum daily doses) aspirin (2000mg/?) a 297, b 335 diclofenac 100 mg/75–150 mg: a 894, b 834 flurbiprofen 200 mg/150–300 mg: a 385, b 367 ibuprofen 1200 mg/600–2400 mg: a 514, b 504 indomethacin 65 mg/50–200 mg: a 115, b 116 ketoprofen 150 mg/100–200 mg: a 131, b 146 naproxen 750 mg/500–1250 mg: a 1014, b 988 piroxicam 20 mg/10–30 mg: a 464, b 473 sulindac 200 mg/400 mg: a 311, b 309 tolmetin 1200mg/?: a 109, b 112 lower dose: a 55 b 52 none of the above NSAIDs: a 46, b 45	Allocated: a 4439, b 4404 **Completed:** a 2822, b 2553 **Drop-out:** a 1617, b 1851 **Assessed for GI symptoms:** a 4439 b 4404 **Outcomes reported:** mortality, serious GI complications, symptomatic ulcers, GI symptoms, GI drop-outs **How were adverse events assessed:** physicians instructed to watch closely for clinical signs of GI bleeding or other GI complications, to inquire about symptoms and to investigate suspicious episodes by appropriate clinical procedures **How was compliance assessed:** tablet count	**Risk factors:** history of ulcers: a 638, b 643 history of bleeds: a 281, b 292 concomitant use of corticosteroids: a 1871, b 1887 >1 NSAID: a 60, b 75 **FUNDING** **Funded by:** G D Searle **Affiliation of contact author:** G D Searle **Affiliation of statistician:** Quintiles Transnational **Affiliation of trial administrator:** data collection done by Quintiles Transnational **No. of authors employed by sponsor:** unclear but at least 1 of 7 worked for Searle Other: some participants not taking NSAIDs a 40, b 40. Sulindac less than minimum recommended dose in BNF

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
			Endoscopy: none **Other medication:** could continue with DMARDs such as gold and corticosteroids and take antacids (not containing magnesium), were allowed to receive more than 1 NSAID **Aspirin allowed:** yes **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 7 (baseline 1, 2, 3, 4, 5, 6 months)		

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Bocanegra, 1998[83] **Location:** 56 sites in USA	**Method of randomisation:** 'randomly allocated' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** free of ulcers and with 10 or fewer erosions in stomach or duodenum on baseline endoscopy **Type and duration of arthritis (years):** OA: a 11.9 years, b 10.3 years, c 11.9 years **Age:** a 62.9, b 62.8, c 62.3 **Sex:** M/F: a 44/110, b 58/117, c 49/103 **Inclusion criteria:** adult patients with symptomatic OA of the knee and/or hip, a functional capacity classification I–III and a documented history but not current presence of significant UGI mucosal damage, females with adequate contraception and not lactating and must have had a negative pregnancy test 72 h before receiving first dose of study medication, worsening of OA symptoms compared to screening evaluation and after washout **Exclusion criteria:** arthritis other than OA, malignancy of any type, renal, hepatic or coagulation disorder that in the opinion of the investigator may pose a safety risk for the patient, presence of gastric or duodenal ulcer or more than 10 erosions at the baseline UGI endoscopy, any active GI disease, a history of any gastric or duodenal surgery other than a simple oversew, recent use of corticosteroids (including intra-articular injections, or anticoagulants or use of any NSAID except aspirin no more than 325 mg/day, or analgesic within 3 days prior to the baseline assessments	**Comparison:** arthrotec 50 (b) vs arthrotec 75 (c) vs diclofenac (a) **Duration:** 6 weeks **Interventions:** c, misoprostol 600 μg /400–800 μg (3×2 00 μg daily) plus diclofenac 150 mg/ 75–150 mg (3× 50 mg daily) (enteric coated diclofenac sodium 50 mg surrounded by a mantle of 200 μg misoprostol, (3× daily); b, misoprostol 400 μg/400–800 μg (2× 200 μg daily) plus diclofenac 150 mg/75–150 mg (2× 75 mg daily) (enteric coated diclofenac sodium 75 mg surrounded by a mantle of 200 μg misoprostol, (2× daily); a, diclofenac sodium, 150 mg/75–150 mg (2× 75 mg daily) **Endoscopy:** at 0 and 6 weeks **Other medication:** not stated **Aspirin allowed:** yes, no more than 325 mg daily **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** 3–14 days for NSAIDs **Number and frequency of visits:** 3 (0, 2 and 6 weeks)	**Allocated:** a 154, b 175, c 152 **Completed:** a 126, b 142, c 131 **Drop-out:** a 28, b 33, c 21 **Assessed for GI symptoms:** a 154, b 175, c 152 **Outcomes reported:** GI symptoms, endoscopic ulcers **How were adverse events assessed:** diaries to record any new symptoms, information collected and transcribed to study case report forms at each visit **How was compliance assessed:** not stated	**Risk factors:** a documented history but not current presence of significant UGI mucosal damage, no renal or hepatic disease at baseline **FUNDING** **Funded by:** GD Searle **Affiliation of contact author:** GD Searle **Affiliation of statistician:** GD Searle **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 5 of 8 worked for GD Searle **Other:** withdrawals due to GI adverse events do not add up, placebo group present but not reported here

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Hawkey 1998b[62,65,209,210] OMNIUM **Location:** 93 centres in 14 countries including UK and USA	**Method of randomisation:** 'randomly assigned', randomisation phase not formally balanced according to treatment assignment in the healing phase **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** endoscopy performed and excluded participants without treatment success following 4–8 weeks healing phase (omeprazole 20 mg/day vs omeprazole 40 mg/day vs misoprostol 200 μg/day); treatment success defined as absence of ulcers in the stomach or duodenum and the presence of fewer than five gastric erosions, fewer than five duodenal erosions and not more than mild symptoms of dyspepsia (corresponded to a 2-point reduction in Lanza scale from grade 4 to grade 2) **Type of arthritis:** OA: a 70, b 129, c 142; RA: a 56, b 107, c 118; Other: a 25, b 33, c 30 **Combination:** a 5, b 5, c 6 **Age:** a 57 (20–80), b 58 (23–79), c 58 (23–85) **Sex:** M/F: a 48/107, b 101/173, c 118/178 **Inclusion criteria:** 18–85 years of age and who had any condition requiring continuous treatment with oral or rectal NSAIDs above a predetermined minimal dose (no maximal dose); treatment success defined as absence of ulcers in the stomach or duodenum and the presence of fewer than five gastric erosions, fewer than five duodenal erosions, and not more than mild symptoms of dyspepsia (corresponded to a 2-point reduction in Lanza scale from grade 4 to grade 2) **Exclusion criteria:** concurrent reflux oesophagitis at stage 3 or 4 according to the Savary–Miller classification, clinically important GI bleeding, pyloric stenosis, history of gastric surgery, or GI disorders that might impair the absorption of the study drugs	**Comparison:** misoprostol plus mixed NSAIDs (c) vs omeprazole plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 6 months **Interventions:** c, misoprostol 400 μg/400–800 μg /day (200 μg ×2 daily; b, omeprazole 20 mg/20 mg (20 mg ×1 daily); a, identical placebo **Endoscopy:** 1, 3 and 6 months **NSAIDs:** (minimum and mean dose) diclofenac (50 mg, 129 mg/day): 23% total participants ketoprofen (100 mg, 137 mg): 16% total participants naproxen (500 mg, 844 mg): 22% total participants **Other medication:** patients could enter the study if they were taking glucocorticoids at a dose less than/equal to 10 mg of prednisolone (or its equivalent) **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 4 (0, 1, 3 and 6 months)	**Allocated:** a 155, b 274, c 296 (7 participants unaccounted for) **Completed:** a 139, b 242, c 247 **Drop-out:** a 16, b 33, c 50 **Assessed:** a 155, b 275, c 297 **Outcomes reported:** serious GI complications, QoL, endoscopic ulcers, total drop-out How were adverse events assessed: participants asked if had specific dyspeptic symptoms during the last 7 days and to describe any upper GI symptoms on that day, symptoms graded, also symptom diary card used during initial 4 weeks **How was compliance assessed:** tablet count, result not reported	**Risk factors:** 63–64% of participants in each group had recent history of ulcers (remaining participants had recent history of more than 10 gastric or duodenal erosions **FUNDING** **Funded by:** Astra Hassle, Sweden **Affiliation of contact author:** Nottingham Gastrointestinal Trials Service, University Hospital Nottingham, UK **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** One author serves as a consultant for Searle, Australia **Other:** participants were discontinued and excluded from analysis if developed more than 10 erosions or more than moderate dyspepsia or adverse events

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Graham, 2002[64,214] **Location:** 63 centres in North America	**Method of randomisation:** 'randomly assigned in blocks of 4', 'randomisation schedule was generated by a statistical specialist who was not involved in the trial design, the randomisation was coded and stored in sealed envelopes' **Allocation concealment:** adequate **Baseline comparability:** yes **Participant blinding:** no Assessor blinding: yes (statistician), endoscopist also blinded **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** low	**Baseline GI status:** baseline endoscopy performed, patients had to be without *H. pylori*, have history of endoscopically documented gastric ulcer with or without coexisting duodenal ulcer or GI bleeding (2/3 participants had previously completed participation in a healing trial for NSAID-associated gastric ulcer); excluded patients with gastric or duodenal ulcer crater at least 5 mm in diameter or more than 25 erosions or erosive reflux oesophagitis **Baseline NSAID status:** treatment with stable full therapeutic doses of an NSAID for at least the previous month (except nabumetone or aspirin at 1300 mg/day or more) **Type and duration of arthritis (years):** no details **Age:** a 60.5, b 59.4, c 61.6, d 60.2 **Sex:** M/F: a 46/87, b 43/91, c 50/86, d 48/84 **Inclusion criteria:** 18 years or older, history of endoscopically documented gastric ulcer with or without duodenal ulcer or GI bleeding, treatment with stable full therapeutic doses of an NSAID (with the exception of nabumetone or aspirin at 1300 mg/day or more; low-dose aspirin for cardiovascular protection was permitted) for at least the previous month **Exclusion criteria:** positive for *H. pylori*, gastric or duodenal ulcer crater of 5 mm or more or severe erosions defined as more than 25 erosions, erosive reflux oesophagitis, use of PPI, misoprostol or H_2RAs within 24 h of start of study	**Comparison:** lansoprazole (c, d) plus mixed NSAIDs vs misoprostol (b) plus mixed NSAIDs vs mixed NSAIDs (a) **Duration:** 12 weeks **Interventions:** d, lansoprazole 30 mg/15–30 mg (30 mg ×1 daily); c lansoprazole, 15 mg/15–30 mg (15 mg ×1 daily); b, misoprostol 800 μg/400–800 μg (200 μg ×4 daily); a, placebo **NSAID use:** ibuprofen: 40% naproxen: 35% diclofenac: 32% aspirin or aspirin combinations: 22% piroxicam: 17% other NSAIDs: 34% **Endoscopy:** 1, 2 and 3 months **Other medication:** antacid provided for use as needed for symptom relief, instructed to avoid antiulcer medication other than study medication, ulcerogenic medication and agents that alter hemostasis **Aspirin allowed:** yes **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** ?4 (0, 4, 8 and 12 weeks)	**Allocated:** a 134, b 134, c 136, d 133 **Completed:** a 111, b 111, c 122, d 114 **Drop-out:** a 23, b 23, c 14 d 19 **Assessed:** a 133, b 134, c 136, d 132 **Outcomes reported:** mortality, serious GI complications, serious cardiovascular or renal illness (extra data) endoscopic ulcers, total drop-outs **How were adverse events assessed:** participants kept diary of daily symptoms and asked direct questions at each visit **How was compliance assessed:** tablet count, 90% in groups a, c and d were compliant compared with 73% in group b (misoprostol)	**Risk factors:** history of ulcers: all participants **FUNDING** **Funded by:** TAP Pharmaceutical Products **Affiliation of contact author:** Veterans Affairs Medical Center, Houston, TX, USA **Affiliation of statistician:** Abbott Laboratories **Affiliation of study administrator:** TAP Pharmaceutical Products **No. of authors employed by sponsor:** 2 of 7

(d) Cox-2 NSAID versus Cox-1 NSAID

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Bensen, 1999[84,220,221] **Location:** 71 clinical sites in USA and Canada	**Method of randomisation:** 'randomly assigned', stratified by centre using block size of 10 **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** endoscopy not performed but excluded participants with oesophageal or gastroduodenal ulceration within 30 days prior to start of study **Type and duration of arthritis (years):** OA: a 10, b 10, c 9 **Age:** a: 62 (33–86), b 62 (32–84), c 63 (25–87) **Sex:** M/F: a 57/141, b 53/144, c 57/145 **Inclusion criteria:** outpatients 18 years or more, primary OA (knee, ACR criteria) and functional class I, II or III, symptomatic OA [defined worsening of signs and symptoms following discontinuation NSAIDs or other analgesics, or if not receiving NSAIDs or analgesics with uncontrolled OA patient assessment of arthritis pain 40 mm or more on VAS, OA Severity Index Score of 7 or more, patient global assessment grade poor or very poor, physician global assessment grade poor or very poor (3 of these 4 criteria need to be met)], no corticosteroids within 4 weeks of start of study **Exclusion criteria:** active concomitant GI tract, renal, hepatic or coagulation disorders, malignancy (unless removed surgically with no recurrence within 5 years), or oesophageal or gastroduodenal ulceration within 30 days prior to receiving study drug, any inflammatory arthritis, gout or acute trauma of the knee, known hypersensitivity to NSAIDs or sulfonamides	**Comparison:** celecoxib (b, c) vs naproxen (a) **Duration:** 12 weeks **Interventions:** b, celecoxib 200 mg/200–400 mg (100 mg ×2 daily); c, celecoxib 400 mg/200–400 mg (200 mg ×2 daily); a, naproxen, 1000 mg/500–1250 mg (500 mg ×2 daily) **Other medication:** other NSAIDs, corticosteroids and anticoagulants were prohibited **Aspirin allowed:** yes, in stable doses 325 mg/day or less and for 3 consecutive days or less (not in 48 h prior to assessments) **Analgesic allowed:** yes, paracetamol 2 g/day or less and for 3 consecutive days or less (not in 48 h prior to assessments) **Participant education:** not stated Washout: 2–7 days **Number and frequency of visits:** 4 (0, 1, 2, 6 and 12 weeks)	**Allocated:** a 198, b 197, c 202 **Completed:** unclear (569 in total, including placebo arm and celecoxib 100 mg daily arm) **Drop-out:** unclear (434 in total) **Assessed:** a 198, b 197, c 202 **Outcomes reported:** serious GI complications, symptomatic ulcers, GI symptoms, GI drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** not stated, but 33/1003 patients were discontinued due to non-compliance	**Risk factors:** concomitant use of anticoagulants: a 0, b 0, corticosteroids: a 0, b: 0 >1 NSAIDs: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** in part by GD Searle **Affiliation of contact author:** 26 Charlton Avenue, Suite 203, Hamilton, ON, Canada **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 7 of 10 authors worked for Searle Research and Development, Skokie, IL, USA **Other:** placebo arm and celecoxib 100 mg daily arm excluded from analysis

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Emery, 1999[85,222] **Location:** 132 centres in Europe, Israel, South Africa, Australia, New Zealand	**Method of randomisation:** 'computer-generated randomisation numbers' **Allocation concealment:** unclear **Baseline comparability:** no **Participant blinding:** yes **Assessor blinding:** yes, perforation, bleeding or obstructions were assessed by a committee of independent gastroenterologists unaware of treatment status **Intention-to-treat:** yes ***A priori* sample size:** yes **Summary risk of bias:** high	**Baseline GI status:** no baseline endoscopy but excluded participants with active or suspected peptic ulceration or GI bleeding **Type and duration of arthritis:** RA: a 9.9, b 11.0 **Age:** a 54.5, b 55.9 **Sex:** F/M: a 95/234, b 79/247 **Inclusion criteria:** diagnosis of adult-onset RA of 6 months or longer duration (ARA criteria), functional capacity classification of III or less, anticipated to require continuous treatment with NSAID for duration of trial **Exclusion criteria:** diagnosis of any concomitant rheumatic condition, active or suspected peptic ulceration or GI bleeding, important coagulation defect or any disorder that might preclude NSAID use, malignant disease, renal or hepatic disorder, inflammatory bowel disease, diclofenac intolerance, or hypersensitivity to Cox-2 inhibitors, sulfonamides or NSAIDs, clinically abnormal values on pretreatment laboratory tests, pregnant or lactating, received any DMARD or oral corticosteroid started less than12 weeks before start of study, injected corticosteroid given within 4 weeks or any other study medication within 30 days of the first dose of the study drug	**Comparison:** celecoxib (b) vs diclofenac SR (a) **Duration:** 24 weeks **Interventions:** b, celecoxib 400 mg/200–400 mg (200 mg ×2 daily); a, diclofenac SR 150 mg/75–150 mg (75 mg x2 daily); double dummies used **Other medication:** use of anticoagulants, NSAIDs other than study drug or anti-ulcer drugs prohibited **Aspirin allowed:** no **Analgesic allowed:** yes, but chronic use prohibited **Participant education:** not stated **Washout:** no **Number and frequency of visits:** 7 (0, 4, 8, 12, 16, 20 and 24 weeks)	**Allocated:** a 329, b 326 **Completed:** a 235, b 258 **Drop-out:** a 94, b 68 **Assessed:** a 329, b 326 **Outcomes reported:** serious GI complications, symptomatic ulcer, GI symptoms, endoscopic ulcers, anaemia, GI drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** tablet count	**Risk factors:** history of ulcers: a 27, b 28 history of bleeds: a 1, b 4 concomitant use of anticoagulants: a 0, b 0 corticosteroids: a 157, b 124; renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** GD Searle, Skokie, IL, USA **Affiliation of contact author:** Searle Research & Development, Skokie, IL, USA **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 6 or 10 authors employed by Searle

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Laine, 1999[41,223] **Location:** 34 sites in USA	**Method of randomisation:** 'randomly assigned' and stratified regarding presence or absence of history of GI events (PUBs) in blocks of 4 from a computer-generated list, each centre provided with individually sealed envelopes Allocation concealment: unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** yes **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and excluded participants with active duodenal, gastric or oesophageal ulcers, pyloric obstruction or erosive oesophagitis **Type and duration of arthritis (years):** OA no other details **Age:** a 62 (49–87), b 62 (49–83), c 62 (49–86) **Sex:** M/F: a 62/121, b 60/135, c 58/128 **Inclusion criteria:** 50 years or more, OA, requiring NSAID treatment for 6 months or longer **Exclusion criteria:** history of UGI surgery, inflammatory bowel disease, serum creatinine of more than 2 mg/dl, creatinine clearance of 30 ml/min or less, faecal occult blood, unstable medical disease, history of malignancy in past 5 years, cerebrovascular events in past 2 years, bleeding diasthesis, requirement for anticoagulant therapy, corticosteroids, ticlopidine or aspirin	**Comparison:** rofecoxib (b, c) vs ibuprofen (a) **Duration:** 24 weeks **Interventions:** b, rofecoxib 25 mg/12.5–25 mg (once daily); c, rofecoxib 50 mg/12.5–25 mg (once daily); a, ibuprofen 2400 mg/600–2400 mg (800 mg ×3 daily); double dummy design **Other medication:** antacid permitted as needed (Gelusil). Non-study NSAIDs, corticosteroids, anticoagulants, ticlopidine, H_2RAs, sucralfate, PPIs, misoprostol or antacids other than Gelusil not permitted **Aspirin allowed:** no **Analgesic allowed:** acetaminophen (max. 2600 mg daily) supplied, allowed non-NSAID pain medication **Participant education:** not stated **Washout:** yes, 2 weeks for previous NSAIDs, anti-secretory medications, cytoprotective drugs and antibiotics **Number and frequency of visits:** 4 (0, 6, 12 and 24 weeks)	**Allocated:** a 183, b 195, c 186 **Completed:** a 72, b 136, c 122 **Drop-out:** a 112, b 59, c 64 **Assessed:** a 167, b 186, c 178 **Outcomes reported:** serious GI complications, symptomatic ulcers, GI symptoms, endoscopic ulcers **How were adverse events assessed:** no details **How was compliance assessed:** assessed at each visit, method not stated, was more than 95% in all groups	**Risk factors:** history of PUBs: a 35, b 43, c 33 concomitant use of anticoagulants: a 0, b 0 corticosteroids: a 0, b 0 >1 NSAIDs: a 0, b 0 **FUNDING** **Funded by:** Helsinn Healthcare, Switzerland **Affiliation of contact author:** Helsinn Healthcare **Affiliation of statistician:** IDV Datenanalse und Versuchsplanung, Germany **Affiliation of study administrator:** unclear, Helsinn Healthcare contributed to development of study **No. of authors employed by sponsor:** 1 of 8

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Simon, 1999[86,219] **Location:** 79 clinical sites in USA and Canada	**Method of randomisation:** 'computer-generated randomisation schedule stratified by centre in blocks of 10' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** yes **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and excluded patients with oesophageal, gastric or duodenal ulcer or more than 10 erosions **Type and duration of arthritis (years):** RA: a 10, b 11, c 11, d 10 **Age:** a 55 (28–81), b 54 (22–85), c 55 (20–90), d 54 (22–85) **Sex:** M/F: a 63/162, b 62/178, c 63/172, d 61/157 **Inclusion criteria:** outpatients 18 years or more, ACR criteria for diagnosis of RA (evident for at least 3 months) and in functional class I, II or III. Doses of any glucocorticoids, DMARDs or methotrexate had been stable and were expected to remain constant throughout the study, symptomatic RA flare following washout of NSAIDs or any analgesics confirmed at baseline by physicians and patients **Exclusion criteria:** active GI tract, renal, hepatic or coagulation disorders, history of malignancy (unless removed surgically with no recurrence within 5 years), oesophageal or gastroduodenal ulceration within the previous 30 days, history of gastric or duodenal surgery other than oversew, oesophageal, gastric or duodenal ulcer or 10 erosions or more at baseline endoscopy	**Comparison:** celecoxib (b, c, d) vs naproxen **Duration:** 12 weeks **Interventions:** b, celecoxib 200 mg/200–400 mg (100 mg ×2 daily); c, celecoxib 400 mg/200–400 mg (200 mg ×2 daily); d, celecoxib 800 mg/200–400 mg (400 mg ×2 daily); a, naproxen 1000 mg/500–1250 mg (500 mg ×2 daily) **Other medication:** other NSAIDS, injectable corticosteroids, anticoagulants and anti-ulcer drugs prohibited, stable doses of oral glucocorticoids, DMARDs allowed **Aspirin allowed:** yes, stable doses of 325 mg/day or less **Analgesic allowed:** yes, acetaminophen 2 g daily or less for 3 consecutive days or less (except within 48 h of arthritis assessment) **Participant education:** not stated **Washout:** yes, 2–7 days for previous NSAIDs or any analgesic medication **Number and frequency of visits:** 4 (0, 2, 6, 12 weeks)	**Allocated:** a 225, b 240 c 235, d 218 **Completed:** a 138, b 154, c 158, d 137 **Drop-out:** a 87, b 86, c 77, d 81 **Assessed:** a 225, b 240, c 235, d 218 **Outcomes reported:** serious GI complications, symptomatic ulcers, serious cardiac or renal illness, QoL, GI symptoms, endoscopic ulcers, GI drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** tablet count, plasma levels at day 21	**Risk factors:** concomitant use of corticosteroids: a 31, b 42, c 37, d 34 >1 NSAID: a 0, b 0 **FUNDING** Funded by: GD Searle **Affiliation of contact author:** Beth Israel Deaconess Medical Center, MA, USA **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 6 of 11 authors employed by Searle

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Bombardier, 2000[87] **Location:** 301 centres in 22 countries	**Method of randomisation:** 'randomly assigned', stratified according to presence or absence of history of gastroduodenal ulcer, upper GI bleeding, gastroduodenal perforations **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** yes, independent blinded end-point committee **Intention-to-treat:** yes ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** endoscopy not performed but excluded if had positive test for faecal occult blood at baseline **Type and duration of arthritis:** RA for less than 2 years: a 455, b 430 2–10 years: a 1996, b 1991 >10 years: a 1571, b 1623 **Age:** a 58, b 58 **Sex:** M/F: a 814/3215, b 824/3223 **Inclusion criteria:** RA, 50 years or more (or 40 years or more and receiving long-term glucocorticoid therapy) and expected to require NSAIDs for at least 1 year **Exclusion criteria:** history of any other type of inflammatory arthritis, UGI surgery, or inflammatory bowel disease, estimated creatinine clearance 30 ml/minute or less, a positive test for faecal occult blood, an unstable medical condition, history of cancer or alcohol or drug abuse in past 5 years, a history of cerebrovascular events in past 2 years, history of MI or coronary bypass in past year, morbid obesity, required treatment with aspirin, ticlopidine, anticoagulants, cyclosporine, misoprostol, sucralfate, PPIs or H_2RAs in prescription-strength doses	**Comparison:** rofecoxib (b) vs naproxen (a) **Duration:** median 9 months **Interventions:** b, rofecoxib 50 mg/12.5–25 mg (once daily); a, naproxen 1000 mg/500–1250 mg (500 mg ×2 daily) **Other medication:** DMARDs, antacids and H_2RAs allowed (up to 150 mg daily ranitidine or nizatidine, 20 mg daily famotidine, 400 mg daily cimetidine); ticlopidine, anticoagulants, cyclosporine, misoprostol, sucralfate, PPIs or H_2RAs in prescription-strength doses were excluded **Aspirin allowed:** no **Analgesic allowed:** yes, acetaminophen and non-NSAID analgesics **Participant education:** not stated **Washout:** yes, 3–14 days **Number and frequency of visits:** 0, 6 weeks, 4 months, 8 months and then every 4 months (telephone contact at week 10 and then every 4 months)	**Allocated:** a 4029, b 4047 **Completed:** a 2881, b 2861 **Drop-out:** a 1148, b 1186 **Assessed:** unclear **Outcomes reported:** mortality, serious GI complications, symptomatic ulcers, serious cardiovascular or renal events, GI symptoms, endoscopy, GI drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** tablet count and questioning during telephone calls, 99% of participants in both groups took their medication on at least 75% of study days	**Risk factors:** history of clinical GI events: a 316, b 314 concomitant H_2RAs: a 335, b 365 >1 NSAID: a 0, b 0 CVD: a 0, b 0 **FUNDING** **Funded by:** Merck **Affiliation of contact author:** Institute for Work and Health, Toronto, Canada **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 11 of 13 principal authors have had financial associations with Merck and in most cases with many other companies, 2 principal authors were employees of Merck **Doses:** rofecoxib prescribed above maximum recommended dose

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Cannon, 2000[88] **Location:** multicentre, USA	**Method of randomisation:** 'randomisation occurred following an eligibility visit by a computer-generated randomisation schedule' **Allocation concealment:** adequate **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** yes **Summary risk of bias:** low	**Baseline GI status:** no baseline endoscopy performed, GI status not assessed, people with history of gastroduodenal ulcer or GI bleeding were allowed to participate **Type and duration of arthritis (years):** OA: a 11.4, b 11.1, c 11.5 **Age:** a 62.5, b 62.8, c 62.8 **Sex:** M/F: a 83/185, b 90/169, c 82/175 **Inclusion criteria:** 40 years or more, clinical and radiographic evidence of OA (knee, joint space narrowing and the presence of osteophytes, or hip, joint space narrowing) with study joint primary source of pain or disability, functional class I, II or III (Steinbrocker criteria), those on NSAIDs had to have at least moderate pain when walking (40 mm or more on VAS) and an increase in pain when walking (15 mm or more on VAS compared with screening level) after washout, also physician's assessment of disease state worse than at screening, those on acetaminophen had at least moderate pain when walking after 12 h without acetaminophen (40 mm or more on VAS), patient's and physician's assessment of disease status had to be fair, poor or very poor, women post-menopausal or non-gravid **Exclusion criteria:** significant renal impairment, clinically significant abnormalities on physical or laboratory examinations, positive faecal occult blood, class III/IV angina, uncontrolled congestive heart failure, uncontrolled hypertension, stroke or transient ischaemic attack within 2 years of study, active hepatic disease, history of recent neoplastic disease, allergy to acetaminophen or NSAIDs, requiring aspirin (any dose), corticosteroids, warfarin or ticlopidine	**Comparison:** rofecoxib (b, c) vs diclofenac (a) **Duration:** 52 weeks **Interventions:** b, rofecoxib 12.5 mg/12.5–25 mg (once daily); c, rofecoxib 25 mg/12.5–25 mg (once daily); a, diclofenac 150 mg/75–150 mg (50 mg ×3 daily); double dummies used **Other medication:** no details **Aspirin allowed:** no **Analgesic allowed:** yes, acetaminophen (max. 2.6 g/day) **Participant education:** not stated **Washout:** yes **Number and frequency of visits:** 11 (0, 2, 4, 8, 12, 19, 26, 33, 39, 45, 52 weeks)	**Allocated:** a 268, b 259, c 257 **Completed:** a 145, b 161, c 142 **Drop-out:** a 123, b 98, c 115 **Assessed:** a 268, b 259; c 257 **Outcomes reported:** serious GI complications, symptomatic ulcers, serious cardiovascular or renal illness, GI symptoms, GI drop-outs **How were adverse events assessed:** spontaneously reported **How was compliance assessed:** not stated	**Risk factors:** concomitant use of corticosteroids: a 0, b 0 CVD: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** Merck Research Laboratories **Affiliation of contact author:** Merck **Affiliation of statistician**: Merck **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 5 out of 9 authors worked for Merck

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Class, 2000[89] **Location:** USA and Canada	**Method of randomisation:** 'randomly assigned', stratified by OA/RA status, remote interactive voice-activated response system used to randomise after baseline visit **Allocation concealment:** adequate **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** yes (GEC committee blinded and study personnel blinded) **Intention-to-treat:** yes ***A priori* sample size:** yes **Summary risk of bias:** low	**Baseline GI status:** baseline endoscopy performed and patients excluded if had oesophageal, gastric, pyloric channel or duodenal ulcer **Type and duration of arthritis (years):** OA/RA: a 10.9/9.9, b 10.5/10.4, c 11.2/10.3 **Age:** a 59.5, b 60.1, c 60.6 **Sex:** M/F: a 580/1405, b 650/1346, c 1255/2732 **Inclusion criteria:** legal age of consent or older, for women of childbearing potential, had been using adequate contraception since last menses and agreed to continue to use adequate contraception during the study, not been lactating and had a negative serum pregnancy test within 7 days before receiving the first dose of study medication; had a documented clinical diagnosis of OA or RA of at least 3 months duration; required chronic NSAID therapy in the investigator's opinion; expected to participate for the full duration of the study **Exclusion criteria:** active malignancy of any type or a history of malignancy (except history of basal cell carcinoma that had been treated and history of other malignancies that had been surgically removed and who had no evidence of recurrence for at least 5 years before start of the study); diagnosed as having or had received treatment for oesophageal, gastric, pyloric channel or duodenal ulcer within 30 days prior to receiving first dose of study medication; active GI disease (e.g. inflammatory bowel disease); history of gastric or duodenal surgery other than simple oversew of an ulcer or perforation; significant renal or hepatic dysfunction or a significant coagulation defect considered by the	**Comparison:** celecoxib (c) vs diclofenac (b), vs ibuprofen (a) **Duration:** 26–65 weeks **Interventions:** c, celecoxib 800 mg/200–400 mg (400 mg ×2 daily); b, diclofenac, 150 mg/75–150 mg (75 mg ×2 daily); a, ibuprofen 2400 mg/600–2400 mg (800 mg ×3 daily) **Other medication:** patients encouraged to take only study drugs if possible, other NSAIDs, anti-ulcer drugs, antibiotics, antineoplastics (except methotrexate at 25 mg per week or less or azathioprine) were prohibited; antacids and calcium supplements allowed and oral, intramuscular and intra-articular corticosteroids permitted **Aspirin allowed:** yes, 325 mg daily or less: a 383, b 429, c 833 **Analgesic allowed:** yes, paracetamol up to 2000 mg daily alone or in combination with propoxyphene hydrochloride or napsalate, hydromorphone hydrochloride, oxycodone hydrochloride or codeine phosphate **Participant education:** not stated **Washout:** no details **Number and frequency of visits:** 6–7 (0, 4, 13, 26, 39, 52 and some at 65 weeks)	**Allocated:** a 2009, b 2019, c 4031 **Completed:** a 691, b 939, c 1779 **Drop-out:** a 1318, b 1080, c 2252 **Assessed:** a 1985, b 1996, c 3987 **Outcomes reported:** mortality, serious GI complications, symptomatic ulcers, serious cardiovascular or renal illness, quality of life, GI symptoms, GI drop-outs, anaemia, total drop-outs **How were adverse events assessed:** participants asked 'do you have any symptoms that are not associated with your arthritis?' if suggestive of CSUGIE (Clinically Significant Upper Gastrointestinal Event) then initiated workup of potential events according to predefined algorithm, coded according to WHOART (World Health Organization Adverse Reactions Terminology)	**Risk factors:** history of ulcers: a 151, b 170, c 334 history of bleeds: a 28, b 30, c 68 concomitant use of anti-coagulants: a 20, b 24 c 42 corticosteroids: a 607, b 568, c 1219 >1NSAID: a 0, b 0, c 0; CVD: a 794, b 805, c 1602 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** pharmacia **Affiliation of contact author:** Pharmacia **Affiliation of statistician:** unclear, but named as Clem Maurath **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 6/16 work for Pharmacia, all other authors have been paid consultants for Pharmacia

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
		investigator to be clinically significant; abnormal screening laboratory test values more than 1.5 times the upper limit of normal for either AST or ALT or any other laboratory abnormality at screening considered by the investigator to be clinically significant; positive screening faecal occult blood result; known hypersensitivity to Cox-2 inhibitors, sulfonamides, ibuprofen or diclofenac; received any investigational medication within 30 days before the first dose of study medication or was scheduled to receive an investigational drug other than celecoxib during the course of the study; had previously been admitted to either of these protocols or a prior study with celecoxib		**How was compliance assessed:** tablet count, non-compliance defined as taking less than 70% study medication, diary card used to list any medication taken in last 30 days	

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Day, 2000[90,224] **Location:** 49 sites in 26 countries in North and South America, Europe, Australia and New Zealand (not UK)	**Method of randomisation:** 'randomised', computer-generated randomisation schedule, masked allocation schedule generated by an individual not otherwise involved in the study and kept concealed from all study participants, allocation schedule unblinded once all data was entered, received and certified **Allocation concealment:** adequate **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** low	**Baseline GI status:** no baseline endoscopy, no further details **Type and duration of arthritis (years):** OA: a 9.0, b 8.3, c 8.5 **Age:** a 64.1 b 64.9 c 62.8 **Sex:** M/F: a 54/195, b 46/198, c 51/191 **Inclusion criteria:** 40 years or more, clinical and radiographic evidence of OA (joint space narrowing and osteophytes for knee and joint space narrowing for hip), functional class I, II or III (Steinbrocker), symptomatic for at least 6 months, knee or hip the primary source of pain or disability and women postmenopausal or demonstrably non-gravid, NSAID users: following washout, participants' pain on walking (flat) was assessed using question 1 of WOMAC index and if 40 mm or more and an increase of 15 mm or more on the VAS compared with pre-washout, and if the investigator's global assessment of disease status worsened by at least 1 point on a 0–4 Likert scale; acetaminophen users: if met all 3 of the following criteria at both the screening and randomisation visits: 40 mm or more on the pain VAS (question 1 of WOMAC), reported 40 mm or more on a VAS evaluating patient's global assessment of disease status and the investigator rated the global assessment of disease status as fair, poor or very poor **Exclusion criteria:** significant renal impairment, clinically significant abnormal results of physical examination or laboratory screening, positive faecal occult blood test, malabsorption, class III/IV angina or congestive heart failure, uncontrolled hypertension, stroke or transient ischaemic attack within 2 years, active hepatic disease, history of recent neoplastic disease or allergy to NSAIDs or acetaminophen, requiring aspirin (any dose), corticosteroids, warfarin sodium or ticlopidine hydrochloride	**Comparison:** rofecoxib (b, c) vs ibuprofen (a) **Duration:** 6 weeks **Interventions:** b, rofecoxib 12.5 mg/12.5–25 mg (once daily); c, rofecoxib 25 mg/12.5–25 mg (once daily); a, ibuprofen 2400 mg/600–2400 mg (800 mg ×3 daily), double dummies used **Other medication:** corticosteroids, warfarin and ticlopidine prohibited **Aspirin allowed:** no **Analgesic allowed:** yes, acetaminophen 2600 mg/day or less **Participant education:** not stated **Washout:** yes, longer than 5 plasma half-lives of prior NSAID use **Number and frequency of visits:** 4 (0, 2, 4 and 6 weeks)	**Allocated:** a 249, b 244, c 242 **Completed:** a 214, b 224, c 219 **Drop-out:** a 30, b 18, c 16 **Assessed:** a 244, b 242, c 235 **Outcomes reported:** symptomatic ulcers, GI symptoms **How were adverse events assessed:** spontaneously reported **How was compliance assessed:** not stated	**Risk factors:** concomitant use of corticosteroids: a 0, b 0 CVD: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** Merck **Affiliation of contact author:** Merck **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 7 out of 13 authors employed by Merck

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Hawkey, 2000[91,223] **Location:** 5 USA sites and 31 international sites	**Method of randomisation:** 'randomly assigned', randomisation stratified by presence or absence of history of GI events (PUBs), 95% of participants taking placebo and 5% of participants in the other groups were randomly selected and discontinued from the trial in a blinded manner at week 16 **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and participants excluded if pyloric obstruction, erosive oesophagitis or oesophageal, gastric or duodenal ulcers, participants with gastroduodenal erosions were permitted to enter trial **Baseline NSAID status:** 49.4% of all participants reported prior NSAID use **Type and duration of arthritis (years):** OA: no other details **Age:** a 61 (49–89), b 62 (50–85) c 61 (50–81) **Sex:** M/F: a 50/143, b 45/150, c 54/139 **Inclusion criteria:** OA, 50 years or more, required treatment for at least 6 months **Exclusion criteria:** endoscopic evidence of erosive oesophagitis, oesophageal, gastric or duodenal ulceration or pyloric obstruction, previous UGI surgery, inflammatory bowel disease, serum creatinine levels more than 2.0 mg/dl, estimated creatinine clearance 30 ml/min or less, faecal occult blood, unstable medical disease, history of malignancy in prior 5 years, pregnancy, cerebrovascular events in the prior 2 years, bleeding diathesis, requirement for anticoagulant therapy, corticosteroids, ticlopidine or aspirin	**Comparison:** rofecoxib (b, c) vs ibuprofen (a) **Duration:** 16–24 weeks **Interventions:** b, rofecoxib 25 mg/12.5–25 mg (once daily); c, rofecoxib 50 mg/12.5–25 mg (once daily), a, ibuprofen 2400 mg/600–2400 mg (800 mg 3× daily); double dummies used **Endoscopy:** baseline, 6, 12 and 24 weeks, at unscheduled discontinuation or to evaluate moderate/severe upper GI symptoms occurring for 2 days or more **Other medication:** antacid supplied as needed, non-study NSAIDs, corticosteroids, anticoagulants, ticlopidine, H_2RAs, sucralfate, prostaglandins, PPIs or unapproved antacids not permitted **Aspirin allowed:** no **Analgesic allowed:** yes, acetaminophen 2600 mg daily or less and non-NSAID pain medication **Participant education:** not stated **Washout:** 2 weeks for NSAIDs, antisecretaory medications, cytoprotective drugs and antibiotics **Number and frequency of visits:** 4 (0, 6, 12 and 24 weeks)	**Allocated:** a 193, b 195, c 193 **Completed:** a 80, b 138, c 127 **Drop-out:** a 113, b 57, c 66 **Assessed:** a 187, b 187, c 182 **Outcomes reported:** serious GI complications, GI symptoms, endoscopic ulcers **How were adverse events assessed:** not stated **How was compliance assessed:** not stated but more than 95% compliance reported in all study groups	**Risk factors:** history of of PUBs: a 24, b 23 c 19 >1 NSAIDs: a 0, b 0 concomitant use of anticoagulants: a 0, b 0 corticosteroids: a 0, b 0 **FUNDING** **Funded by:** unclear **Affiliation of contact author:** Merck **Affiliation of statistician:** unclear **Affiliation of administrator:** unclear **No. of authors employed by sponsor:** 5 of 10 authors employed by Merck

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Saag, 2000A[92] **Location:** 62 clinical centres in USA	**Method of randomisation:** 'computer-generated allocation schedule' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** yes, investigators making assessments were blinded to treatment status **Intention-to-treat:** unclear ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy performed but patients excluded if had evidence of active GI bleeding **Type and duration of arthritis (years):** OA: a 9 (1–47), b 8 (1–57), c 9 (1–37) **Age:** a 63 (38–85), b 62 (39-85), c 62 (39–79) **Sex:** M/F: a 42/188, b 44/187, c 52/180 **Inclusion criteria:** 40 years or more, OA (knee or hip), met clinical and radiographic criteria for OA and were ARA functional classes I, II or III, history of positive therapeutic benefit from NSAIDs (90% of patients) or acetaminophen (10%), eligible patients who used a pre-study NSAID had to demonstrate worsening of signs and symptoms of OA after washout period, eligible patients who used acetaminophen were required to have consistently at least moderate symptoms of OA **Exclusion criteria:** using corticosteroids, topical analgesics, low-dose aspirin, regular antacid, H_2 blocker, PPIs, warfarin or ticlopidine, significant renal impairment, evidence of active GI bleeding, GI malabsorption syndrome, class III/IV angina or congestive heart failure, uncontrolled hypertension, stroke, transient ischaemic attack within 2 years, active hepatic disease, recent neoplastic disease, allergy to acetaminophen or NSAIDs, any condition that could interfere with study participation, confound results, or pose an unacceptable risk to the patient	**Comparison:** rofecoxib (b, c) vs ibuprofen (a) **Duration:** 1 year **Interventions:** b, rofecoxib 12.5 mg/12.5–25 mg (once daily in the morning); c, rofecoxib 25 mg/12.5–25 mg (once daily in the morning); a, diclofenac 150 mg/75–150 mg (50 mg ×3 daily), double dummies used **Other medication:** corticosteroids, topical analgesics, regular antacid, H_2 blocker, PPIs, warfarin or ticlopidine excluded **Aspirin allowed:** no **Analgesic allowed:** yes, acetaminophen provided (325 mg) for breakthrough pain, after first 26 weeks of study topical or systemic analgesics or corticosteroids were allowed for breakthrough pain **Participant education:** not stated **Washout:** yes, no further details **Number and frequency of visits:** 8 (0, 2, 4, 8, 12, 24, 39, 52 weeks)	**Allocated:** a 230, b 231, c 232 **Completed:** a 154, b 149, c 158 **Drop-out:** a 76, b 82, c 74 **Assessed:** ?a 230, b 231 c 232 **Outcomes reported:** mortality, cardiovascular events, GI symptoms, GI drop-outs **How were adverse events assessed:** non-directed interview, all adverse events evaluated as mild, moderate, severe, relationship to study drug, outcome and action taken recorded **How was compliance assessed:** tablet count	**Risk factors:** CVD: a 0, b 0 diabetes: total $n = 35$ hypertension: total $n = 236$; renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** Merck **Affiliation of contact author:** Merck Research Laboratories **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 4 of 8 main authors employed by Merck

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Saag, 2000B[92] **Location:** 62 clinical centres in USA	**Method of randomisation:** 'computer-generated allocation schedule' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** yes, investigators making assessments were blinded to treatment status **Intention-to-treat:** unclear ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy performed but patients excluded if had evidence of active GI bleeding **Type and duration of arthritis (years):** OA: a 10 (1–47), b 10 (0–48), c 11 (0–49) **Age:** a 61 (41–82), b 60 (39–91), c 62 (39–85) **Sex:** M/F: a 58/163, b 52/167, c 65/162 **Inclusion criteria:** 40 years or more, OA (knee or hip), met clinical and radiographic criteria for OA and were ARA functional classes I, II or III, history of positive therapeutic benefit from NSAIDs (90% of patients) or acetaminophen (10%), eligible patients who used a pre-study NSAID had to demonstrate worsening of signs and symptoms of OA after washout period, eligible patients who used acetaminophen were required to have consistently at least moderate symptoms of OA **Exclusion criteria:** using corticosteroids, topical analgesics, low-dose aspirin, regular antacid, H_2 blocker, PPIs, warfarin or ticlopidine, significant renal impairment, evidence of active GI bleeding, GI malabsorption syndrome, class III/IV angina or congestive heart failure, uncontrolled hypertension, stroke, transient ischaemic attack within 2 years, active hepatic disease, recent neoplastic disease, allergy to acetaminophen or NSAIDs, any condition that could interfere with study participation, confound results, or pose an unacceptable risk to the patient	**Comparison:** rofecoxib (b, c) vs ibuprofen (a) **Duration:** 6 weeks **Interventions:** b, rofecoxib 12.5 mg/12.5–25 mg (once daily in the morning); c, rofecoxib 25 mg/12.5–25 mg (once daily in the morning); a, ibuprofen 2400 mg/600–2400 mg (800 mg ×3 daily); double dummies used **Other medication:** corticosteroids, topical analgesics, regular antacid, H_2 blocker, PPIs, warfarin or ticlopidine excluded **Aspirin allowed:** no **Analgesic allowed:** yes, acetaminophen provided (325 mg) for breakthrough pain **Participant education:** not stated **Washout:** yes, no further details **Number and frequency of visits:** 4 (0, 2, 4 and 6 weeks)	**Allocated:** a 221, b 219, c 227 **Completed:** a 189, b 186, c 200 **Drop-out:** a 32, b 33, c 27 **Assessed:** ?a: 221, b 219, c 227 **Outcomes reported:** mortality, GI symptoms, GI drop-outs **How were adverse events assessed:** non-directed interview, all adverse events evaluated as mild, moderate, severe, relationship to study drug, outcome and action taken recorded **How was compliance assessed:** tablet count	**Risk factors:** concomitant use of corticosteroids: a 0, b 0 CVD: a 0, b 0 diabetes: total $n = 44$ hypertension: total $n = 316$ renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** Merck **Affiliation of contact author:** Merck Research Laboratories **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 4 of 8 main authors employed by Merck

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Dougados, 2001[93] **Location:** 76 rheumatology centres in France	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy performed but participants were excluded if had ulcer in previous year **Type and duration of arthritis (years):** AS: a 11, b 11 **Age:** a 38, b 38 **Sex:** M/F: a 60/30, b 56/24 **Inclusion criteria:** outpatients fulfilling the modified New York criteria for AS, daily NSAID intake during the preceding month, NSAID washout 2–14 days before baseline visit, a flare at baseline defined both by pain (40 mm or more on a 100 mm VAS) and by an increase in pain of at least 30% between screening and baseline visits **Exclusion criteria:** peripheral articular disease defined by the presence of active (with swelling) peripheral arthritis (excluding hip and shoulder) at screening visit, active inflammatory bowel disease, concomitant severe medical illness, corticosteroids within previous month and/or any DMARD with a change of dosage during previous 6 months, peptic ulcer confirmed by endoscopy within previous year; at screening concomitant therapies with GI protective effects (misoprostol, PPIs) were stopped where no history of gastroduodenal ulcers and initiated/continued when a positive history of gastroduodenal ulcers	**Comparison:** celecoxib (b) vs ketoprofen (a) **Duration:** 6 weeks **Interventions:** b, celecoxib 200 mg/200–400 mg (100 mg ×2 daily); a, ketoprofen 200 mg/100–200 mg (100 mg ×2 daily), double dummies used (4 capsules/day, 2 at breakfast, 2 at dinner) **Other medication:** concomitant therapies with GI protective effects (misoprostol, PPIs) were stopped where no history of gastroduodenal ulcers and initiated/continued when a positive history of gastroduodenal ulcers **Aspirin allowed:** not stated **Analgesic allowed:** yes, acetaminophen, max. 6 × 500 mg tablets/day **Participant education:** not stated **Washout:** yes, 2–14 days, part of inclusion criteria **Number and frequency of visits:** 4 (0, 1, 3 and 6 weeks)	**Allocated:** a 90, b 80 **Completed:** a 67, b 54 **Drop-out:** a 23, b 26 **Assessed:** a 90, b 80 **Outcomes reported:** mortality, serious GI complications, symptomatic ulcer, serious cardiac or renal illness, GI symptoms, anaemia, GI drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** capsule count, a 100% mean capsule intake; b 97.5% mean capsule intake	**Risk factors:** concomitant use of corticosteroids: a 0, b 0 **FUNDING** **Funded by:** in part by a grant from Searle **Affiliation of contact author:** Université Réné Descartes, Paris, France **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 1 of 8 authors worked for Searle **Other:** GI protective effects (misoprostol, PPIs) were initiated and/or continued when there was a positive history of gastroduodenal ulcers, no further details given

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Goldstein, 2001[39] **Location:** multicentre, 75 sites in USA	**Method of randomisation:** 'randomly assigned' according to a computer-generated randomisation schedule (separate schedules were prepared for OA and RA), patients were assigned in the order in which they enrolled into the study at each site to receive allocated treatment according to the sponsor-prepared (GD Searle) **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** yes **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and excluded participants with ulcers **Type and duration of arthritis (years):** OA: a $n = 195$ (11.0 years), b $n = 194$ (9.5 years); RA: a $n = 72$ (8.9 years), b $n = 76$ (11.6 years) **Age:** a 57.7 (22–84), b 56.7 (23–86) **Sex:** M/F: a 91/179, b 89/181 **Inclusion criteria:** legal age of consent, active OA or RA for at least 3 months and required chronic NSAIDs, functional capacity classification I to III, confirmed use of adequate contraception and negative pregnancy test within 7 days of first dose of study medication **Exclusion criteria:** largely or wholly incapacitated permitting little or no self-care, any other inflammatory arthritis, acute gout, active GI disease, diagnosis of any acute UGI ulceration within 30 days before the first dose of study medication (or if they had taken 1000 mg/day or more of naproxen within 30 days of first dose of study medication); those with ulcers of 3 mm or more at pre-enrolment endoscopy	**Comparison:** celecoxib (b) vs Naproxen (a) **Duration:** 12 weeks **Interventions:** b, celecoxib 400 mg/200–400 mg (200 mg ×2 daily); a, naproxen 1000 mg/500–1250 mg (500 mg ×2 daily); double dummies used, all medication taken with breakfast and dinner **Endoscopy:** 0, 4, 8 and 12 weeks and if symptomatic **Other medication:** use of other drugs discouraged, NSAIDs, anti-ulcer drugs (e.g. misoprostol, antibiotics to treat *H. pylori*, anticoagulants, antacids, antineoplastics) were prohibited, oral corticosteroids allowed on stable dose only **Aspirin allowed:** yes, 325 mg/day or less **Analgesics allowed:** yes, acetaminophen **Participant education:** not stated **Washout:** yes, NSAIDs discontinued 7 days before first dose of study medication **Number and frequency of visits:** 4 (0, 4, 8, 12 weeks)	**Allocated:** a 267, b 270 **Completed:** a 149, b 210 **Drop-out:** a 118, b 60 **Assessed:** a 267, b 269 **Outcomes reported:** mortality, serious GI complications, symptomatic ulcers, serious cardiovascular or renal illness (extra data) GI symptoms, endoscopic ulcers, GI drop-outs **How were adverse events assessed:** not stated	**Risk factors:** history of ulcers: a 53, b 57 history of bleeds: a 13, b 11 >1 NSAIDs: a 0, b 0 CVD: a 134, b 151 **FUNDING** **Funded by:** GD Searle and Pfizer **Affiliation of contact author:** University of Illinois **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** at least 1 author employed by GD Searle **Other:** 1 of 267 naproxen participants had baseline gastric ulcer

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Kivitz, 2001[94] **Location:** multicentre, 176 sites in USA and Canada	**Method of randomisation:** 'randomly assigned', stratified by site in blocks of 10 **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy performed but patients excluded if they had been diagnosed with or treated for oesophageal/gastroduodenal ulceration within 30 days of receiving the study drug **Type and duration of arthritis (years):** OA: a 7.3, b 7.2, c 6.9 **Age:** a 64 (32–87), b 62 (30–86), c 61 (28–88) **Sex:** M/F: a 70/137, b 72/135, c 70/143 **Inclusion criteria:** adult outpatients, ACR clinical and radiographic criteria diagnosis of primary OA (hip), functional class I, II, or III and symptomatic OA flare at baseline visit **Exclusion criteria:** received oral, intramuscular, intra-articular or soft-tissue injections of corticosteroids within 4 weeks of the first dose of study medication, hypersensitivity to Cox-2 inhibitors, sulfonamides or NSAIDs, received any investigational medication within 30 days of the first study dose, taken any NSAIDs or analgesics within 48 h of baseline assessments, or received piroxicam and/or oxaprozin within 4 days of baseline assessment; active concomitant GI tract, renal, hepatic or coagulation disorders, malignancy, oesophageal/gastroduodenal ulceration within 30 days of receiving the study drug, inflammatory arthritis, gout, or acute joint trauma at the hip or an anticipated need for surgery during the study period	**Comparison:** celecoxib (b, c) vs naproxen (a) **Duration:** 12 weeks **Interventions:** b, celecoxib 200 mg/200–400 mg (100 mg ×2 daily); c, celecoxib 400 mg/200–400 mg (200 mg x2 daily); a, naproxen 1000 mg/500–1250 mg (500 mg x2 daily); double masked **Other medication:** corticosteroids not allowed in first 4 weeks, other medication permitted **Aspirin allowed:** yes, 325 mg/day or less **Analgesic allowed:** yes, acetaminophen less than 3 g daily for 3 consecutive days or less (except within 48 h of assessment) **Participant education:** not stated **Washout:** yes, 2–4 days for NSAIDs and other analgesics (4 days for piroxicam and/or oxaprozin **Number and frequency of visits:** 4 (0, 2, 4, 12 and 24 weeks and by telephone at 8, 16 and 20 weeks)	**Allocated:** a 207, b 207, c 213 **Completed:** a 118, b 111, c 119 **Drop-out:** a 89, b 96, c 94 **Assessed:** a 207, b 207, c 213 **Outcomes reported:** serious GI complications, GI symptoms, GI drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** history of ulcers: 9–18% in each group; history of bleeds: 1–3% in each group; concomitant use of corticosteroids: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** unclear but writing of the article was supported by Pharmacia and Pfizer **Affiliation of contact author:** Altoona Center for Clinical Research, PA, USA **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 5 of 7 authors employed by Pharmacia **Other:** celecoxib 100 mg daily and placebo arms were excluded from analyses

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
McKenna, 2001[95] **Location:** multicentre, 54 sites in USA	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy performed but participants excluded if had active GI disease **Baseline NSAID status:** 78.4% diclofenac group, 77.6% celecoxib group had prior NSAID use **Type and duration of arthritis (years):** OA: a 8.5, b 8.4 **Age:** a 62.7 (29–87), b 61.9 (32–85) **Sex:** M/F: a 76/123, b 64/137 **Inclusion criteria:** OA (knee, ACR criteria), symptomatic as evidenced by worsening of signs and symptoms of the disease following discontinuation of treatment with NSAIDs or other analgesic medications **Exclusion criteria:** active GI disease, chronic or acute renal or hepatic disease	**Comparison:** celecoxib (b) vs diclofenac (a) **Duration:** 6 weeks **Interventions:** b, celecoxib 200 mg/200–400 mg (100 mg 2× daily); a, diclofenac 150 mg/75–150 mg (50 mg 3× daily) **Other medication:** concomitant corticosteroids, NSAIDs or intra-articular injections of haluronic acid prohibited **Aspirin allowed:** yes for non-arthritis indications if dose stable **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** yes, flare needed on discontinuation of NSAIDs or other analgesics **Number and frequency of visits:** 3 (0, 2 and 6 weeks)	**Allocated:** a 199, b 201 **Completed:** a 162, b 159 **Drop-out:** a 37, b 42 **Assessed:** a 199, b 199 **Outcomes reported:** serious cardiovascular or renal illness, GI symptoms, anaemia, GI drop-outs **How were adverse events assessed:** spontaneously reported, serious adverse events were recorded **How was compliance assessed:** not stated	**Risk factors:** history of ulcers: a 12, b 16 history of bleeds: a 4, b 2 concomitant use of corticosteroids: a 0, b 0 >1 NSAIDs: a 0, b 0 CVD: a 133, b 131; renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** Pharmacia **Affiliation of contact author:** Pharmacia **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 5 of 6 authors employed by Pharmacia

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Kivitz, 2002[96] **Location:** 85 centres in USA and Canada	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** yes **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and excluded participants with 10 or more oesophageal, gastric or duodenal erosions or oesophageal, gastric, pyloric channel or duodenal ulcer **Type and duration of arthritis (years):** OA: a 9.4, b 9.8, c 8.7, d 9.2 **Age:** a 60.4, b 58.7, c 59.8, d 59.6 **Sex:** M/F: a 76/129, b 73/128, c 72/134, d 66/136 **Inclusion criteria:** ambulatory patients diagnosed with moderate to severe OA (knee, ACR criteria), baseline scores of 40 mm or more on the Patients Assessment of Arthritis Pain VAS scale and baseline categorical scores of poor to very poor on the Patient and Physician Global Assessment of Arthritis **Exclusion criteria:** inflammatory arthritis, gout, pseudo-gout, Paget disease, any chronic pain syndrome that might interfere with assessment of the index knee, severe anserine bursitis, acute joint trauma or complete loss of articular cartilage on the index knee, active GI disease, GI tract ulceration within 30 days, significant bleeding disorder or history of gastric or duodenal surgery, oesophageal, gastric, pyloric channel or duodenal ulcer or a score of 10 or more for oesophageal, gastric or duodenal erosions at the pretreatment endoscopy	**Comparison:** Valdecoxib (b, c, d) vs naproxen (a) **Duration:** 12 weeks **Interventions:** b, valdecoxib 5 mg/? (once daily); c, Valdecoxib 10 mg/? (once daily); d, Valdecoxib 20mg/? (once daily); a, naproxen 1000 mg/500–1250 mg (500 mg ×2 daily) **Endoscopy:** 0 and 12 weeks or early termination or any time if symptomatic **Other medication:** not stated **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** 48 h for NSAIDs (including aspirin at 325 mg/day or less), 4 weeks for corticosteroid injections, 3 months for intra-articular injections of corticosteroid, 6 months for intra-articular injection of hyaluronic acid, 24 h for H_2RAs, PPIs, misoprostol, sucralfate **Number and frequency of visits:** 4 (0, 2, 6, 12 weeks)	**Allocated:** a 205, b 201, c 206, d 202 **Completed:** a 149, b 162, c 150, d 168 **Drop-out:** a 56, b 39, c 56, d 44 **Assessed:** a 204, b 201, c 205, d 201 **Outcomes reported:** symptomatic ulcers, GI symptoms, endoscopic ulcers **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** history of ulcers: a 31, b 21, c 24, d 28 history of bleeds: a 3, b 0, c 3, d 2 **FUNDING** **Funded by:** Pharmacia and Pfizer **Affiliation of contact author:** has acted in past as consultant for Pharmacia **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 3 employees of Pharmacia and have stock interest within the company

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
McKenna 2002[97] **Location:** multicentre, international (mainly European, no USA)	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy performed but peptic ulceration and GI bleeding excluded **Type and duration of arthritis (years):** OA: a 6.6, b 7.3 **Age:** a 64.1 b 63.3 **Sex:** M/F a 95/246 b 99/247 **Inclusion criteria:** adults with OA (hip and/or knee) for at least 6 months and diagnosed according to ACR criteria, Patient Global Assessment score of fair, poor or very poor, symptomatic disease at baseline and a Functional Capacity Classification of I, II or III **Exclusion criteria:** any other rheumatic condition, acute trauma of joints under examination, peptic ulceration, GI bleeding, inflammatory bowel disease, renal or hepatic failure, a significant coagulation defect, malignancy	**Comparison:** celecoxib (b) vs diclofenac (a) **Duration:** 6 weeks **Interventions:** b, celecoxib 200 mg/200–400 mg (100 mg ×2 daily); a, diclofenac 100 mg/75–150 mg (50 mg ×2 daily); other medication: no details **Aspirin allowed:** yes, low-dose **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 4 (0, 2, 4 and 6 weeks)	**Allocated:** unclear **Completed:** a ?309, b ?320 **Drop-out:** a ?32, b ?26 **Assessed:** a 341 b 346 **Outcomes reported:** GI symptoms, GI drop-outs **How were adverse events assessed:** 'since your last visit, have you experienced or do you currently have any symptoms that are not associated with your arthritis?' Summarised in case report form as mild, moderate or severe according to WHOART classification with start and stop date **How was compliance assessed:** not stated	**Risk factors:** history of ulcers: a 9, b 9; concomitant use of corticosteroids: a 17, b 19; renal/hepatic disease; a 0, b 0 **FUNDING** **Funded by:** unclear **Affiliation of contact author:** Trafford General Hospital, Manchester, UK **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 3 of 5 authors employed by Pharmacia **Other:** published as part of pooled data analysis

(e) Cox-2 preferential NSAID versus Cox-1 NSAID

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Fossaluzza, 1989[98] **Location:** City Hospital of Udine, Italy	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy but those with active peptic ulcer were excluded **Type and duration of arthritis (years):** OA: no other details **Age:** a 71.3 (66–76), b 72.8 (68–77) **Sex:** M/F: a 0/20, b 0/20 **Inclusion criteria:** female outpatients with hip and/or knee OA **Exclusion criteria:** known hypersensitivity to NSAIDs, active peptic ulcer or severe liver, renal or heart failure, undergoing surgical treatment of joints, non-cooperative or non-compliant patients, already on nimesulide or naproxen, concurrent treatments with other NSAIDs, analgesics or corticosteroid agents were not allowed	**Comparison:** nimesulide (b) vs naproxen (a) **Duration:** 28 days **Interventions:** b, nimesulide 200 mg/? (100 mg granules ×2 daily); a, naproxen 500 mg/500–1250 (250 mg granules ×2 daily). All medication taken each morning and evening after meals **Other medication:** concurrent use of other NSAIDs, or corticosteroid agents not allowed **Aspirin allowed:** not stated **Analgesic allowed:** no **Participant education:** not stated **Washout:** yes, 7 days for NSAIDs **Number and frequency of visits:** 4 (0, 7, 14 and 28 days)	**Allocated:** a 20, b 20 **Completed:** a 18, b 19 **Drop-out:** a 2, b 1 **Assessed:** a 20, b 20 **Outcomes reported:** GI symptoms, occult bleeding, GI drop-outs **How were adverse events assessed:** patient disorders reported on data collection forms **How was compliance assessed:** not stated	**Risk factors:** concomitant use of corticosteroids: a 0, b 0 >1 NSAID: a 0, b 0 severe renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** LBP Instituto Farmaceutico **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 1 of 2 authors employed by LBP Instituto Farmaceutico

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Platt, 1989A[99] **Location:** 10 countries, including the UK	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy but those with peptic ulcer disease or history of GI bleed in the last 5 years were excluded **Type and duration of arthritis (years):** OA knee, no other details **Age:** a 61, b 61 **Sex:** M/F: a 17/29, b 7/29 **Inclusion criteria:** OA of the knee with at least 2 of the following radiological criteria: asymmetric joint space narrowing with subchondral sclerosis, marginal osteophyte formation, or subchondral pseudocysts with sclerotic walls; pain in the affected knee and at least one of the following conditions: limitation of motion, tenderness on pressure, swelling, crepitus on motion, morning stiffness or stiffness after inactivity; 18–75 years, responded in the past to NSAIDs, free of peptic ulcer disease, had had no GI bleeding in the last 5 years, no significant renal, haematological or cardiovascular disease, no severe complications or diabetes, no other disease that could affect the joints, no severe infection or tuberculosis, no significant rheumatoid factor, not taking NSAIDs and had active knee joint symptoms (as previously described) or if their disease worsened after a washout period free of any NSAIDs **Exclusion criteria:** previously treated with NSAIDs without effect or who had experienced adverse reactions to NSAIDs, patients taking oral or parenteral anticoagulants, oral hypoglycaemics or drugs known to cause hepatic enzyme changes or drug-induced hepatitis, pregnant or breast-feeding women	**Comparison:** etodolac (b) vs diclofenac (a) **Duration:** 8 weeks **Interventions:** b, etodolac 600 mg/600 mg daily (200 mg ×3 daily); a, diclofenac 150 mg/75–150 mg daily (50 mg ×3 daily) **Other medication:** oral or parenteral anticoagulants, oral hypoglycaemics or drugs known to cause hepatic enzyme changes or drug-induced hepatitis, concurrent use of other NSAIDs, or corticosteroid agents not allowed, type or intensity of physiotherapy remained unchanged **Aspirin allowed:** not stated **Analgesic allowed:** yes, acetaminophen during washout and up to day 14 **Participant education:** not stated **Washout:** yes, 1 week for aspirin and most other NSAIDs, 2 weeks for piroxicam and SR indomethacin **Number and frequency of visits:** 5 (0, 2, 4, 6 and 8 weeks)	**Allocated:** a, 47, b 38 **Completed:** a 40, b 32 **Drop-out:** a, 7, b 6 **Assessed:** unclear **Outcomes reported:** total drop-outs **How were adverse events assessed:** no details **How was compliance assessed:** not stated	**Risk factors:** concomitant use of anticoagulants: a 0, b 0 CVD: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** Freeman Hospital, Newcastle, UK **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/1 **Other:** this is an interim report

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Platt, 1989B[99] **Location:** 10 countries, including the UK	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy but those with peptic ulcer disease or history of GI bleed in the last 5 years were excluded **Type and duration of arthritis (years):** OA: knee, no other details **Age:** a 61, b 59 **Sex:** M/F: a 7/10, b 5/10 **Inclusion criteria:** OA of the knee with at least 2 of the following radiological criteria: asymmetric joint space narrowing with subchondral sclerosis, marginal osteophyte formation or subchondral pseudocysts with sclerotic walls; pain in the affected knee and at least one of the following conditions: limitation of motion, tenderness on pressure, swelling, crepitus on motion, morning stiffness or stiffness after inactivity; 18–75 years, responded in the past to NSAIDs, free of peptic ulcer disease, had had no GI bleeding in the last 5 years, no significant renal, haematological or cardiovascular disease, no severe complications or diabetes, no other disease that could affect the joints, no severe infection or tuberculosis, no significant rheumatoid factor, not taking NSAIDs and had active knee joint symptoms (as previously described) or if their disease worsened after a washout period free of any NSAIDs **Exclusion criteria:** previously treated with NSAIDs without effect or who had experienced adverse reactions to NSAIDs, patients taking oral or parenteral anticoagulants, oral hypoglycaemics or drugs known to cause hepatic enzyme changes or drug-induced hepatitis, pregnant or breast-feeding women	**Comparison:** etodolac (b) vs naproxen (a) **Duration:** 6 weeks **Interventions:** b, etodolac 600 mg/600 mg daily (300 mg ×2 daily); a, naproxen 1000 mg/500–1250 mg daily (500 mg ×2 daily) **Other medication:** oral or parenteral anticoagulants, oral hypoglycaemics or drugs known to cause hepatic enzyme changes or drug-induced hepatitis, concurrent use of other NSAIDs or corticosteroid agents not allowed, type or intensity of physiotherapy remained unchanged **Aspirin allowed:** not stated **Analgesic allowed:** yes, acetaminophen during washout and up to day 14 **Participant education:** not stated **Washout:** yes, 1 week for aspirin and most other NSAIDs, 2 weeks for piroxicam and SR indomethacin **Number and frequency of visits:** 4 (0, 2, 4 and 6 weeks)	**Allocated:** a 19, b 18 **Completed:** a 18, b 17 **Drop-out:** a 1, b 1 **Assessed:** unclear **Outcomes reported:** total drop-outs **How were adverse events assessed:** no details **How was compliance assessed:** not stated	**Risk factors:** concomitant use of anticoagulants: a 0, b 0 CVD: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** Freeman Hospital, Newcastle, UK **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/1 **Other:** this is an interim report

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Platt, 1989C[99] **Location:** 10 countries, including the UK	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy, but those with peptic ulcer disease or history of GI bleed in the last 5 years were excluded **Type and duration of arthritis (years):** OA knee, no other details **Age:** a 59, b 59 **Sex:** M/F: a 20/57, b 17/63 **Inclusion criteria:** OA of the knee with at least 2 of the following radiological criteria: asymmetrical joint space narrowing with subchondral sclerosis, marginal osteophyte formation or subchondral pseudocysts with sclerotic walls; pain in the affected knee and at least one of the following conditions: limitation of motion, tenderness on pressure, swelling, crepitus on motion, morning stiffness or stiffness after inactivity; 18–75 years, responded in the past to NSAIDs, free of peptic ulcer disease, had had no GI bleeding in the last 5 years, no significant renal, haematological or cardiovascular disease, no severe complications or diabetes, no other disease that could affect the joints, no severe infection or tuberculosis, no significant rheumatoid factor, not taking NSAIDs and had active knee joint symptoms (as previously described) or if their disease worsened after a washout period free of any NSAIDs **Exclusion criteria:** previously treated with NSAIDs without effect or who had experienced adverse reactions to NSAIDs, patients taking oral or parenteral anticoagulants, oral hypoglycaemics or drugs known to cause hepatic enzyme changes or drug induced hepatitis, pregnant or breast-feeding women	**Comparison:** etodolac (b) vs piroxicam (a) **Duration:** 12 weeks **Interventions:** b, etodolac 600 mg/600 mg daily (300 mg ×2 daily); a, piroxicam 20 mg/10–30 mg daily (20 mg once daily) **Other medication:** oral or parenteral anticoagulants, oral hypoglycaemics or drugs known to cause hepatic enzyme changes or drug-induced hepatitis, concurrent use of other NSAIDs or corticosteroid agents not allowed, type or intensity of physiotherapy remained unchanged **Aspirin allowed:** not stated **Analgesic allowed:** yes, acetaminophen during washout and up to day 14 **Participant education:** not stated **Washout:** yes, 1 week for aspirin and most other NSAIDs, 2 weeks for piroxicam and SR indomethacin **Number and frequency of visits:** 7 (0, 2, 4, 6, 8, 10 and 12 weeks)	**Allocated:** a 77, b 80 **Completed:** a 70, b 71 **Drop-out:** a 7, b 9 **Assessed:** unclear **Outcomes reported:** total drop-outs **How were adverse events assessed:** no details **How was compliance assessed:** not stated	**Risk factors:** concomitant use of anticoagulants: a 0, b 0 CVD: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** Freeman Hospital, Newcastle, UK **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/1 **Other:** this is an interim report

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Freitas, 1990[100] **Location:** Brazil	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy, no further details **Type and duration of arthritis (years):** OA knee, no other details **Age:** a 50 (23–71), b 53 (37–71) **Sex:** M/F: a 6/26, b 1/32 **Inclusion criteria:** radiologically proven OA of the knee with at least 2 of the following radiological criteria: asymmetric joint space narrowing with subchondral sclerosis, marginal osteophyte formation, or subchondral pseudocysts with sclerotic walls; pain in the affected knee and at least one of the following conditions: limitation of motion, tenderness on pressure, swelling, crepitus or stiffness after inactivity or sleep; 18–75 years, history of a positive response to NSAID therapy with no hypersensitivity reactions, flare of disease symptoms after washout of NSAIDs (presence of 3 of the following: moderate to very severe pain when performing a weight-bearing activity, moderate to very severe pain at night, at least 10 minutes of stiffness after inactivity or sleep, pain intensity recorded as moderate to very severe and the patients global evaluation reported as fair to very poor) **Exclusion criteria:** pregnant or breast-feeding women, serious disease, patients taking medication with a potential for interaction with NSAIDs	**Comparison:** etodolac (b) vs piroxicam (a) **Duration:** 8 weeks **Interventions:** b etodolac 600 mg/600 mg daily (300 mg ×2 daily); a, piroxicam 20 mg/10–30 mg daily (20 mg once daily) **Other medication:** no details **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol during washout **Participant education:** not stated **Washout:** yes, patients to return for baseline visit when symptoms of OA had flared **Number and frequency of visits:** 5 (0, 2, 4, 6 and 8 weeks)	**Allocated:** a 32, b 33 **Completed:** a 27, b 30 **Drop-out:** a 5, b 3 **Assessed:** a 30, b 33 **Outcomes reported:** mortality, serious cardiovascular or renal illness, total drop-outs, GI drop-outs **How were adverse events assessed:** no details **How was compliance assessed:** not stated	**Risk factors:** no details **FUNDING** **Funded by:** Wyeth-Ayerst Laboratories **Affiliation of contact author:** Clinical practice, Recife-Pernambuco, Brazil **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/1

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Taha, 1990[101,225,226] **Location:** Glasgow Royal Infirmary, UK	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** no **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** baseline endoscopy performed and definite or presumptive peptic ulceration excluded **Baseline NSAID status:** 12 of 15 in each group had previous NSAID use **Type and duration of arthritis (years):** RA: a 6 (4–8), b 11 (5–17) **Age:** a 57 (45–65), b 50 (41–63) **Sex:** M/F: a 5/10, b 4/11 **Inclusion criteria:** ARA criteria for RA, functional class I, II or III, showed evidence of disease activity as suggested by all of the following: 5 or more tender or painful joints on motion, 3 or more swollen joints, morning stiffness of 30 minutes or more; patients receiving gold salts, antimalarials or penicillamine were admitted provided that they were started at least 6 months prior to the start of the study, the dosage regimen had been constant for 2 months and would not be changed during the study, the dose of hydroxychloroquine did not exceed 400 mg daily **Exclusion criteria:** arthritis which started before the age of 16 years, any other disease of the kidneys, liver or cardiovascular systems; allergic reactions or disease, definite or presumptive peptic ulceration, patients taking sulfasalazine, systemic or intrarticluar steroids, cytotoxics, and peptic ulcer healing agents	**Comparison:** etodolac (b) vs naproxen (a) **Duration:** 4 weeks **Interventions:** b, etodolac 600 mg/600 mg daily (300 mg ×2 daily); a, naproxen 1000 mg/500–1250 mg daily (500 mg ×2 daily) **Other medication:** sulfasalazine, systemic or intrarticluar steroids, cytotoxics, and peptic ulcer healing agents were not allowed, gold salts, antimalarials and penicillamine could be continued unchanged **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol provided **Participant education:** not stated **Washout:** yes, 4–7 days **Number and frequency of visits:** 2 (0 and 4 weeks)	**Allocated:** 32 in total **Completed:** a 15, b 15 **Drop-out:** 2 in total **Assessed:** a 15, b 15 **Outcomes reported:** mortality, GI symptoms, endoscopic ulcers **How were adverse events assessed:** no details **How was compliance assessed:** tablet count, naproxen group took median of 90% tablets, etodolac group took median of 87% tablets	**Risk factors:** concomitant use of corticosteroids: a 0, b 0 CVD: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** Wyeth-Ayerst Laboratories **Affiliation of contact author:** Royal Infirmary, Glasgow, UK **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/4

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Astorga Paulsen, 1991[102] **Location:** South America and Portugal	**Method of randomisation:** 'assigned at random' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy, no further details **Type and duration of arthritis (years):** OA knee, no further details **Age:** a 58 (23–75), b 58 (20–79) **Sex:** M/F: a 25/83, b 25/87 **Inclusion criteria:** radiologically proven OA of the knee with at least 2 of the following radiological criteria demonstrated within the previous 6 months: asymmetric joint space narrowing with subchondral sclerosis, marginal osteophyte formation or subchondral pseudocysts with sclerotic walls; pain in the affected knee on motion or at rest with at least one of the following conditions: limitation of motion, tenderness on pressure, swelling, crepitus or stiffness after prolonged inactivity or sleep; patients who were not hypersensitive to NSAIDs, including aspirin, and who had experienced a therapeutic response to NSAIDs in the past **Exclusion criteria:** history of serious medical or psychological disorders or any concomitant disease that affected the joints or connective tissue, women who were pregnant or breast-feeding, those who had recently undergone surgery or who had a clinically significant positive finding for rheumatoid factor, patients who used anticoagulant, oral hypoglycaemic, hepatotoxic or corticosteroid drugs, those who had taken investigational NSAIDs within 1 month of the study, those who had previously taken etodolac	**Comparison:** etodolac (b) vs piroxicam (a) **Duration:** 8 weeks **Interventions:** b, etodolac 600 mg/600 mg daily (300 mg ×2 daily); a, piroxicam 20 mg/10–30 mg daily (20 mg once daily) **Other medication:** anticoagulant, oral hypoglycaemic, hepatotoxic or corticosteroid drugs not allowed **Aspirin allowed:** not stated **Analgesic allowed:** yes, acetaminophen for washout and first 7 days **Participant education:** not stated **Washout:** yes, 1–2 weeks for aspirin or NSAIDs **Number and frequency of visits:** 5 (0, 2, 4, 6 and 8 weeks)	**Allocated:** a 108, b 112 **Completed:** a 95, b 100 **Drop-out:** a 13, b 12 **Assessed:** a 106, b 112 **Outcomes reported:** mortality, serious GI complications, serious cardiovascular or renal illness, GI symptoms, GI drop-outs, total drop-outs **How were adverse events assessed:** no details **How was compliance assessed:** not stated	**Risk factors:** concomitant use of anticoagulants: a 0, b 0 corticosteroids: a 0, b 0 **FUNDING** **Funded by:** Wyeth-Ayerst Laboratories **Affiliation of contact author:** Universidad de Chile **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/5 by Wyeth-Ayerst

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Braseur, 1991[103] **Location:** Belgium	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy, no further details **Type and duration of arthritis (years):** OA knee, no further details **Age:** a 60.2 (39–72), b 63.3 (44–81) **Sex:** M/F: a 9/20, b 6/26 **Inclusion criteria:** pain in the affected knee on motion or at rest with at least one of the following conditions: limitation of motion, tenderness on pressure, swelling, crepitus or stiffness (either in the morning or after prolonged inactivity), radiologically proven OA of the knee with at least 2 of the following conditions: asymmetric joint space narrowing with subchondral sclerosis, marginal osteophyte formation or subchondral pseudocysts with sclerotic walls **Exclusion criteria:** patients who were hypersensitive to NSAIDs including aspirin or whose symptoms had not been relieved by NSAIDs in the past, history of serious medical or psychological disorders or any concomitant disease affecting the joints or connective tissue, women who were pregnant or nursing, those who had recently undergone surgery, patients with a clinically significant positive finding for rheumatoid factor, patients who used anticoagulant, oral hypoglycaemic, hepatotoxic or corticosteroid drugs, those who had taken investigational NSAIDs within 1 month of the study, those who had previously taken etodolac	**Comparison:** etodolac (b) vs diclofenac SR (a) **Duration:** 6 weeks **Interventions:** b etodolac 600 mg/600 mg daily (300 mg ×2 daily); a, diclofenac SR 100 mg/75–150 mg daily (100 mg once daily) **Other medication:** anticoagulant, oral hypoglycaemic, hepatotoxic or corticosteroid drugs excluded **Aspirin allowed:** no, from 1–2 weeks prior to study **Analgesic allowed:** yes, acetaminophen could be continued during washout and first 7 days **Participant education:** not stated **Washout:** yes, 1–2 weeks for aspirin or NSAIDs **Number and frequency of visits:** 4 (0, 2, 4 and 6 weeks)	**Allocated:** a 29, b 32 **Completed:** a 23, b 26 **Drop-out:** a 6, b 6 **Assessed:** a 29, b 32 **Outcomes reported:** GI drop-outs, total drop-outs **How were adverse events assessed:** patients complaints recorded **How was compliance assessed:** not stated	**Risk factors:** concomitant use of anticoagulants; a 0, b 0 corticosteroids: a 0, b 0 **FUNDING** **Funded by:** Wyeth-Ayerst Laboratories **Affiliation of contact author:** University of Louvain, Belgium **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/3

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Karbowski, 1991[104] **Location:** Germany	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy, no further details **Type and duration of arthritis (years):** OA knee, no further details **Age:** a 53.8 (33–74), b 53.5 (22–76) **Sex:** M/F: a 13/20, b 12/19 **Inclusion criteria:** OA of the knee with at least 2 of the following conditions shown by radiological study: asymmetric joint space narrowing with subchondral sclerosis, marginal osteophyte formation or subchondral pseudocysts with sclerotic walls; clinical signs of OA defined by pain in the affected knee on motion or at rest and at least one of the following conditions: limitation of motion, tenderness on pressure, swelling, crepitus or stiffness (either in the morning or after prolonged inactivity), patients who were not hypersensitive to NSAIDs including aspirin or who had responded therapeutically to NSAIDs in the past, a flare of disease activity and a worsening of the patient's evaluation of his or her overall condition were required for patients withdrawn from NSAIDs (defined as worsening of at least 2 of the following variables: weight-bearing pain activity, night pain, stiffness upon arising or after prolonged activity and pain intensity) **Exclusion criteria:** history of serious medical or psychological disorders or any concomitant disease affecting the joints or connective tissue, women who were pregnant or lactating, those who had recently undergone surgery, patients with a clinically significant positive finding for rheumatoid factor, patients who used anticoagulant, oral hypoglycaemic, hepatotoxic or corticosteroid drugs, those who had taken investigational NSAIDs within 1 month of the study, those who had previously taken etodolac	**Comparison:** etodolac (b) vs indomethacin (a) **Duration:** 6 weeks **Interventions:** b etodolac 600 mg/600 mg daily (300 mg ×2 daily); a, indomethacin 150 mg/50–200 mg daily (50 mg ×3 daily) **Other medication:** anticoagulant, oral hypoglycaemic, hepatotoxic or corticosteroid drugs excluded **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol for washout and first 7 days **Participant education:** not stated **Washout:** yes, 1–2 weeks for aspirin or NSAIDs **Number and frequency of visits:** 4 (0, 2, 4 and 6 weeks)	**Allocated:** a 33, b 31 **Completed:** a 27, b 28 **Drop-out:** a 6, b 3 **Assessed:** a 33, b 31 **Outcomes reported:** serious GI complications, symptomatic ulcers, GI drop-outs, total drop-outs, occult bleeding **How were adverse events assessed:** no details **How was compliance assessed:** not stated	**Risk factors**: concomitant use of anticoagulants: a 0, b 0 corticosteroids: a 0, b 0 **FUNDING** **Funded by:** Wyeth-Ayerst Laboratories **Affiliation of contact author:** Klinik und Poliklinik fur Allegemeine Abteilung Orthopadie der WWU, Munster, Germany **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/1

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Palferman, 1991[105] **Location:** 3 sites in UK	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy but excluded if GI bleeding or peptic ulcer disease **Type and duration of arthritis (years):** OA, no further details **Age:** a 64.5 (47–76), b 61.6 (27–74) **Sex:** M/F: a 9/18, b 12/17 **Inclusion criteria:** 18–76 years, OA of the knee with active degenerative joint disease confirmed by the following roentgenological and clinical criteria: radiographs of the affected taken within the previous 6 months had to show at least 2 of the following conditions: asymmetric joint space narrowing with subchondral sclerosis, marginal osteophyte formation or subchondral pseudocysts with sclerotic walls; clinical criteria for OA included pain in the affected knee on motion or at rest and at least one of the following conditions: limitation of motion, tenderness on pressure, swelling, crepitus, or stiffness (either in the morning or after prolonged inactivity), only patients who had a history of positive therapeutic response with no hypersensitivity to NSAIDs were included, criteria for active OA required at least 3 of the following conditions to be met: score of at least 3 in weight-bearing pain activity, in night pain, in pain intensity, in patient's overall evaluation of his or her condition of disease activity or in stiffness of at least 10 minutes' duration on arising or after prolonged inactivity; a flare of disease and a worsening of at least 2 of the above criteria were required for patients withdrawn from NSAIDs **Exclusion criteria:** history of serious renal, hepatic or cardiovascular disease; chronic skin disease; GI bleeding or peptic ulcer disease;	**Comparison:** etodolac (b) vs naproxen (a) **Duration:** 6 weeks **Interventions:** b, etodolac 600 mg/600 mg daily (300 mg ×2 daily); a, naproxen 1000 mg/500–1250 mg daily (500 mg ×2 daily); "double dummy" **Other medication:** hypoglycaemic agents, anticoagulant therapy, any medication that caused liver enzyme abnormalities, corticosteroids excluded **Aspirin allowed:** not stated **Analgesic allowed:** yes, acetaminophen for washout and first 7 days **Participant education:** not stated **Washout:** yes, 1–2 weeks for aspirin or NSAIDs **Number and frequency of visits:** 4 (0, 2, 4 and 6 weeks)	**Allocated:** a 27, b 29 **Completed:** a 22, b 24 **Drop-out:** a 5, b 5 **Assessed:** a 27, b 29 **Outcomes reported:** GI symptoms, GI drop-outs, total drop-outs **How were adverse events assessed:** patient complaints recorded **How was compliance assessed:** not stated	**Risk factors:** concomitant use of anticoagulants: a 0, b 0; corticosteroids: a 0, b 0; CVD: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** Yeovil District General Hospital, UK **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/3

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
		substance abuse; malignancy except resected basal cell carcinoma; major surgery in the last 6 months; or serious psychological disorders; clinically significant levels of rheumatoid factor, concomitant disease affecting the joints or connective tissue, current or severe infections or any condition that interfered with taking the study medication; women who were pregnant or lactating, patients who were receiving hypoglycaemic agents, anticoagulant therapy, any medication that caused liver enzyme abnormalities, corticosteroids within the previous 6 months, investigational NSAIDs within the previous month or etodolac at any time previously			
Pena, 1991[106] **Location:** Columbia	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy, no further details **Baseline NSAID status:** 5 in naproxen group and 3 in etodolac group did not have 'flare' during washout **Type and duration of arthritis (years):** OA knee, no further details **Age:** a 62.3 (48–75), b 62.7 (42–74) **Sex:** M/F: a 3/28, b 5/26 **Inclusion criteria:** 18–75 years, radiological evidence of OA of the knee with pain in the affected knee and at least one of the following: limitation of motion, tenderness on pressure, swelling, crepitus, or stiffness (either in the morning or after prolonged inactivity), history of a positive therapeutic response to NSAIDs **Exclusion criteria:** women of childbearing potential, patients who had received oral corticosteroids in the previous 6 months or injection of corticosteroids within the last 4 weeks	**Comparison:** etodolac (b) vs naproxen (a) **Duration:** 8 weeks **Interventions:** b, etodolac 600 mg/600 mg daily (300 mg ×2 daily); a, naproxen 1000 mg/500–1250 mg daily (500 mg ×2 daily) **Other medication:** corticosteroids not allowed **Aspirin allowed:** not stated **Analgesic allowed:** yes, acetaminophen during washout only **Participant education:** not stated **Washout:** yes, 2 weeks **Number and frequency of visits:** 5x (0, 2, 4, 6 and 8 weeks)	**Allocated:** a 31, b 31 **Completed:** a 31, b 30 **Drop-out:** a 0, b 1 **Assessed:** a 30, b 30 **Outcomes reported:** GI symptoms, total drop-outs **How were adverse events assessed:** patient complaints recorded **How was compliance assessed:** not stated	**Risk factors:** concomitant use of corticosteroids: a 0, b 0 **FUNDING** **Funded by:** Wyeth-Ayerst Laboratories **Affiliation of contact author:** Hospital San Juan de Dios, Colombia **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/2

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Perpignano, 1991[107] **Location:** Italy	**Method of randomisation:** 'randomly allocated' (predetermined randomisation list) **Allocation concealment:** unclear **Baseline comparability:** no **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** baseline endoscopy performed and patients with less than erosions were included **Type and duration of arthritis (years):** OA hip or knee, no further details **Age:** a 55.7, b 51.9 **Sex:** M/F: a 3/7, b 6/4 **Inclusion criteria:** 39–65 years, OA of the hip or knee which required treatment with NSAIDs, acute OA defined as spontaneous pain aggravated by movement, pain on pressure, functional limitations, swollen joint, rigid greater than 30° **Exclusion criteria:** endoscopic score of greater than 2, history of peptic ulcer or grave liver, renal or cardiovascular disorders; bronchial asthmas, pregnant women, hypertension treated with nifedipine	**Comparison:** etodolac (b) vs naproxen (a) **Duration:** 4 weeks **Interventions:** b, etodolac 600 mg/600 mg daily; a, naproxen 750 mg/500–1250 mg daily **Other medication:** no details **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** yes, 7 days **Number and frequency of visits:** 2 (0 and 4 weeks)	**Allocated:** a 10, b 10 **Completed:** a 8, b 10 **Drop-out:** a 2, b 0 **Assessed:** a 10, b 10 **Outcomes reported:** GI drop-outs, total drop-outs, endoscopic ulcers **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** CVD: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** University of de Cagliari, Italy **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/3 **Other:** paper translated
Dick, 1992[108] **Location:** four sites including The Netherlands and the UK	**Method of randomisation:** 'randomised' (predetermined randomisation schedule) **Allocation concealment:** unclear **Baseline comparability:** no, 'more severe arthritic symptoms' in etodolac group **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** no baseline endoscopy but excluded serious symptomatic disease **Baseline NSAID status:** excluded patients with no NSAID experience **Type and duration of arthritis (years):** degenerative joint disease of the knee, no further details **Age:** a 57.3 (32–77), b 59.5 (38–80) **Sex:** M/F: a 21/38, b 16/41 **Inclusion criteria:** 18–75 years, active OA of the knee confirmed by X-ray findings and clinical criteria and had prior positive therapeutic response to one or more NSAIDs including aspirin **Exclusion criteria:** no NSAID experience, hypersensitivity to NSAIDs, previous no response or adverse reaction with piroxicam, unacceptable concomitant medication, serious symptomatic disease, or neurological or psychological disorders; women of childbearing potential	**Comparison:** etodolac (b) vs piroxicam (a) **Duration:** 6 weeks **Interventions:** b, etodolac 600 mg/600 mg daily (300 mg ×2 daily); a, piroxicam 20 mg/10–30 mg daily (20 mg once daily) **Other medication:** physical therapy and walking aids could be continued **Aspirin allowed:** not stated **Analgesic allowed:** yes, acetaminophen 650 mg ×4 daily for washout and first 7 days **Participant education:** not stated **Washout:** yes, 2 weeks **Number and frequency of visits:** 4 (0, 2, 4 and 6 weeks)	**Allocated:** a 59, b 57 **Completed:** a 52, b 42 **Drop-out:** a 7, b 15 **Assessed:** a 59, b 57 **Outcomes reported:** GI symptoms, GI drop-outs, total drop-outs **How were adverse events assessed:** patient complaints recorded **How was compliance assessed:** not stated	**Risk factors:** no details **FUNDING** **Funded by:** Wyeth-Ayerst Laboratories **Affiliation of contact author:** Royal Victoria Infirmary, Newcastle, UK **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/4

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Grisanti, 1992[109] **Location:** Portugal, Brazil and Chile	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy but excluded patients with a history of peptic ulcer disease or GI bleed in the last 5 years **Baseline NSAID status:** excluded patients who had never received an NSAID **Type and duration of arthritis (years):** OA knee, no further details **Age:** a 59 (35–75), b 59 (17–73) **Sex:** M/F: a 12/75, b 12/73 **Inclusion criteria:** roentgenogram within previous 6 months that confirmed degenerative joint disease of the knee, X-ray film had to show at least two of the following three signs: asymmetric joint space narrowing with subchondral sclerosis, marginal osteophyte formation or subchondral pseudocysts with sclerotic walls; knee pain either during motion or at rest and at least one of the following symptoms: limited motion, tenderness during pressure, swelling, crepitus, morning stiffness or stiffness after prolonged activity; patients who had withdrawn from NSAIDs had to show a flare at baseline defined as a worsening of at least two of the following variables: weight-bearing activity, night pain, stiffness after sleeping or after prolonged activity or pain intensity **Exclusion criteria:** never received an NSAID to treat OA, previously taken diclofenac and had not responded well to treatment, previously taken etodolac, taken investigational drugs within the last month, peptic ulcer disease or GI bleeding in the last 5 years; women who were pregnant or breast-feeding or intended to breast-feed; patients receiving oral hypoglycaemic, hepatotoxic or oral or parenteral anticoagulant drugs	**Comparison:** etodolac (b) vs diclofenac (a) **Duration:** 8 weeks **Interventions:** b, etodolac 600 mg/600 mg daily (200 mg ×3 daily); a, diclofeanc 150 mg/75–150 mg daily (50 mg x3 daily) **Other medication:** oral hypoglycaemic, hepatotoxic or oral or parenteral anticoagulant drugs excluded **Aspirin allowed:** not stated **Analgesic allowed:** yes, acetaminophen for washout and first 7 days **Participant education:** not stated **Washout:** yes, 1 week for aspirin and 2 weeks for piroxicam **Number and frequency of visits:** 5 (0, 2, 4, 6 and 8 weeks)	**Allocated:** a 87, b 85 **Completed:** a 79, b 78 **Drop-out**: a 8, b 7 **Assessed:** a 84, b 84 **Outcomes reported:** GI drop-outs, total drop-outs **How were adverse events assessed:** patient complaints recorded **How was compliance assessed:** not stated	**Risk factors:** concomitant use of anticoagulants: a 0, b 0 **FUNDING** **Funded by:** Wyeth-Ayerst Laboratories **Affiliation of contact author:** University of Chile **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/3

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Jubb, 1992[110] **Location:** UK	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy but excluded history of gastric ulcer or haemorrhage **Baseline NSAID status:** excluded patients who had never received an NSAID **Type and duration of arthritis (years):** RA, no further details **Age**: a 54 (24–73), b 58 (29–76) **Sex:** M/F: a 8/17, b 5/19 **Inclusion criteria:** active RA with at least five of the ARA diagnostic criteria and within Steinbrocker progression (anatomic) stages I, II or III and in functional classes I, II or III; active RA confirmed by the presence of at least three of the following four criteria: six or more tender or painful joints on motion, three or more swollen joints, morning stiffness duration of 45 minutes or more, Westergen erythrocyte sedimentation rate of 28 mm/h or more; several joint signs and symptoms, such as morning stiffness, pain on motion or tenderness, swelling in at least one joint and symmetrical joint swelling involvement, had to be present continuously for at least 6 weeks; history of a positive therapeutic response to one or more NSAIDs, including aspirin, patients discontinuing NSAIDs were required to have a worsening in at least two of the criteria for active disease at the end of the washout **Exclusion criteria:** Steinbrocker progression stage IV or functional class IV, or met any of the ARA exclusion criteria, hypersensitivity to NSAIDs including aspirin or who had never received an NSAID for the treatment of RA, active peptic ulcer, history of GI ulcer or haemorrhage, serious symptomatic disease or neurological or psychological disorders; pregnant or nursing women	**Comparison:** etodolac SR (b) vs piroxicam (a) **Duration:** 4 weeks **Interventions:** b, etodolac SR 600 mg/600 mg daily; a, piroxicam 20 mg/10–30 mg daily (20 mg once daily) **Other medication:** no details **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol up to 500 mg ×4 daily during washout and first 7 days **Participant education:** not stated **Washout:** yes, up to 2 weeks **Number and frequency of visits:** 3 (0, 2 and 4 weeks)	**Allocated:** a 25, b 24 **Completed:** a 20, b 21 **Drop-out:** a 5, b 3 **Assessed:** a 25, b 24 **Outcomes reported:** GI symptoms, GI drop-outs, total drop-outs **How were adverse events assessed:** patient complaints recorded **How was compliance assessed:** not stated	**Risk factors:** history of ulcers: a 0, b 0 history of bleeds: a 0, b 0 **FUNDING** **Funded by:** Wyeth-Ayerst Laboratories **Affiliation of contact author:** Greenwich District Hospital, UK **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/3 **Other:** this is an interim report

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Khan, 1992[111] **Location:** Wales, UK	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy but excluded patients with active peptic ulcer or haemorrhage **Type and duration of arthritis (years):** degenerative joint disease of the knee, no further details **Age:** a 64 (52–76), b 60 (46–76) **Sex:** M/F: a 10/22, b 13/19 **Inclusion criteria:** 46–76 years diagnosed as suffering from degenerative joint disease of the knee, X-ray radiographs of the knee were required to show at least two of the following conditions: asymmetric joint space narrowing with subchondral sclerosis, marginal osteophyte formation or subchondral pseudocysts with sclerotic walls; clinical criteria were pain of the affected knee on motion or at rest, plus at least one of the following conditions: limitation of motion, tenderness on pressure, swelling, crepitus, stiffness either in the morning or after prolonged inactivity; at baseline active disease was defined as any three of the following five criteria: a score of moderate or greater for weight-bearing pain, night pain and pain intensity, stiffness of at least 10 minutes duration on arising or after prolonged inactivity and a rating of fair or worse for the overall assessment of his/her condition; history of positive therapeutic response to one or more NSAID, including aspirin; routine laboratory tests were required to be within the normal range except for mild elevation of erythrocyte sedimentation rate; patients discontinuing NSAIDs were required to have a flare at the end of the washout defined as a worsening in the patient's overall assessment of his/her condition and a worsening in two of the following four	**Comparison:** etodolac SR (b) vs diclofenac SR (a) **Duration:** 4 weeks **Interventions:** b, etodolac 600 mg/600 mg daily; a, diclofenac 100 mg/75–150 mg daily **Other medication:** no details **Aspirin allowed:** not stated **Analgesic allowed:** no details **Participant education:** not stated **Washout:** yes, up to 14 days for NSAIDs **Number and frequency of visits:** 3 (0, 2 and 4 weeks)	**Allocated:** a ?32, b ?32 **Completed:** a: ?28, b ?27 **Drop-out:** a ?4, b ?5 **Assessed:** a 32, b 32 **Outcomes reported:** mortality, serious cardiovascular or renal illness, GI drop-outs **How were adverse events assessed:** patient complaints and study event (any adverse experience, treatment emergent sign or symptom, new intercurrent illness or clinically significant laboratory abnormality) recorded **How was compliance assessed:** not stated	**Risk factors:** history of ulcer: a 0, b 0; history of bleed: a 0, b 0; CVD: a 0, b 0; renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** Bridgend General Hospital, UK **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/2 **Other:** this is an interim report

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
		criteria: weight-bearing pain, night pain, pain intensity and stiffness duration **Exclusion criteria:** hypersensitivity to NSAIDs, active peptic ulcer, history of GI ulcer or haemorrhage, significant renal, hepatic, haemotological or cardiovascular disease, concomitant disease affecting the joints or the connective tissue, history of skin disorders precipitated or aggravated by drugs, clinically significant levels of rheumatoid factor, pregnant or lactating women			
Waterworth, 1992[112] **Location:** New Zealand	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** no **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** no baseline endoscopy but excluded patients with definite peptic ulcer disease in the last 5 years **Baseline NSAID status:** excluded patients if never taken an NSAID **Type and duration of arthritis (years):** OA of the knee, no further details **Age:** a 59.3 (47–70), b 59.8 (33–72) **Sex:** M/F: a 9/20, b 16/12 **Inclusion criteria:** 18–75 years with radiologically and clinically confirmed OA of the knee and with a history of a positive therapeutic response to one or more NSAIDs, X-ray findings included two of the following within the previous 6 months: asymmetric joint space narrowing with subchondral sclerosis, marginal osteophyte formation, or subchondral pseudocysts with sclerotic walls; at least one of the following clinical conditions was required: limitation of motion, tenderness on pressure, swelling, crepitus, stiffness after sleep or prolonged inactivity; patients who had withdrawn from NSAIDs had to exhibit a worsening of at least	**Comparison:** etodolac (b) vs piroxicam (a) **Duration:** 6 weeks **Interventions:** b, etodolac 600 mg/600 mg daily (300 mg ×2 daily); a piroxicam 20 mg/10–30 mg daily (20 mg once daily) **Other medication:** anticoagulant, oral hypoglycaemic, hepatotoxic or corticosteroid drugs were excluded **Aspirin allowed:** not stated **Analgesic allowed:** yes, acetaminophen for washout and the first week **Participant education:** not stated **Washout:** yes, 2 weeks for aspirin and NSAIDs **Number and frequency of visits:** 4 (0, 2, 4 and 6 weeks)	**Allocated:** a 29, b 28 **Completed:** a 20, b 23 **Drop-out:** a 9, b 5 **Assessed:** a 29, b 28 **Outcomes reported:** mortality, serious GI complications, serious cardiovascular or renal illness, GI symptoms, GI drop-outs, anaemia **How were adverse events assessed:** patient complaints recorded **How was compliance assessed:** not stated	**Risk factors:** history of ulcers: a 0, b 0 concomitant use of anticoagulants: a 0, b 0 corticosteroids: a 0, b 0 **FUNDING** **Funded by:** Wyeth-Ayerst Laboratories **Affiliation of contact author:** Hawkes Bay Area Health Board, New Zealand **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/2

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
		two of the following variables: weight-bearing pain activity, night pain, stiffness after sleeping or prolonged inactivity or pain intensity **Exclusion criteria:** patients who had never received an NSAID, had an unsatisfactory response to piroxicam, had received etodolac at any time, had a history of serious medical or psychological disorders, had definite peptic ulcer disease within the previous 5 years or had any concomitant disease that affected the joints or connective tissue; women who were pregnant or breast-feeding, patients who had undergone major surgery on the past 6 weeks and those who used anticoagulant, oral hypoglycaemic, hepatotoxic or corticosteroid drugs			
Burssens, 1993[113] **Location:** 5 sites in Belgium, Germany and Switzerland	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** no **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** no baseline endoscopy but excluded patients with history of active peptic ulcer and GI haemorrhage **Type and duration of arthritis (years):** OA, no further details **Age:** a 59 (44–73), b 64 (47–80) **Sex:** M/F: a 13/23, b 14/23 **Inclusion criteria:** clinical and radiographic evidence of OA of the knee, diagnosis of active OA required any three of the following five criteria: a score which was at least moderate for weight-bearing pain, night pain and pain intensity, stiffness of at least 10 minutes duration on arising or after prolonged inactivity and a patient rating of fair or worse for the overall assessment of his/her condition; history of positive therapeutic response to one or more NSAID, including aspirin; routine laboratory tests were required to be within the normal range except for mild elevation of erythrocyte	**Comparison:** etodolac SR (b) vs tenoxicam (a) **Duration:** 4 weeks **Interventions:** b, etodolac 600 mg/600 mg daily; a, tenoxicam 20 mg/20 mg daily **Other medication:** no details **Aspirin allowed:** not stated **Analgesic allowed:** no details **Participant education:** not stated **Washout:** yes, up to 14 days for NSAIDs **Number and frequency of visits:** 3 (0, 2 and 4 weeks)	**Allocated:** a 36, b 37 **Completed:** a 34, b 35 **Drop-out:** a 2, b 2 **Assessed:** a 36, b 37 **Outcomes reported:** GI symptoms, GI drop-outs, total drop-outs **How were adverse events assessed:** no details **How was compliance assessed:** not stated	**Risk factors:** history of ulcers: a 0, b 0 history of bleeds: a 0, b 0 CVD: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** University Hospital Peltenberg, Belgium **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/3 **Other:** this is an interim report

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
		sedimentation rate; patients discontinuing NSAIDs were required to have a flare or a worsening in their overall assessment, at the end of the washout defined as a worsening in the patients overall assessment of his/her condition and a worsening in two of the following four criteria: weight-bearing pain, night pain, pain intensity and stiffness duration **Exclusion criteria:** hypersensitivity to NSAIDs, active peptic ulcer, history of peptic ulcer, GI haemorrhage, significant renal, hepatic, haemotological or cardiovascular disease, clinically significant levels of rheumatoid factor, pregnant or lactating women			
Dreiser, 1993A[114] **Location:** France	**Method of randomisation:** 'random allocation' **Allocation concealment:** unclear **Baseline comparability:** no **Participant blinding:** unclear **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** no baseline endoscopy but excluded patients with active ulcer **Type and duration of arthritis (years):** OA, hip/knee, no further details **Age:** a 61.2, b 67.2 **Sex:** M/F: a 12/18, b 12/17 **Inclusion criteria:** 30–80 years, OA of the hip or knee confirmed by radiology **Exclusion criteria:** presence of non-degenerative joint diseases (e.g. infectious, microcrystalline), severe and disabling arthritis and/or eligibility for surgical intervention; treatment with intra-articular injections of corticosteroids within the month preceding the study; treatment with anticoagulants, hydantoin or antidiabetic drugs; history of severe hepatic, renal or haemopoietic disease; history of hypersensitivity to NSAIDs; presence of an active peptic ulcer; pregnancy or lactation	**Comparison:** nimesulide (b) vs piroxicam(a) **Duration:** 3 weeks **Interventions:** b, nimesulide 200 mg/? mg daily (100 mg ×2 daily); a, piroxicam 20 mg/10–30 mg daily (20 mg once daily) **Other medication:** intra-articular injections of corticosteroids, anticoagulants, hydantoin or antidiabetic drugs excluded, no other medication likely to interfere with the investigational drugs was permitted **Aspirin allowed:** not stated **Analgesic allowed:** paracetamol prescribed to all patients **Participant education:** not stated **Washout:** no details **Number and frequency of visits:** 3 (0, unclear and at 3 weeks)	**Allocated:** a 30, b 29 **Completed:** a 26, b 26 **Drop-out:** a 4, b 3 **Assessed:** a 30, b 29 **Outcomes reported:** total drop-outs **How were adverse events assessed:** nature and severity of all adverse events recorded whether spontaneously reported by patient or elicited by indirect non-specific questioning by investigator or 12 preselected questions and rated on a 4-point verbal rating scale by investigator and patient **How was compliance assessed:** not stated	**Risk factors:** concomitant use of anticoagulants: a 0, b 0 corticosteroids: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** 25 Rue Clapeyron, Paris, France **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 1/2 by Helsinn Healthcare

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Dreiser, 1993B[114] Location: France	**Method of randomisation:** 'random allocation' **Allocation concealment:** unclear **Baseline comparability:** no **Participant blinding:** unclear **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** no baseline endoscopy but excluded patients with active ulcer **Type and duration of arthritis (years):** OA, hip/knee, no further details **Age:** a 60.3, b 60.2 **Sex:** M/F: a 9/18, b 15/13 **Inclusion criteria:** 30–80 years, OA of the hip or knee confirmed by radiology **Exclusion criteria:** presence of nondegenerative joint diseases (e.g. infectious, microcrystalline), severe and disabling arthritis and/or eligibility for surgical intervention; treatment with intra-articular injections of corticosteroids within the month preceding the study; treatment with anticoagulants, hydantoin or antidiabetic drugs; history of severe hepatic, renal or haemopoietic disease; history of hypersensitivity to NSAIDs; presence of an active peptic ulcer; pregnancy or lactation	**Comparison:** nimesulide (b) vs ketoprofen (a) **Duration:** 8 weeks **Interventions:** b, nimesulide 200 mg/? mg daily (100 mg ×2 daily); a, ketoprofen 200 mg/100–200 mg daily (100 mg ×2 daily) **Other medication:** intra-articular injections of corticosteroids, anticoagulants, hydantoin or antidiabetic drugs excluded, no other medication likely to interfere with the investigational drugs was permitted **Aspirin allowed:** not stated **Analgesic allowed:** paracetamol prescribed to all patients **Participant education:** not stated **Washout:** no details **Number and frequency of visits:** 4 (0, unclear, unclear and at 8 weeks)	**Allocated:** a ?27, b ?28 **Completed:** a: 25 b 24 **Drop-out:** a 2, b 4 **Assessed:** a 27, b 28 **Outcomes reported:** GI symptoms, GI drop-outs, total drop-outs **How were adverse events assessed:** nature and severity of all adverse events recorded whether spontaneously reported by patient or elicited by indirect non-specific questioning by investigator or 12 preselected questions and rated on a 4-point verbal rating scale by investigator and patient **How was compliance assessed:** not stated	**Risk factors:** concomitant use of anticoagulants: a 0, b 0 corticosteroids: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** 25 Rue Clapeyron, Paris, France **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 1/2 by Helsinn Healthcare

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Eisenkolb, 1993[115] **Location:** Germany, UK and Switzerland	**Method of randomisation:** 'randomised', predetermined randomisation schedule **Allocation concealment:** unclear **Baseline comparability:** no, etodolac group had more severe arthritic symptoms **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** no baseline endoscopy, no further details **Type and duration of arthritis (years):** OA, knee, no further details **Age:** a 60.5 (37–76), b 61.4 (37–78) **Sex:** M/F: a 24/45, b 23/43 **Inclusion criteria:** 18–75 years with active OA of the knee confirmed by X-ray studies and clinical criteria, prior positive therapeutic response to one or more NSAIDs including aspirin **Exclusion criteria:** no details	**Comparison:** etodolac (b) vs diclofenac (a) **Duration:** 6 weeks **Interventions:** b, etodolac 600 mg/600 mg daily (200 mg ×3 daily); a, diclofenac 150 mg/75–150 mg daily (50 mg ×3 daily) **Other medication:** physical therapy and walking aids could be continued **Aspirin allowed:** Not stated **Analgesic allowed:** yes, acetaminophen 500 mg ×4 daily during washout and first 7 days **Participant education:** not stated **Washout:** yes, 2 weeks **Number and frequency of visits:** 4 (0, 2, 4 and 6 weeks)	**Allocated:** a 69, b 66 **Completed:** a 52, b 51 **Drop-out:** a 17, b 15 **Assessed:** a 69, b 66 **Outcomes reported:** GI drop-outs, total drop-outs **How were adverse events assessed:** no details **How was compliance assessed:** not stated	**Risk factors:** no details **FUNDING** **Funded by:** Wyeth-Ayerst Laboratories **Affiliation of contact author:** Arzt fur Orhopadie, Rheumatologie, Chirotherapie, Munster, Germany **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/4
Estevez, 1993[116] **Location:** Uruguay	**Method of randomisation:** 'assigned at random' **Allocation concealment:** unclear **Baseline comparability:** no, regarding age **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** no baseline endoscopy, no further details **Type and duration of arthritis (years):** OA, no further details **Age:** a 64, b 70 **Sex:** M/F: a 1/9, b 1/9 **Inclusion criteria:** OA stages II–III according to clinical radiological evaluation **Exclusion criteria:** OA stages I and IV, other types of arthritis, severe renal or hepatic illnesses, blood problems, allergies to diclofenac or nimesulide	**Comparison:** nimesulide (b) vs diclofenac (a) **Duration:** 12 weeks **Interventions:** b, nimesulide 200 mg/? mg daily, a, diclofenac 100 mg/75–150 mg daily **Other medication:** no details **Aspirin allowed:** not stated **Analgesic allowed:** no details **Participant education:** not stated **Washout:** yes, 1 week **Number and frequency of visits:** 7 (0, 2, 4, 6, 8, 10 and 12 weeks)	**Allocated:** a 10, b 10 **Completed:** a 9, b 10 **Drop-out:** a 1, b 0 **Assessed:** a 10, b 10 **Outcomes reported:** GI symptoms **How were adverse events assessed:** no details **How was compliance assessed:** not stated	**Risk factors:** severe renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** Universidad de la Republica, Montevideo **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 4/5 by Laboratories Gautier **Other:** translated

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Porzio, 1993[117] **Location:** Germany and Italy	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** no **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** no baseline endoscopy but excluded patients with active peptic ulcer, history of GI ulcer or haemorrhage **Baseline NSAID status:** excluded patients that had never received NSAIDs **Type and duration of arthritis (years):** RA, no further details **Age:** a 55 (26–73), b 58 (18–74) **Sex:** M/F: a 7/34, b 8/42 **Inclusion criteria:** exhibited at least five of the ARA diagnostic criteria and were within Steinbrocker progression (anatomic) stages I, II or III and in functional class I, II or III; active RA confirmed by at least three of the following four criteria: six or more tender or painful joints on motion, three or more swollen joints, morning stiffness duration of 45 minutes or more, Westergen erythrocyte sedimentation rate of 28 mm/h or longer; several joint signs and symptoms such as morning stiffness, pain on motion or tenderness, swelling in at least one joint and symmetrical joint swelling involvement, had to be present continuously for at least 6 weeks; history of positive therapeutic response to one or more NSAID, including aspirin; patients discontinuing NSAIDs were required to have a worsening in at least two of the criteria for active RA **Exclusion criteria:** Steinbrocker progression stage IV or functional class IV or those who met any of the ARA exclusion criteria; hypersensitivity to NSAIDs including aspirin, had never received an NSAID for the treatment of RA, active peptic ulcer, history of GI ulcer or haemorrhagia, serious symptomatic diseases, or neurological or psychological disorders; women who were pregnant or lactating	**Comparison:** etodolac SR (b) vs diclofenac SR (a) **Duration:** 4 weeks **Interventions:** b, etodolac SR 600 mg/600 mg daily; a diclofenac SR 100 mg/75–100 mg daily **Other medication:** no details **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol up to 500 mg ×3 daily during washout and first 7 days **Participant education:** not stated **Washout:** yes up to 2 weeks **Number and frequency of visits:** 3 (0, 2 and 4 weeks)	**Allocated:** a 41, b 50 **Completed:** a 38, b 43 **Drop-out:** a 3, b 7 **Assessed:** a 41, b 50 **Outcomes reported:** GI drop-outs, total drop-outs **How were adverse events assessed:** no details **How was compliance assessed:** not stated	**Risk factors:** history of ulcer: a 0, b 0 history of bleeds: a 0, b 0 >65 years **FUNDING** **Funded by:** Wyeth-Ayerst Laboratories **Affiliation of contact author:** Ludwig-Maximilians Universität, Munich, Germany **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/2 **Other:** this is an interim report

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Roth, 1993[78] **Location:** 6 centres in the USA	**Method of randomisation:** 'randomised', participants assigned a treatment number that corresponded with treatment medication **Allocation concealment:** unclear **Baseline comparability:** No, misoprostol group contained younger participants and more with normal endoscopies **Participant blinding:** unclear **Assessor blinding:** yes **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** no more than 3 erosions at baseline endoscopy, normal endoscopy: a 17, b 18, c 27 hyperemia: a 24, b 20, c 17 erosions: a 17, b 15, c 13 **Type and duration of arthritis:** OA: all participants, no other details **Age:** 60–64: a 15, b 17, c 22; 65–74: a 34, b 32, c 35; ≥75: a 9, b 4, c 3 **Sex:** F/M: a 19/39, b 12/41, c 11/49 **Inclusion criteria:** OA aged 60 years or older, ACR functional class II or III, used an NSAID for at least 3 months before enrolment and expected to continue the use of this class of medication for at least 3 months **Exclusion criteria:** history of hypersensitivity reaction to any of the study drugs, inefficacy or intolerance to ibuprofen, history of MI within last 6 months, congestive heart failure, medically uncontrolled hypertension or arrhythmias, history of an ulcer or GI tract bleeding within 1 year of study entry, history of gastroduodenal or eosophageal surgery, significant lower-bowel disease (including regional enteritis, ulcerative colitis, intestinal bypass surgery, frequently bleeding haemorrhoids), OA which required treatment with multiple NSAIDs within 3 months of enrolment, patients considered to be candidates for joint replacement during time of the study, patients who had received intra-articular steroid injections or oral steroids within 1 month of enrolment	**Comparison:** misoprostol plus ibuprofen (c) vs ibuprofen (b) vs nabumetone (a) **Duration:** 12 weeks **Interventions:** c, misoprostol 800 μg/400–800 μg (4× 200 μg daily) **NSAIDs:** c, ibuprofen 2400 mg/600–2400 mg (4× 600 mg daily, administered concurrently with misoprostol); b, ibuprofen 2400 mg/600–2400 mg (4× 600 mg daily); a, nabumetone 1000 mg/500–2000 mg daily (no other details) **Endoscopy:** 0, 2, 6, 12 weeks and at early withdrawal **Other medication:** concomitant medication was allowed with the exception of anticoagulants, other anti-inflammatories, corticosteroids, immunosuppressant therapy, ulcer therapy (H_2RAs, sucralfate, long-term antacid therapy) **Aspirin allowed:** not stated **Analgesic allowed:** paracetamol max. 12× 325 mg tablets in 24 h **Participant education:** not stated **Washout:** yes, 3–10 days during which administered placebo 3x daily **Number and frequency of visits:** 7 (0, 2, 4, 6, 8, 10 and 12 weeks)	**Allocated:** a 58, b 53, c 60 **Completed:** a 46, b 25, c 45 **Drop-out:** a 12, b 28, c 15 **Assessed for GI symptoms:** a 58, b 53, c 60 **Outcomes reported:** GI symptoms, endoscopic ulcers, anaemia, GI drop-outs **How were adverse events assessed:** participants asked if there had been any problems since last visit **How was compliance assessed:** tablet count	**Risk factors:** history of ulcers (1 year or more ago): a 10, b 14, c 14 all participants aged 60 years or more CVD: a 0, b 0 **FUNDING** **Funded by:** SmithKline Beecham Pharmaceuticals **Affiliation of contact author:** Arthritis Center, Phoenix, AZ, USA **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** unclear

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Perpignano, 1994[118] **Location:** Italy	**Method of randomisation:** predetermined randomisation schedule provided by Wyeth Italia **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy but excluded patients with active peptic ulcer, history of GI ulcer or haemorrhage either associated with NSAID use or in the last 3 years **Baseline NSAID status:** excluded patients who had never received NSAIDs **Type and duration of arthritis (years):** OA: of the hip or knee, no further details **Age:** a 71.0 b 70.4 **Sex:** M/F a 5/55 b 9/51 **Inclusion criteria:** 65 years or older with active OA of the hip or knee confirmed by roentgenological and clinical criteria; patients had to show a grade 3 (reduction of joint space, moderate marginal osteophytosis) or grade 4 (reduction of joint space, remarkable marginal osteophytosis and subchondral sclerosis) in the Kellgren's scale; an X-ray examination of the affected joint must have been done in the previous 12 months, clinical criteria of the activity of the disease were: a score of at least 4 in the viso-analogue scale of global pain and a score of at least 8 in the Lequesne algofunctional index, history of positive therapeutic response to one or more NSAID, including aspirin; patients discontinuing NSAIDs **Exclusion criteria:** hypersensitivity to NSAIDs including aspirin, those who had never received NSAIDs for the treatment of OA, received investigational NSAIDs within the preceding month; the following medical conditions and medications also precluded entry to the study: active peptic ulcer, history of GI ulcer or haemorrhage, either associated with NSAID use or within the last 3 years; significant renal, hepatic, haematological or cardiovascular disease; any condition likely to	**Comparison:** etodolac SR (b) vs tenoxicam (a) **Duration:** 8 weeks **Interventions:** double dummy b, etodolac SR 600 mg/600 mg daily; a, tenoxicam 20 mg/20 mg daily **Other medication:** no other NSAIDs or analgesics, corticosteroids, anticoagulants excluded, medication for chronic conditions tolerated if not disallowed in the protocol, physical therapy not allowed but walking aids permitted **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol up to 500 mg ×4 daily during washout only **Participant education:** not stated **Washout:** yes, at least 7 days for NSAIDs and 14 days for oxicam derivatives **Number and frequency of visits:** 4 (0, 2, 4 and 8 weeks)	**Allocated:** a 60, b 60 **Completed:** a 48, b 48 **Drop-out:** a 12, b 12 **Assessed:** a 60, b 60 **Outcomes reported:** symptomatic ulcers, GI drop-outs, endoscopic ulcers, total drop-outs **How were adverse events assessed:** any negative event was classed as an adverse event, specific condition was recorded, any per study indication, dates and times of occurrence, severity, relationship to study medication, countermeasures and outcome **How was compliance assessed:** not stated	**Risk factors:** history of ulcer: a 0, b 0; history of bleeds: a 0, b 0; concomitant use of anticoagulants: a 0, b 0 corticosteroids: a 0, b 0 >1 NSAID: a 0, b 0 CVD: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** University of Pisa, Italy **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/3 **Note:** Wyeth provided the randomisation schedule and the medical monitoring of the study

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
		interfere with drug absorption, distribution, metabolism or excretion; evidence of concomitant disease that could have affected joints, such as psoriasis, syphilitic neuropathy, ochronosis, metabolic bone disease, inflammatory bowel disease or acute trauma; coexistence of any connective-tissue disorder; major surgery within the past 6 weeks; diabetes treated with hypoglycaemic agents or with significant complications; history of alcoholism and/or drug abuse within the past year; significant psychiatric disorder; past or present malignancy, except successfully resected basal-cell carcinoma; history of skin disorders precipitated or aggravated by drugs; any condition that required new drug therapy at the time of entry into the study; clinically significant positive results of test for rheumatoid factor; current or recent severe infections, including tuberculosis, or prophylactic treatment with anti-tuberculosis agents; oral corticosteroids within the previous 6 months, or intra-articular or parenteral injection of corticosteroids within the previous 4 weeks; oral or parenteral anticoagulants, and significant abnormalities in laboratory performed prior to the start of therapy			

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Carrabba, 1995[119,227] **Location:** 21 centres in Italy, 3 centres in Germany	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** no, piroxicam and meloxicam suppositories differed in shape and colour and 'may have been recognised by some participants' **Assessor blinding:** no **Intention-to-treat:** yes ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy, participants excluded if evidence of active peptic ulcer in previous 6 months **Type and duration of arthritis (years):** OA: a 5.9, b: 5.8 **Age:** a 62.5, b: 61.4 **Sex:** M/F: a 17/92, b: 33/183 **Inclusion criteria:** 35–80 years with clinically defined diagnosis of OA (hip or knee), required NSAID treatment for symptoms, stabilised regimen of corticosteroids therapy allowed **Exclusion criteria:** meloxicam previously taken, or other study drugs in last 4 weeks, pregnancy, lactation or of childbearing potential without adequate contraception, liver insufficiency, renal insufficiency, New York Heart Association class III or IV heart failure, severe uncontrolled hypertension, any severe metabolic or haematological disease, cancer, mental disturbance or bronchial asthma, clinical evidence of active peptic ulcer during the previous 6 months, Crohn's disease, ulcerative colitis, proctitis, haemorrhoids, any disease which would interfere with suppository absorption, worsen local tolerance or interfere with evaluation of local tolerance, clinically significant abnormal laboratory investigations, history of hypersensitivity to analgesics, antipyretics or NSAIDs, history of poor tolerance to suppositories, treatment with other NSAIDs (systemic or topical), topical anti-inflammatory preparations, muscle relaxants, anticoagulants, lithium, hydantoins or any drug administered as a suppository, due to undergo orthopaedic surgery during the study, receiving changes in physiotherapy or presenting with any other disease which could interfere with evaluation of safety or efficacy	**Comparison:** meloxicam suppositories (b) vs piroxicam suppositories (a) **Duration:** 3 weeks **Interventions:** b, meloxicam 15 mg/7.5–15 mg daily; a, piroxicam 20 mg/10–30 mg daily; all inserted rectally in evening before bed **Other medication:** corticosteroids allowed if stabilised regimen used **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol up to 4 g/day **Participant education:** not stated **Washout:** yes, half life of previously taken NSAIDs **Number and frequency of visits:** 3 (0, day 7 and day 21)	**Allocated**: a 109, b 216 **Completed:** a 100, b 204 **Drop-out:** a 9, b 12 **Assessed:** a 108, b 216 **Outcomes reported:** serious GI complications, GI symptoms **How were adverse events assessed:** coded according to WHOART, no other details **How was compliance assessed:** not stated	**Risk factors:** concomitant use of anticoagulants: a 0, b 0 >1 NSAID: a 0, b 0 CVD: a 0, b 0; renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** Boehringer Ingelheim Italia **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 2 out of 6 authors worked for Boehringer Ingelheim Italia

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Dore, 1995[120] **Location:** 11 centres in the USA	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy but excluded patients with history of GI bleed **Type and duration of arthritis (years):** OA knee, no further details **Age:** a 63.7 b 63.8 **Sex:** M/F: a 30/52, b 34/52 **Inclusion criteria:** outpatients, 40 years or over, radiologically confirmed OA of the knee that required NSAID treatment, patients had to have active disease after the washout as defined by the following primary efficacy variables: overall assessment of condition by both the patient and the investigator had to be fair or poor; joint tenderness and walking pain had to be assessed as moderate to very severe; secondary efficacy variables studied included inactivity stiffness, night time pain and quality of sleep **Exclusion criteria:** connective tissue disorder; scheduled for joint replacement within 1 year; had a history of GI bleeding, renal or hepatic impairment, drug-induced skin disorder or any other illness likely to interfere with the evaluation or disposition of the study drug; had a contraindication to NSAIDs; or had recent corticosteroid, investigational anticoagulant, or cytoprotective therapy; women who were pregnant, breastfeeding or of childbearing potential and not using birth control	**Comparison:** etodolac (b) vs naproxen (a) **Duration:** 4 weeks **Interventions:** b, etodolac 800 mg/600 mg daily (400 mg ×2 daily); a, naproxen 1000 mg/750–1250 mg daily (500 mg ×2 daily) **Other medication:** other concomitant NSAIDs, corticosteroids, salicylate-containing topical preparations and new or altered physiotherapy were prohibited **Aspirin allowed:** low-dose (5% etodolac group and 10% naproxen group took aspirin) **Analgesic allowed:** yes, acetaminophen (12% etodolac group and 16% naproxen group took acetaminophen), occasional NSAID for non-arthritic pain also allowed **Participant education:** not stated **Washout:** yes, long-acting NSAIDs required 7 days and other NSAIDs required at least 5 half-lives **Number and frequency of visits:** 3 (0, 2 and 4 weeks)	**Allocated:** a 82, b 86 **Completed:** a 67, b 66 **Drop-out:** a 15, b 20 **Assessed:** a 82, b 86 **Outcomes reported:** serious GI complications, GI symptoms, total drop-outs **How were adverse events assessed:** recorded any negative event, study events and vital signs **How was compliance assessed:** capsule count (more than 90% compliance in each group)	**Risk factors:** history of bleeds: a 0, b 0 concomitant anticoagulants: a 0, b 0 corticosteroids: a 0, b 0 >1 NSAID: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** Wyeth-Ayerst Laboratories **Affiliation of contact author:** private practice, Anaheim, CA, USA **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 3/4 by Wyeth-Ayerst

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Quattrini, 1995[121] **Location:** Italy	**Method of randomisation:** 'randomly allocated', double dummy technique, code for each medication package was supplied in a sealed envelope and opened at the end of the trial **Allocation concealment:** adequate **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy performed but excluded patients with history of peptic ulceration or GI bleeding in previous 12 months **Type and duration of arthritis (years):** OA, approximately 5 years duration for all participants **Age:** a 65.4, b 66.4 **Sex:** M/F: a 25/35 b 25/35 **Inclusion criteria:** active OA, history of ≥12 months' duration and uni- or bilateral hip pain, patients with diffuse OA pain were only eligible if the hip was the main source of all symptoms, disease, clinical diagnosis confirmed by X-ray of affected joint during last 12 months, pain of moderate to severe intensity **Exclusion criteria:** known hypersensitivity to any NSAID, history of peptic ulceration or GI bleeding in last 12 months, oral, intra-articular or systemic corticosteroids up to 2 weeks prior to study, clinically significant GI, hepatic and/or renal impairment, other systemic inflammatory diseases, pregnancy or lactation	**Comparison:** nimesulide (b) vs naproxen (a) **Duration:** 4 weeks **Interventions:** b, nimesulide 200 mg/? (100 mg ×2 daily); a, naproxen 1000 mg/500–1250 mg (500 mg ×2 daily), double dummy used **Other medication:** concurrent use of anti-inflammatory analgesic or muscle-relaxant drugs not permitted **Aspirin allowed:** not stated **Analgesic allowed:** yes, occasional use of paracetamol up to 3 g/day **Participant education:** not stated **Washout:** yes, 7 days for NSAIDs **Number and frequency of visits:** 3 (0, 2 and 4 weeks)	**Allocated:** a 60, b 60 **Completed:** a 51, b 52 **Drop-out:** a 9, b 8 **Assessed:** a ?60, b ?60 **Outcomes reported:** GI symptoms, GI drop-outs **How were adverse events assessed:** asked directly whether treatment had upset him/her in any way, all subjective and objective adverse events were recorded (nature, severity, day of onset and duration) **How was compliance assessed:** tablet count, 4 of nimesulide group and 1 of naproxen group failed to take one or both daily doses (for more than 1 day in only 1 patient in nimesulide group)	**Risk factors:** history of ulcers (last 12 months): a 0, b 0 history of bleeds (last 12 months): a 0, b 0 concomitant disorders (predominantly heart disease, emphysema and/or hypertension): a 20, b 20 >1 NSAID: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** Helsinn Healthcare SA **Affiliation of contact author:** Bergamo Hospital, Italy **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** none

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Degner, 1996[122,128] [abstract] **Location:** Germany and UK	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy, no further details **Type and duration of arthritis (years):** RA, no further details **Age:** no details **Sex:** no details **Inclusion criteria:** RA (ARA criteria), no further details **Exclusion criteria:** no details	**Comparison:** meloxicam (b) vs piroxicam (a) **Duration:** 3 weeks **Interventions:** b, meloxicam 15 mg/7.5 mg–15 mg daily; a, piroxicam 20 mg/10–30 mg daily **Other medication:** no details **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** unclear	**Allocated:** a 135, b 141 **Completed:** no details **Drop-out:** no details **Assessed:** a 135, b 141 **Outcomes reported:** GI symptoms **How were adverse events assessed:** no details **How was compliance assessed:** not stated	**Risk factors:** no details **FUNDING** **Funded by:** not stated **Affiliation of contact author:** Dr Karl Thomae, Biberach/riss, Germany **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 3 of 4 employed by Dr Karl Thomae

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Hosie, 1996[123] **Location:** 52 GP centres in UK	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** no, regarding duration of OA across treatment groups **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** yes **Summary risk of bias:** high	**Baseline GI status:** no baseline endoscopy performed, patients excluded if evidence of active peptic ulceration in previous 6 months **Type and duration of arthritis (years):** RA, a 7.0, b 5.6 **Age:** a 64.2, b 64.3 **Sex:** M/F: a 68/98, b 69/100 **Inclusion criteria:** 18 years or more, clinically and radiographically confirmed OA (knee or hip) with symptoms present for ≥3 months (X-rays indicated narrowing of femoropatellar and/or femorotibial space in the knee or narrowing of the acetabulofemoral space in the hip, plus knee or hip must show presence of osteophytes, subchondral sclerosis and/or cysts), at least moderate overall pain in affected joint (score of 35 mm or greater on patient-assessed 100 mm VAS with 0 mm = no pain, 100 mm = unbearable pain), requiring treatment with NSAID, ambulant **Exclusion criteria:** pregnant, lactating or of childbearing potential without adequate contraception, any concomitant clinically unstable disease, clinically relevant laboratory test abnormalities, clinical evidence of active peptic ulceration in previous 6 months, hypersensitivity to analgesics, antipyretics or NSAIDs, any drug or procedure which might interact with or obscure effects of the study medication	**Comparison:** meloxicam (b) vs diclofenac sodium SR (a) **Duration:** 6 months **Interventions:** b, meloxicam 7.5 mg/7.5–15 mg (once daily); a, diclofenac sodium SR 100 mg/75–150 mg (once daily), double dummy used **Other medication:** massage and exercise continued unchanged, medications not considered to affect study outcome were allowed to continue **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol up to 4 g daily **Participant education:** not stated **Washout:** yes, 3 days or more for any previous NSAID **Number and frequency of visits:** 6 (0, 2 weeks then at 1, 2, 3 and 6 months)	**Allocated:** a 167, b 169 **Completed:** a 129, b 141 **Drop-out:** a 38, b 28 **Assessed:** a 166, b 169 **Outcomes reported:** mortality, serious GI complications, serious cardiac or renal illness, QoL, participant satisfaction, GI symptoms, GI drop-outs **How were adverse events assessed:** used WHO body systems organ classification **How was compliance assessed:** plasma level of meloxicam determined at 3 months and tablet count	**Risk factors:** no details **FUNDING** **Funded by:** unclear **Affiliation of contact author:** Great Western Medical (GP centre), Glasgow, UK **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 2 of 3 employed by Boehringer Ingelheim, Biberach/Riss, Germany

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Linden, 1996[42,228] **Location:** 22 centres in Sweden, Denmark, Belgium, The Netherlands and Germany	**Method of randomisation:** 'randomised', sealed envelopes **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** no **Intention-to-treat:** yes ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy performed, no further details **Type and duration of arthritis (years):** OA: a 5.5, b 6.2 **Age:** a 67.2 b 67.2 **Sex:** M/F: a 47/80, b 48/81 **Inclusion criteria:** 18 years or more, clinical diagnosis of OA (hip) for at least 3 months (radiological confirmation in the target hip), at least moderate pain on active movement in affected hip (score of 35 mm or more on patient-assessed VAS with 0 mm = no pain, 100 mm = unbearable pain), able to perform their daily routine **Exclusion criteria:** no details	**Comparison:** meloxicam (b) vs piroxicam (a) **Duration:** 6 weeks **Interventions:** b, meloxicam 15 mg/7.5–15 mg (once daily); a, piroxicam 20 mg/10–30 mg (once daily) **Other medication:** continued therapy for concomitant diseases, other NSAIDs and analgesics except paracetamol, anti-inflammatories were not allowed, massage and exercise continued unchanged **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol **Participant education:** not stated **Washout:** yes, 3–7 days for previous NSAIDs **Number and frequency of visits:** 4 (0, 7, 21 and 42 days)	**Allocated:** a 127, b 129 **Completed:** a 112, b 113 **Drop-out:** a 15, b 16 **Assessed:** a 127, b 129 **Outcomes reported:** mortality, serious GI complications, symptomatic ulcers, serious cardiovascular or renal illness (extra) participant satisfaction, GI symptoms **How were adverse events assessed:** not stated **How was compliance assessed:** tablet count, plasma levels at day 21	**Risk factors:** >1 NSAID: a 0, b 0 **FUNDING** **Funded by:** unclear **Affiliation of contact author:** Eksjo Hospital, Sweden **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** at least 1 of 3 authors employed by Dr Karl Thomae, Biberach/Riss, Germany **Other:** meloxicam 30 mg daily arm discontinued

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Wojtulewski, 1996[124,229] **Location:** 48 centres, in UK, Germany, France, Belgium, Mexico and Spain	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** participants excluded with clinical evidence of peptic ulceration **Baseline NSAID status:** previous NSAID use: a, 93.3%, b 86.4% **Type and duration of arthritis (years):** RA: a 9.2, b 9.3 **Age:** no details **Sex:** no details **Inclusion criteria:** 18–75 years with RA defined according to ACR criteria and belonging to functional class I, II or III, required NSAID therapy and demonstrated active disease before and/or during washout period (active disease defined as presence of 3 of the following: 6 or more joints painful or tender on motion, 3 or more swollen joints, duration of morning stiffness of 45 minutes or more, Westergren sedimentation rate of 28 mm/h or more). **Exclusion criteria:** participation in previous meloxicam trial, clinical evidence of peptic ulceration or any other disease which would interfere with the evaluation of efficacy and safety [including collagensosis, dermatomyositis, gout, infectious arthritis, sarcoidosis, psoriatic arthritis, AS, Still's disease, mixed connective tissue disease, arthritis associated with inflammatory bowel disease, systemic lupus erythematosus, fibromyalgia, Reiter's syndrome, arteritis (general), polymyalgia rheumatic and scleroderma], second-line anti-rheumatic therapies if not stable for at least 3 months prior to study	**Comparison:** meloxicam (b) vs naproxen (a) **Duration:** 26 weeks **Interventions:** b, meloxicam 7.5 mg/7.5–15 mg (7.5 mg once daily); a, naproxen 750 mg/500–1250 mg (250 mg ×2 morning plus 1 × 250 mg evening), double dummies used, all medication taken with water and after food **Other medication:** glucocorticosteroids of 7.5 mg/day or less of prednisolone or equivalent and stabilised for a month could be continued, concomitant medication allowed including second-line anti-rheumatic therapies if stable for 3 months prior to study, oral corticosteroid and second-line therapy doses could not be increased but could be reduced, physiotherapy could continue, intramuscular or intravenous injections of glucocorticoids or adrenocorticotrophic hormone and more than 2 intra-articular injections of corticosteroids in month before or during study not permitted **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol only and no more than 4 g daily **Participant education:** not stated **Washout:** yes, 3–11 days for NSAIDs **Number and frequency of visits:** 7 (0, 14 and, 28 days, 8, 12, 19 and 26 weeks)	**Allocated:** a 180, b 199 **Completed:** a 106, b 117 **Drop-out:** a 74 b 82 **Assessed:** a 180, b 199 **Outcomes reported:** serious GI complications, symptomatic ulcers, GI symptoms, GI drop-outs **How were adverse events assessed:** incidence, time, severity and causal relationship or adverse event tabulated by body systems organ classification **How was compliance assessed:** not stated	**Risk factors:** no details **FUNDING** **Funded by:** unclear **Affiliation of contact author:** Eastbourne District General Hospital, UK **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 1 of 7 authors employed by Boehringer Ingelheim and 1 author employed by Dr Karl Thomae

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Goei Thé, 1997[125] **Location:** 23 centres in Belgium, Denmark, Germany and The Netherlands	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** unclear **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy, no further details **Type and duration of arthritis (years):** OA: a 7.3, b 7.6 **Age:** a 71.4, b 71.5 **Sex:** M/F: a 23/107 b 19/109 **Inclusion criteria:** 18 years or more, ambulatory, clinically and radiographically confirmed diagnosis of OA (knee) for at least 3 months (movement of knee by extreme flexion and extension elicited pain, X-rays in different projections demonstrated at least narrowing of the femoropatellar and/or femorotibial space and osteophytes and/or subchondral sclerosis and/or cysts), had experienced ≥moderate pain in the worst affected knee, (score of ≥35 mm on patient assessed VAS) judged by investigator to require treatment with NSAIDs, patients receiving therapy for concomitant disease were allowed to continue their medication. **Exclusion criteria:** treatment with oral or intra-articular steroids was not permitted during or 3 months preceding study	**Comparison:** meloxicam (b) vs diclofenac SR (a) **Duration:** 6 weeks **Interventions:** b, meloxicam 15 mg/7.5–15 mg (once daily); a, diclofenac SR 100 mg/75–150 mg (once daily), double dummy used **Other medication:** therapy for concomitant disease allowed (except if excluded by protocol), treatment with other NSAIDs and oral or intra-articular steroids not permitted **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol maximum 4 g/day **Participant education:** not stated **Washout:** yes, 7 days for piroxicam and tenoxicam, at least 3 days for other NSAIDs **Number and frequency of visits:** 4 (0, 1, 3 and 6 weeks)	**Allocated:** a, 130, b 128 **Completed:** unclear **Drop-out:** unclear **Assessed:** a 130, b 128 **Outcomes reported:** symptomatic ulcers, GI symptoms **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** >1 NSAID: a 0, b 0 **FUNDING** **Funded by:** not stated **Affiliation of contact author:** De Wever Hospital, The Netherlands **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 2 of 4 authors employed by Dr Karl Thomae GmbH Biberach/an der Liss **Other:** ?same population as in Linden paper[42]

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Hosie, 1997[126] **Location:** General practices in UK	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy but patients excluded if had clinical evidence of peptic ulceration during the last 6 months **Type and duration of arthritis (median and IQR, years):** OA: a 5 years (2.2–10), b 5 years (2–10) **Age:** a 64.0 (57.4–74.0), b 65.5 (55.1–73.0) **Sex:** M/F: a 69/80, b 128/178 **Inclusion criteria:** 18 years or more, clinically and radiographically confirmed OA (knee or hip) for at least 3 months, ambulant and at least moderate overall pain in the target joint (35 mm or more on VAS scale) **Exclusion criteria:** pregnant, lactating or women not using adequate contraception, evidence of hepatic, renal, cardiac, haematological or metabolic disease; patients receiving therapy for bronchial asthma; clinical evidence of peptic ulceration during the last 6 months; hypersensitivity to analgesics, antipyretics or NSAIDs; clinically abnormal laboratory values; treatment with oral corticosteroids; intra-articular corticosteroid injections in previous 3 months; treatment with topical anti-inflammatory agents, anticoagulants, lithium or anti-ulcer drugs; the possibility of undergoing orthopaedic surgery during study; undergoing active physiotherapy during study; removal of fluid from effusion of the affected joint, other rheumatological diseases	**Comparison:** meloxicam (b) vs piroxicam (a) **Duration:** 6 weeks **Interventions:** b, meloxicam 15 mg/7.5–15 mg (once daily); a, piroxicam 20 mg/10–30 mg (once daily) **Other medication:** not stated **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol up to 4 g daily **Participant education:** not stated **Washout:** 7 days for piroxicam or tenoxicam, at least 3 days for all other NSAIDs **Number and frequency of visits:** 6 (0, 2, 4, 8, 12, 24 weeks)	**Allocated:** a 149, b 306 **Completed:** a 118, b 252 **Drop-out:** a 31, b 54 **Assessed:** a 149, b 306 **Outcomes reported:** serious GI complications, QoL, GI symptoms, anaemia, total drop-outs, GI drop-outs **How were adverse events assessed:** participants asked 'Have you experienced anything unusual since your last visit?' **How was compliance assessed:** non compliance assessed as taking less than 20% study medication by return of unused capsules but not reported	**Risk factors:** concomitant use of anticoagulants: a:0, b 0 corticosteroids: a 0, b; 0 CVD: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** Dr Karl Thomae, Biberach/Riss, Germany **Affiliation of contact author:** has acted in past as consultant for Pharmacia **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 3 employees of Pharmacia and have stock interest within the company

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Jennings, 1997[127] **Location:** New York, USA	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** no regarding age **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** no baseline endoscopy but excluded patients with stomach ulcer **Type and duration of arthritis (years):** OA of the foot, no further details **Age:** a 50.8, b 45.0 **Sex:** M/F: a 8/23, b 7/22 **Inclusion criteria:** 31–71 years, symptomatic OA of the foot or ankle or both as confirmed by radiographic examination; enrolled at the Foot Clinics of New York **Exclusion criteria:** patients already stable with etodolac or naproxen or who would have been treated with other NSAIDs during the study interval; women who were pregnant or lactating; patients with a history of anaemia, liver disease, renal disease, stomach ulcer or NSAID allergy	**Comparison:** etodolac (b) vs naproxen (a) **Duration:** 5 weeks **Interventions:** b, etodolac 800 mg/600 mg daily (400 mg ×2 daily), a, naproxen 1000 mg/500–1250 mg daily (500 mg ×2 daily) **Other medication:** no details **Aspirin allowed:** no details **Analgesic allowed:** no details **Participant education:** not stated **Washout:** yes, no details **Number and frequency of visits:** 6 (0, 1, 2, 3, 4 and 5 weeks)	**Allocated:** a 31, b 29 **Completed:** a: 18 b 16 **Drop-out:** a 13, b 13 **Assessed:** unclear **Outcomes reported:** total drop-outs **How were adverse events assessed:** no details **How was compliance assessed:** not stated	**Risk factors:** renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** Wyeth-Ayerst Laboratories **Affiliation of contact author:** New York College of Podiatric Medicine, USA **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 0/2

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Lightfoot, 1997[128] **Location:** 28 sites in USA and Europe	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy performed, no further details **Type and duration of arthritis (years):** RA, no other details **Age:** a 56 (28–76), b 58 (34–76) **Sex:** M/F: a 43/96, b 44/103 **Inclusion criteria:** 18–75 years, definite or classical RA as defined by ARA of at least 6 months' duration (age of onset16 years or over), history of positive response to NSAID therapy with no serious adverse reactions, had to have a flare of RA regardless of prior NSAID use (indicated by worsening in patient global assessment of painful joints, number of swollen joints, Westergren ESR or duration of morning stiffness), those taking DMARDs or corticosteroids were eligible if treatment initiated at least 6 months prior to study and fixed dosage maintained for at least 2 months **Exclusion criteria:** women of childbearing potential, no further details	**Comparison:** etodolac (b) vs piroxicam (a) **Duration:** 12 weeks **Interventions:** b, etodolac 600 mg/600 mg (300 mg ×2 daily); a, piroxicam 20 mg/10–30 mg (once daily) matching placebos **Endoscopy:** only if participant symptomatic **Other medication:** DMARDs and corticosteroids only if maintained at constant dose, minimum allowable cumulative dose of methotrexate = 2 g, oral corticosteroid 7.5 mg/day or less, no other anti-inflammatories allowed **Aspirin allowed:** not stated **Analgesic allowed:** yes, acetaminophen up to 650 mg 4× daily during washout and first week of treatment only **Participant education:** not stated **Washout:** not more than 14 days for NSAIDs, at least 10 days for SR or long acting NSAIDs **Number and frequency of visits:** 5 (0, 1, 4, 8, 12 weeks)	**Allocated:** a 139, b 147 **Completed:** a 98, b 103 **Drop-out:** a 41, b 44 **Assessed:** a 139, b 147 **Outcomes reported:** serious GI complications, symptomatic ulcers, GI symptoms, GI drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** concomitant use of corticosteroids: a 50, b 55 **FUNDING** **Funded by:** Wyeth-Ayerst Pharmaceuticals **Affiliation of contact author:** University of Kentucky, USA **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** unclear **Note:** there was also an etodolac 200 mg ×2 daily, which was excluded from this review

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Neustadt, 1997[129] **Location:** 96 centres in USA	**Method of randomisation:** 'assigned randomly' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** unclear, study enrolment discontinued after 4.5 years due to inadequate power **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy performed, no further details **Baseline NSAID status:** 90% all participants had previously taken NSAIDs **Type and duration of arthritis (years):** RA, a 3.6, b 3.5 **Age:** a 53.1, b 53.0 **Sex:** M/F: a 118/299, b 126/283 **Inclusion criteria:** early stage RA, disease duration 1–7 years, Steinbrocker's stage of disease classification as well as functional class rating of I or II for progression of radiological changes, those not taking NSAID at screening visit were required to meet the criteria for active disease, those taking NSAIDs at screening were required to discontinue them for up to 21 days during which time they were required to develop a flare (flare defined as first 3 of following, plus at least 1 of the other 2 had to be met: worsening in the number of tender or painful joints on motion, joint swelling and morning stiffness plus worsening of investigator's or patient's opinion of disease symptoms) **Exclusion criteria:** treatment with a DMARD within 6 months of start of study	**Comparison:** etodolac (b) vs Ibuprofen (a) **Duration:** 3 years **Interventions:** b, etodolac 1000 mg/600 mg (500 mg ×2 daily) (for initial 2 weeks 300 mg daily, next 2 weeks 600 mg daily); a, ibuprofen 2400 mg/600–2400 mg (600 mg ×4 daily) (for initial 2 weeks 1600 mg daily) **Other medication:** DMARDs not permitted, low-dose oral corticosteroids (e.g. 5 mg/day or less prednisone or equivalent) permitted if dosage constant from 4 weeks before enrolment to end of study **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** yes, up to 21 days for any NSAIDs **Number and frequency of visits:** 26 (12-week intervals in second and third years, more frequent in first year)	**Allocated:** a 417, b 409 **Completed:** a 71, b 86 **Drop-out:** a 346, b 323 **Assessed:** a 417, b 409 **Outcomes reported:** total drop-out **How were adverse events assessed:** collected complaints using a 6 page checklist that allowed for questioning of presence of more than 70 specific symptoms **How was compliance assessed:** not stated	**Risk factors:** about 20% of all participants took low-dose corticosteroids throughout study **FUNDING** **Funded by:** unclear **Affiliation of contact author:** University of Louisville, USA **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** none **Other:** etodolac 300 mg daily arm excluded from analyses as dose below minimum recommended in BNF

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Rogind, 1997[130,230] **Location:** 19 centres in Denmark	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** yes **Intention-to-treat:** yes ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy but excluded patients with history of GI bleed or peptic ulcer disease **Type and duration of arthritis (years):** OA of the hip or knee, no further details **Age:** a 67.5 (37–91), b 67.0 (39–88) **Sex:** M/F: a 30/103, b 28/110 **Inclusion criteria:** radiologically proven OA of the hip or knee showing at least two of the following conditions: weight-bearing pain, joint stiffness, pain on motion; 40 years of age or over, women of childbearing potential were required to use contraception **Exclusion criteria:** women who were breast-feeding or pregnant, impaired renal or liver function, history of GI bleeding or peptic ulcer disease; inflammatory joint disease; allergy towards aspirin or other NSAIDs; patients receiving lithium; H_2RA antagonists; anticoagulants; systemic or intra-articular corticosteroids within the previous 2 months; penicillamine, gold, immunosuppressive drugs or cytotoxic agents within the previous 6 months	**Comparison:** etodolac (b) vs piroxicam (a) **Duration:** 8 weeks **Interventions:** b, etodolac 600 mg/600 mg daily (300 mg ×2 daily); a, piroxicam 20 mg/10–30 mg daily (20 mg once daily **Other medication:** lithium; H_2RA antagonists; anticoagulants; systemic or intra-articular corticosteroids; penicillamine, gold, immunosuppressive drugs or cytotoxic drugs were excluded **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol up to 4000 mg daily during washout and entire study **Participant education:** not stated **Washout:** yes, 1 week **Number and frequency of visits:** 3 (0, 4 and 8 weeks)	**Allocated:** a 133, b 138 **Completed:** a 102, b 109 **Drop-out:** a 31, b 29 **Assessed:** a 133, b 138 **Outcomes reported:** serious GI complications, symptomatic ulcers, GI symptoms, GI drop-outs, total drop-outs **How were adverse events assessed:** adverse events and patient complaints recorded **How was compliance assessed:** not stated	**Risk factors:** history of ulcer: a 0, b 0 history of bleeds: a 0, b 0; history of H_2RA use: a 0, b 0 concomitant use of anticoagulants: a 0, b 0 corticosteroids: a 0, b 0 >1 NSAID: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** LEO Pharmaceutical Products **Affiliation of contact author:** Copenhagen Municipal Hospita, Denmark **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 1/2 by LEO

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Dequeker, 1998[38,231,232] SELECT **Location:** 12 countries (Europe and Australia, Argentina, South Africa, including UK)	**Method of randomisation:** 'randomised' sealed envelopes **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** no **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy performed but excluded participants with active peptic ulcer **Baseline NSAID status:** 79% in each arm were previously taking NSAIDs **Type and duration of arthritis (months):** OA: a 48, b 45 **Age:** a 61.6, b 61.3 **Sex:** M/F: a 1431/2905, b 1382/2938 **Inclusion criteria:** 18 years or more, acute and painful exacerbation of OA (hip, knee, hand or vertebral spine), pain on active movement (35 mm or more on a 100 mm VAS, 0 mm = no pain, 100 mm = unbearable pain) and considered suitable for treatment with NSAID, diagnosis of OA based on clinical judgement of trialist (but radiological diagnosis required for OA of vertebral spine), OA in multiple sites eligible provided the specified joints were also affected **Exclusion criteria:** active peptic ulcer, hypersensitivity to analgesics, antipyretics or NSAIDs, asthma, nasal polyps, angioneurotic oedema or urticaria following NSAID administration, concomitant anticoagulants, lithium, methotrexate, other NSAIDs or analgesic agents, significant impairment of renal function, severe liver injury, haematological disorder, pregnant, breastfeeding, any disease which could interfere with evaluation of efficacy or tolerability, corticosteroid treatment within 2 months, prior replacement of, trauma to, or infection of the evaluated joint, confinement to bed, previous participation in a clinical trial in the previous month	**Comparison:** meloxicam (b) vs piroxicam (a) **Duration:** 28 days **Interventions:** b, meloxicam 7.5 mg/7.5–15 mg (once daily); a, piroxicam 20 mg/10–30 mg (once daily) **Other medication:** concomitant use of other gastroprotective drugs: a 5.6%, b 4.6% **Aspirin allowed:** yes, low dose allowed **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** yes, 3 days for NSAIDs **Number and frequency of visits:** 2 (0 and 4 weeks)	**Allocated:** a 4641, b 4645 **Completed:** a 3816, b 3845 **Drop-out:** a 520, b 475 **Assessed:** a 4336, b 4320 **Outcomes reported:** mortality, serious GI complications, symptomatic ulcers, serious cardiovascular or renal illness, (extra data) GI symptoms, GI drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** history of PUBs: a 243, b 276 >1 NSAID: a 0, b 0 concomitant use of anticoagulants: a 0, b 0 corticosteroids: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** Boehringer Ingelheim **Affiliation of contact author:** University Hospital Queen's Medical Centre, UK **Affiliation of statistician:** unclear **Affiliation of trial administrator:** trial protocol was developed and the trial was monitored by a steering committee consisting of the authors with the representatives from Boehringer Ingelheim **No. of authors employed by sponsor:** none

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Hawkey, 1998[231–233] MELISSA **Location:** 27 countries (South America, Europe, North America, Australia and New Zealand, Africa, Asia, including UK)	**Method of randomisation:** 'randomised', sealed envelopes **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** no **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy performed but excluded participants with active peptic ulcer **Baseline NSAID status:** a 3847/4688, b 3796/4635 had used NSAID previous to the study **Type and duration of arthritis (median months):** OA: a 48, b 52 **Age:** a 61.7, b 61.5 **Sex:** M/F: a 1538/3144 (?6), b 1536/3096 (?3) **Inclusion criteria:** 18 years or more, acute and painful exacerbation of OA (hip, knee, hand or vertebral spine), pain on active movement (35 mm or more on 100 mm VAS), and considered suitable for treatment with NSAID, diagnosis of OA based on clinical judgement of the trialist (but radiological diagnosis also required for OA of the vertebral spine), participants with OA in multiple sites were eligible provided one of the specified joints was affected **Exclusion criteria:** exactly the same as for Dequeker[38]	**Comparison:** meloxicam (b) vs diclofenac (a) **Duration:** 28 days **Interventions:** b, meloxicam 7.5 mg/7.5–15 mg (once daily); a diclofenac SR 100 mg/75–150 mg (once daily), double dummy used **Other medication:** anticoagulants, methotrexate, lithium and other NSAIDs prohibited **Aspirin allowed:** yes, low dose **Analgesic allowed:** no **Participant education:** not stated **Washout:** yes, 3 days for those previously taking NSAIDs **Number and frequency of visits:** 2 (0 and 4 weeks)	**Allocated:** a 5051, b 5000 **Completed:** a 4138, b 4186 **Drop-out:** a 550, b 449 **Assessed:** a 4688, b 4635 **Outcomes reported:** mortality, serious GI complications, symptomatic ulcers, serious cardiovascular or renal illness, (extra data) GI symptoms, GI drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** history of PUBs: a 249, b 222 concomitant use of drugs for gastroprotection: a 301, b 260 concomitant use of anticoagulants: a 0, b 0 corticosteroids: a 0, b 0 >1 NSAIDs: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** Boehringer Ingelheim **Affiliation of contact author:** University Hospital Nottingham **Affiliation of statistician:** unclear **Affiliation of administrator:** unclear **No. of authors employed by sponsor:** 0/11

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Porto, 1998[131,234] **Location:** multicentre, Portugal	**Method of randomisation:** 'randomly assigned in blocks of 10', computer-generated allocation **Allocation concealment:** unclear **Baseline comparability**: unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and patients only included in study with normal mucosa or 10 petechiae or less **Type and duration of arthritis (years):** OA: less than 1 year duration **Age:** 50 years or more, no further details **Sex:** M/F: 14/75 in total **Inclusion criteria:** 50 years or more, OA (hip or knee), undergone washout from previous NSAID, normal gastroduodenal mucosa or 10 petechiae or less on baseline endoscopy, OA with painful exacerbation for greater than 1 week or requirement for treatment for 1 month with NSAID, and with daily pain (spontaneous or on movement) and functional impairment of the infected joint, spontaneous pain (4.9 cm or more on 10 cm VAS, Huskisson type), lesions rated 1 to 3 on radiological examination 1 year or less before study **Exclusion criteria:** OA: present for 1 year or more, severe or incapacitating OA (unable to walk), necessitating surgical intervention during the study period, being treated with intra-articular corticoids during the 4 weeks prior to study entry, severe renal, hepatic, cardiovascular, endocrine or haematological diseases or bronchial asthma, known history of hypersensitivity to NSAIDs, pregnant women, nursing mothers or women who might become pregnant	**Comparison:** nimesulide (b) vs diclofenac (a) **Duration:** 30 days **Interventions:** b, nimesulide 200 mg/? mg (100 mg ×2 daily); a, diclofenac 150 mg/75–150 mg (50 mg ×3 daily) 'double dummy' **Endoscopy:** before randomisation and day 30 **Other medication:** use of anticoagulants, hydantoin, central or peripheral analgesics, immunosuppressive agents, oral antidiabetics, antimalarials, other NSAIDs, systemic or intra-articular corticoids, muscle relaxants, neuroleptics, antidepressants prohibited throughout study, all other medications were permitted. Physio-therapeutic measures initiated at least 1 month prior to study allowed to continue **Aspirin allowed:** no **Analgesic allowed:** yes, acetaminophen up to 500 mg 6× daily **Participant education:** not stated **Washout:** 48–72 h **Number and frequency of visits:** 2 (0 and day 30)	**Allocated:** a 45, b 44 **Completed:** a 39, b 39 **Drop-out:** a 6, b 5 **Assessed:** a 45, b 44 **Outcomes reported:** symptomatic ulcers, GI symptoms, endoscopic ulcers **How were adverse events assessed:** participants asked non-leading questions regarding adverse events which were then graded in severity, frequency, relationship to study medication and outcome How was compliance assessed: tablet count, 6 or less tablets returned = good, 7–12 tablets returned = fair, more than 12 tablets returned = poor, none in diclofenac group and one in nimesulide group were poorly compliant	**Risk factors:** concomitant use of anticoagulants: a 0, b 0 corticosteroids: a 0, b 0 >1 NSAID: a 0, b 0 CVD: a 0, b 0 diabetes: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** Rhone-Poulenc Rorer, Lisbon, Portugal **Affiliation of contact author:** Helsinn Healthcare, Switzerland **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 1 of 6 employed by Rhone-Poulenc Rorer, 1 of 6 employed by Helsinn Healthcare

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Dougados, 1999[132,235] **Location:** Belgium, France, Germany and UK	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy, no further details **Type and duration of arthritis (years):** AS: a 12, b 13, c 12 **Age:** a 44, b 44, c 42 **Sex:** M/F: a 25/83, b 25/95, c 19/105 **Inclusion criteria:** outpatients fulfilling modified New York criteria for AS, daily NSAID intake during the month preceding the selection visit, NSAID washout period of 2–15 days before baseline visit, flare of disease at baseline defined both by pain (40 mm or more on a 100 mm VAS) and by increase in pain of at least 30% between screening and baseline visits **Exclusion criteria:** peripheral articular disease defined by the presence of active (painful or swollen) peripheral arthritis (excluding hip and shoulder) at screening visit, active inflammatory bowel disease, severe concomitant medical illness, received corticosteroids within previous month and/or any slow-acting drug initiated (or altered dose) in previous 6 months	**Comparison:** meloxicam (b, c) vs piroxicam (a) **Duration:** 52 weeks **Interventions:** b meloxicam 15 mg/7.5–15 mg (once daily); c, meloxicam 22.5 mg/7.5–15 mg (once daily); a, piroxicam 20 mg/10–30 mg (once daily), all took 2 capsules (indistinguishable) each evening **Other medication:** not stated **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol 500-mg tablets **Participant education:** not stated **Washout:** yes, 2–15 days, part of inclusion criteria **Number and frequency of visits:** 8 (0, 1, 3, 6, 13, 26, 39, 52 weeks)	**Allocated:** a 108, b 120, c 124 **Completed:** a 51, b 57, c 78 **Drop-out:** a 57, b 63, c 46 **Assessed:** a 108, b 120, c 124 **Outcomes reported:** serious GI complications, symptomatic ulcers, GI symptoms **How were adverse events assessed:** not stated **How was compliance assessed:** tablet count, result not reported	**Risk factors:** concomitant use of corticosteroids: a 0, b 0 **FUNDING** **Funded by:** in part Boehringer Ingelheim **Affiliation of contact author:** Hopital Cochin, Paris, France **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 1 of 7 authors employed Boehringer Ingelheim **Dose:** 22.5 mg meloxicam arm is above recommended dose **Other:** placebo arm excluded from analysis

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Huskisson, 1999[133] **Location:** 12 rheumatology outpatient clinics in the UK and Ireland and 3 GPs in the UK	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy performed but patients excluded if history or symptoms of gastric or duodenal ulcer **Type and duration of arthritis (years):** OA hip or knee, no other details **Age:** a 64.9 b 64.6 **Sex:** M/F: a 47/97, b 51/84 **Inclusion criteria:** 45–79 years, OA (knee or hip) of 6 months or longer duration and with moderate to severe pain, women of childbearing potential required to use adequate birth control **Exclusion criteria:** target joint required arthroplastic surgery during study, severe intercurrent illness, known hypersensitivity to NSAIDs, a history of or symptoms of gastric or duodenal ulcer, clinically significant laboratory abnormalities, participation in another clinical trial within the preceding 3 months, pregnant or breast-feeding	**Comparison:** nimesulide (b) vs diclofenac (a) **Duration:** 24 weeks **Interventions:** b, nimesulide 200mg/? (100 mg ×2 daily); a, diclofenac 150 mg/75–150 mg (50 mg ×3 daily), double dummy design **Other medication:** other therapy for OA not permitted **Aspirin allowed:** no **Analgesic allowed:** yes, acetaminophen up to 4 g daily **Participant education:** not stated **Washout:** yes, no further details **Number and frequency of visits:** 4 (0, 2, 4, 12 and 24 weeks and by telephone at 8, 16 and 20 weeks)	**Allocated:** a 144, b 135 **Completed:** a 99, b 88 **Drop-out:** a 45 b 47 **Assessed:** a 144, b 135 **Outcomes reported:** mortality, GI symptoms, anaemia, GI drop-outs, total drop-outs **How were adverse events assessed:** participants were telephoned between visits regarding adverse events **How was compliance assessed:** defined as missing fewer than 9 doses in any 4-week period, 70% of participants in each group had good to excellent compliance (N.B. other 30% did not return used medication packs and so exact compliance data are unavailable)	**Risk factors:** history of ulcers: a 0, b 0 **FUNDING** **Funded by:** Merck **Affiliation of contact author:** University of Southern California School of Medicine, USA **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 4 of 9 authors employed by Merck, 1 of 9 by Hill Top Research

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Roy, 1999[134] **Location:** Lok Nayak Hospital, New Delhi, India	**Method of randomisation:** 'randomly administered' **Allocation concealment:** unclear **Baseline comparability:** no **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** no baseline endoscopy performed but excluded participants with active peptic ulcer **Type and duration of arthritis (months):** OA: a 44.9, b 33.2 **Age:** a 47.3 b 46.7 **Sex:** M/F: unclear **Inclusion criteria:** 42–80 years, newly diagnosed OA (knee) for 6 months or longer (ACR criteria with clinical and radiological confirmation), Steinbrocker functional capacity of class I or II **Exclusion criteria:** presence of non-degenerative joint diseases (infectious, microcrystalline), severe and disabling arthritis with eligibility for surgical intervention, treatment with intra-articular injections of corticosteroids within the month preceding the study, history of hypersensitivity to NSAIDs, presence of an active ulcer, pregnancy, lactation, history of hepatic, renal or haematopoietic disease, receiving other NSAIDs or any other medications, history of alcohol intake	**Comparison:** nimesulide (b) vs piroxicam (a) **Duration:** 8 weeks **Interventions:** b, nimesulide 200 mg/? mg (100 mg ×2 daily); a, piroxicam 20 mg/10–30 mg (once daily) plus identical placebo, taken after meals **Other medication:** no other medication likely to interfere with study drug was allowed **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol, 500-mg tablets **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 5 (0, 2, 4, 6 and 8 weeks)	**Allocated:** a 49, b 41 **Completed:** a 40, b 30 **Drop-out:** a 9, b 11 **Assessed:** a 40, b 30 **Outcomes reported:** symptomatic ulcers, GI symptoms, GI drop-outs **How were adverse events assessed:** global evaluation of tolerability as reported by the participant was done on a 4-point verbal rating scale at each follow-up visit **How was compliance assessed:** tablet count	**Risk factors:** >1 NSAID: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** Panacea Biotec **Affiliation of contact author:** MAM College, New Delhi, India **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** none **Other:** 10 participants kept in trial for 24 weeks and had MRI, Table 1 appears inaccurate; design identical with study by Sharma[44]

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Sharma, 1999[44] **Location:** All India Institute of Medical Sciences, New Delhi, India	**Method of randomisation:** 'randomly assigned', stratified into 2 groups (participants belonging to functional class II were chosen for MRI evaluation, *n* = 14), central computer **Allocation concealment:** unclear **Baseline comparability:** no **Participant blinding:** yes **Assessor blinding:** no **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** no baseline endoscopy performed, no further details **Type and duration of arthritis (months):** OA: a 6–144, b 6–140 **Age:** a 52.3, b 50.2 **Sex:** M/F: a 10/18, b 9/12 **Inclusion criteria:** 42–80 years, newly diagnosed OA (knee) for 6 months or longer (ACR criteria with clinical and radiological confirmation), Steinbrocker functional capacity of class I, II or III (diagnosis required at least 3 historical criteria and at least 1 of the radiological findings to be present: history of pain aggravated by motion and at least partly relieved by rest, limitations of the range of movement, inactivity stiffness, tenderness on pressure, synovitis indicative of OA by joint fluid analysis when effusion present, radiology showing joint space narrowing, subchondral bony sclerosis (eburnation), bone cysts, gross deformity and subluxation and/or loose bodies). **Exclusion criteria:** receiving antineoplastic agents, corticosteroids, gold salts, penicillamine, colchicine, anticoagulants, hydantoin, antidiabetic drugs, antimalarials within 1 month preceding the study or at time of inclusion, other types of arthritic conditions, scheduled for hospitalisation or bed rest or for joint replacement surgery because of arthritis with evidence of active GI disease, pregnant and nursing women	**Comparison:** nimesulide (b) vs piroxicam (a) **Duration:** 8 weeks **Interventions:** b, nimesulide 200 mg/? mg (100 mg ×2 daily); a, piroxicam 20 mg/10–30 mg (in the morning plus identical placebo in the evening) **Other medication:** no other NSAIDs permitted antineoplastic agents, corticosteroids, gold salts, penicillamine, colchicine, anticoagulants, hydantoin, antidiabetic drugs, antimalarials excluded **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol administered **Participant education:** not stated **Washout:** yes, 15 days for prior NSAIDs during which identical placebo was administered **Number and frequency of visits:** 5 (0, 2, 4, 6 and 8 weeks)	**Allocated:** a 40, b 25 **Completed:** a 28, b 21 **Drop-out:** a 12, b 4 **Assessed:** a 28, b 21 **Outcomes reported:** mortality, symptomatic ulcers, serious cardiovascular or renal illness, (extra data) serious GI complications, GI symptoms, GI drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** tablet count, participants who didn't take study medication for more than 3 days were considered as drop-outs	**Risk factors:** concomitant use of anticoagulants: a 0, b 0 corticosteroids; a 0, b 0 >1NSAIDs: a 0, b 0 **FUNDING** **Funded by:** Panacea Biotec **Affiliation of contact author:** Institute of Human Behaviour and Allied Sciences, Delhi, India **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 1 or 5 authors employed by Panacea Biotec **Other:** 11 participants kept in trial for 24 weeks and had MRI, design identical with study by Roy[134]

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Zgradie, 1999[135] **Location:** Yugoslavia Military Medical Academy, Belgrade and University of Prishtina	**Method of randomisation:** 'randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** unclear **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy **Type and duration of arthritis (years):** OA, no further details **Age:** 18–80 **Sex:** M/F: a 44/46, b 34/56 **Inclusion criteria:** OA of the hip, knee or lumbar spine, 18–80 years, moderate to marked evident symptoms of OA **Exclusion criteria:** no details	**Comparison:** nimesulide (b) vs diclofenac sodium (a) **Duration:** 4 weeks **Interventions:** b, nimesulide 200 mg/? mg (100 mg ×2 daily); a, diclofenac 150 mg/75–150 mg (50 mg ×3 daily) **Other medication:** no details **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 3 (0, 2 and 4 weeks)	**Allocated:** a 90, b 90 **Completed:** unclear **Drop-out:** unclear **Assessed:** unclear **Outcomes reported:** GI symptoms, GI drop-outs **How were adverse events assessed:** 'did you experience any unpleasant sensation during the last 2 weeks?' If yes, then participants asked to evaluate degree of that adverse event and derive final evaluation of the drug tolerance **How was compliance assessed:** not stated	**Risk factors:** no details **FUNDING** **Funded by:** unclear **Affiliation of contact author:** Yugoslavia Military Medical Academy, Belgrade **Affiliation of statistician:** unclear **Affiliation of study administrator:** Panacea Biotec **No. of authors employed by sponsor:** none

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Patel, 2000[136] **Location:** Seth GS Medical College, Mumbai, India	**Method of randomisation:** 'randomly allotted' **Allocation concealment:** unclear **Baseline comparability:** no regarding age **Participant blinding:** unclear **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** no baseline endoscopy performed, no further details **Type and duration of arthritis (years):** RA: a 16, b 15 OA: a 24, b 22 **Age:** a 45.4, b 51.4 **Sex:** M/F: a 35/31, b 32/29 **Inclusion criteria:** adults, articular rheumatic disorders (OA or RA) or non-articular conditions such as lumbago, sciatica and other subacute/chronic musculoskeletal conditions **Exclusion criteria:** known hypersensitivity to study drugs, acid peptic disease, severe hepatic and/or renal disease, pregnancy, corticosteroid therapy for any other condition	**Comparison:** meloxicam (b) vs diclofenac subsyde CR (a) **Duration:** 28 days **Interventions:** b, meloxicam 7.5 mg OR 15 mg/7.5–15 mg daily; a, diclofenac subsyde CR 100 mg/75–150 mg daily **Other medication:** no details **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 7 (0, 1, 3, 7, 14, 21 and 28 days)	**Allocated:** unclear **Completed:** unclear **Drop-out:** unclear **Assessed:** a 66, b 61 **Outcomes reported:** GI symptoms **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** unclear **Affiliation of contact author:** Seth GS Medical College, Mumbai, India **Affiliation of statistician**: unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** unclear **Other:** dosage of diclofenac arm not stated in study but in advertisement following study

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Yocum, 2000[137] **Location:** 61 study centres in USA	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** no **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** high	**Baseline GI status:** participants excluded if upper GI perforations, ulcers or peptic ulcer bleeding in 6 months prior to enrolment **Baseline NSAID status:** all participants were required to be current NSAID users, mean duration of NSAID use: a 3.9 years, b 3.8 years, c 3.8 years **Type and duration of arthritis (years):** OA: a 9, b 8 c 7 **Age:** a 63.0, b 62.4, c 64.3 **Sex:** M/F: a 49/104, b 57/97, c 56/100 **Inclusion criteria:** current NSAID user, 40 years or more, at least 3-month history of OA (hip or knee) confirmed by X-ray and clinical signs and symptoms, and pain on movement of the target joint; NSAID-free period of at least 3 days during which flare was required (defined as worsening of disease activity from initial screening that met the following criteria: at least 1 grade deterioration in the investigator global assessment of disease activity, an increase of 10 mm or greater on a 100 mm VAS for the patient global assessment of disease activity, and an increase greater than 35 mm on a 100 mm VAS in the patient overall assessment of pain **Exclusion criteria:** intolerance of any NSAID, aspirin, analgesic or antipyretic or any disease that could interfere with evaluation of efficacy or safety, abnormal renal, haematological or hepatic function, history of bleeding disorder or current therapy with an anticoagulant, recent (2 months) use of corticosteroids, treatment with intra-articular injections of hyaluronic acid in prior 3 months, long-term use of GI medications (H_2 blockers, misoprostol, PPIs) that could not be discontinued, history of narcotic and/or alcohol abuse	**Comparison:** meloxicam (b, c) vs diclofenac (a) **Duration:** 12 weeks **Interventions:** b: meloxicam 7.5 mg/7.5–15 mg (once in the morning after food); c, meloxicam 15 mg/7.5–15 mg (once in the morning after food); a, diclofenac 100 mg/75–150 mg (50 mg ×2 daily morning and evening after food), double dummies used **Other medication:** anticoagulants, corticosteroids, intra-articular injections of hyalurinate, H_2RAs, misoprostol and PPIs were not permitted **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** yes, at least 3 days for NSAIDs **Number and frequency of visits:** 5 (0, 2, 4, 8 and 12 weeks)	**Allocated:** a 153, b 154, c 156 (5 participants missing from 5 arms) **Completed:** a 108, b 101, c 107 **Drop-out:** a 45, b 53, c 49 **Assessed:** a 153, b 154, c 156 **Outcomes reported:** mortality, serious GI complications, symptomatic ulcers, serious cardiac or renal illness, GI symptoms, GI drop-outs **How were adverse events assessed:** recorded incidence, duration and intensity and relation to study drug, need for treatment and action taken **How was compliance assessed:** not stated	**Risk factors:** history of bleeds (not in previous 6 months): a 16, b 11, c 8 concomitant use of anticoagulants: a 0, b 0 corticosteroids: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** Boehringer Ingelheim **Affiliation of contact author:** University of Arizona, USA **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 2 of 6 authors employed by Boehringer Ingelheim **Other:** placebo arm and meloxicam 3.75 mg daily arm were excluded from analyses

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Chang, 2001[37] **Location:** Tri Service General Hospital, Taiwan	**Method of randomisation:** 'consecutively randomised' central computer and central personnel **Allocation concealment:** adequate **Baseline comparability:** no **Participant blinding:** yes **Assessor blinding:** yes **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and excluded participants with peptic ulcers **Type and duration of arthritis:** OA: a 5.9, b 2.8 **Age:** a 63.1 (36–77), b 60.8 (45–78) **Sex:** M/F: a 9/27, b 4/32 **Inclusion criteria:** 18 years or more with a confirmed OA (knee) of at least 3 months' duration, defined clinically and radiographically (knee pain on most days of the previous month with periarticular or referred pain excluded on examination, morning stiffness of less than 30 minutes' duration plus presence of osteophytes radiographically plus crepitus or 50 years or more, required continuous NSAID therapy for duration of trial **Exclusion criteria:** endoscopy-detected peptic ulceration, treatment with any study drug in previous 4 weeks, pregnancy or lactation, history of gastric, duodenal or small intestine surgery, severe cardiac, hepatic, renal, haematological or metabolic disease, cancer, mental disturbance, ulcerative colitis, bronchial asthma inducible by aspirin or other NSAIDs, known hypersensitivity to analgesics, antipyretics or NSAIDs, concomitant treatment with anticoagulants, including heparin and aspirin, concomitant intake of NSAIDs, including aspirin even in low doses, concomitant treatment with lithium, hydantoins, clinically significant abnormal laboratory investigations, treatment with corticosteroids (including intra-articular injections) in previous month or during study, treatment with 4 g/day or more paracetamol, any concomitant disease which might lead to premature termination of study, any other disease that would interfere with the evaluation of efficacy and safety	**Comparison:** meloxicam (b) vs piroxicam (a) **Duration:** 4 weeks **Interventions:** b, meloxicam 7.5 mg/7.5–15 mg (once daily); a, piroxicam 20 mg/10–30 mg (once daily), double dummies used **Endoscopy:** (0 and at 4 weeks) **Other medication:** antacid (antagel) was prescribed for both arms throughout the trial, anticoagulants, concomitant intake of NSAIDs, lithium, hydantoins, corticosteroids (including intra-articular injections) treatment with 4 g/day or more paracetamol excluded **Aspirin allowed:** no **Analgesic allowed:** yes, paracetamol distributed, maximum 4 g/day **Participant education:** not stated **Washout:** yes, 7 days for NSAIDs and anti-ulcer drugs **Number and frequency of visits:** 2 (0 and 4 weeks)	**Allocated:** a 36, b 36 **Completed:** a 27, b 26 **Drop-out:** a 9, b 10 **Assessed:** a 36, b 36 **Outcomes reported:** mortality, serious GI complications, symptomatic ulcers, (extra data) serious cardiovascular or renal illness, GI symptoms, endoscopy, GI withdrawals **How were adverse events assessed:** not stated **How was compliance assessed:** tablet count, not reported	**Risk factors:** concomitant use of anticoagulants: a 0, b 0 corticosteroids: a 0, b 0 >1 NSAIDs: a 0, b 0 CVD: a 0, b 0 diabetes: a 0, b 0 renal/hepatic disease: a 0, b 0 **FUNDING** **Funded by:** supported in part by grants from NSC, drugs provided by Boehringer Ingelheim **Affiliation of contact author:** Tri Service General Hospital, Taiwan **Affiliation of statistician:** National Cheng-Kung University, Taiwan **Affiliation of trial administrator:** Genelabs Biotech **No. of authors employed by sponsor:** none

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Kriegel, 2001[138] **Location:** 37 centres in Germany and The Netherlands	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy performed but active GI disease excluded **Type and duration of arthritis (years):** OA: a 4.1, b 4.7 **Age:** a 65.0 (44–80), b 64.0 (42–81) **Sex:** M/F: a 47/140, b 57/126 **Inclusion criteria:** outpatients, 45–80 years, history of OA (knee or hip) for at least 6 months, moderate or severe pain on a four-point scale (0 = no pain, 1 = slight, 2 = moderate, 3 = severe), radiographic evidence of chronic OA in the affected joint documented in previous 12 months and severity of disease between 5 and 12 on the Lequesne functional index (range 0–26) **Exclusion criteria:** acute OA (unable to walk) and/or requiring arthroplastic surgery during the study, treatment with intra-articular corticosteroids in the 3 weeks before study start or use of systemic corticosteroids in the previous week, history of or presence of significant GI disease, presence of other severe concomitant diseases, use of anticoagulant medication	**Comparison:** nimesulide (b) vs naproxen (a) **Duration:** 52 weeks **Interventions:** b, nimesulide 200mg/? mg (100 mg ×2, morning and evening, daily); a, naproxen 750 mg/500–1250 mg (250 mg ×3, 1 morning and 2 evening), double dummies used **Other medication:** other NSAIDs, analgesics, anticoagulants, prophylactic treatment for peptic ulcer, myorelaxants, other treatment for OA, corticosteroids not allowed **Aspirin allowed:** not stated **Analgesic allowed:** yes, paracetamol **Participant education:** not stated Washout: not stated **Number and frequency of visits:** 10 (0, 2, 4, 8, 12, 18, 26, 34, 42 and 52 weeks)	**Allocated:** a 187, b 183 **Completed:** unclear **Drop-out:** unclear **Assessed:** a 187, b 183 **Outcomes reported:** GI symptoms, anaemia **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** concomitant use of anticoagulants: a 0, b 0, corticosteroids: a 0, b 0 >1 NSAIDs: a 0, b 0 **FUNDING** **Funded by:** Helsinn Healthcare **Affiliation of contact author:** Helsinn Healthcare **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 2 of 7 authors employed by Helsinn Healthcare, Switzerland

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Furst, 2002[139] **Location:** multicentre, USA	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy, no further details **Type and duration of arthritis:** RA, a 10.3, b 10.3, c 10.2, d 9.6 **Age:** a 54.7, b 56.3, c 55.6, d 56.7 **Sex:** M/F: a 40/141, b 37/138, c 45/139, d 47/130 **Inclusion criteria:** 18 to 80 years, currently using NSAID therapy for RA, and met at least 3 of the following: 6 or more tender joints, 3 or more swollen joints, patient's assessment of pain 20 mm or more on a 100 mm VAS, morning stiffness lasting at least 45 minutes, ESR more than 22 mm or C-reactive protein more than 1.2 mg/dl; could be taking and continue to take DMARD initiated at least 3 months prior to trial and/or prednisone 10 mg/day or less and stable for at least 3 months prior to trial, if retained stable dose throughout trial; allowed diclofenac as preceding NSAID, a flare with 3 or more of the 5 criteria was observed within 2 weeks of washout: worsening of at least 1 grade from screening on investigator's global assessment of disease activity, worsening of 10 mm or more from screening on the 100 mm VAS patient global assessment of disease activity, worsening of 10 mm or more from screening on the 100 mm VAS patient assessment of pain, 20% or more increase compared with screening visit in the number of swollen joints Exclusion criteria: no details	**Comparison:** meloxicam (b, c, d) vs diclofenac (a) **Duration:** 12 weeks **Interventions:** b, meloxicam, 7.5 mg/7.5–15 mg daily, c, meloxicam 15 mg/7.5–15 mg daily, d, meloxicam 22.5 mg/7.5–15mg daily; a, diclofenac 150 mg/75–150 mg (75 mg ×2 daily) **Other medication:** intra-articular steroids prohibited **Aspirin allowed:** not stated **Analgesic allowed:** yes, acetaminophen (but not within 12 h of clinic visit) **Participant education:** not stated **Washout:** flare needed to be observed within 2 weeks of discontinuing NSAIDs prior to start of study **Number and frequency of visits:** 4 (0, 4, 8 and 12 weeks)	**Allocated:** a 181, b 175, c 184, d 177 **Completed:** a 128, b 105, c 121, d 119 **Drop-out:** a 53, b 70, c 63, d 58 **Assessed:** a 180, b 174, c 184, d 177 **Outcomes reported:** mortality, serious GI complications, symptomatic ulcers, QoL, GI symptoms, occult bleeding, GI drop-outs **How were adverse events assessed:** diary cards **How was compliance assessed:** not stated	**Risk factors:** history of PUBs: a 18, b 21, c 16, d 19 concomitant use of corticosteroids: a 53, b 57, c 65, d 47 **FUNDING** **Funded by:** Boehringer Ingelheim Pharmaceuticals **Affiliation of contact author:** Virginia Mason Research Center, Seattle, WA, USA **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 2 or 8 authors employed by Boehringer Ingelheim Pharmaceuticals **Dose:** meloxicam 22.5 mg daily arm above recommended dose **Other:** 1 patient in diclofenac arm received intra-articular injection of steroid during study

(f) H_2RA plus NSAID versus PPI plus NSAID

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Yeomans, 1998[140,162,165,192] ASTRONAUT **Location:** 73 centres in 15 countries, including UK	**Method of randomisation:** 'randomly assigned' in blocks of 2 per site **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** endoscopy performed following healing phase for ulcers had to show treatment success defined as the disappearance of ulcer and the presence of fewer than 5 erosions in the stomach, fewer than 5 erosions in the duodenum and not more than mild dyspeptic symptoms **Type and duration of arthritis (years):** RA: c 99, b 88 OA: c 67, b 71 Psoriatic arthritis: a 16, b: 11 AS: c 11, b 12 Others: c 11, b 18 Combination: c 6, b 15 **Age:** c: 56 (31–78), b 56 (20–80) **Sex:** M/F: c 64/146, b 66/149 **Inclusion criteria:** 18–85 years, any condition requiring continuous therapy with NSAIDs above specified therapeutic doses (no maximum dose), and not more than 10 mg of prednisolone or its equivalent per day (50 mg/day diclofenac, 50 mg/day indomethacin, 500 mg/day naproxen); following endoscopy, those found to have any or all of the following were included: ulcers 3 mm or more in diameter, more than 10 erosions in the stomach, more than 10 erosions in the duodenum, successful treatment during healing phase, using therapeutic doses of NSAIDs at least 5 days per week **Exclusion criteria:** neck instability that would compromise endoscopy, concurrent erosive or ulcerative oesophagitis, pyloric stenosis, major active GI bleeding, or disorders that might modify the absorption of the drug, no abnormalities in laboratory tests regarded as clinically important by the investigator	**Comparison:** omeprazole plus mixed NSAIDs (b) vs ranitidine plus mixed NSAIDs (c) **Duration:** 26 weeks **Interventions:** c, ranitidine 300 mg/150–300 mg (150 mg ×2 daily); b, omeprazole 20 mg/20 mg (20 mg × daily) **NSAIDs:** b + c: naproxen: 16% indomethacin: 23% diclofenac: 29% **Endoscopy:** 1, 3 and 6 months **Other medication:** no details **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 4 (0, 1, 3 and 6 months)	**Allocated:** unclear **Completed:** unclear **Drop-out:** b 30, c: 29 **Assessed:** b 210, c: 215 **Outcomes reported:** serious GI complications, endoscopic ulcers, total drop-out **How were adverse events assessed:** participants asked standardised questions regarding overall upper GI symptoms and dyspeptic symptoms in the previous 7 days and these were graded as absent, mild, moderate or severe **How was compliance assessed:** returned medication, result not reported	**Risk factors:** all participants had recent history of ulcers and/or erosions **FUNDING** **Funded by:** Astra Hassle **Affiliation of contact author:** University of Melbourne, but also serves as consultant for Searle Australia **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** unclear **Other:** ?0/8 main authors

(g) H_2RA plus NSAID versus misoprostol plus NSAID

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Valentini, 1995[141] **Location:** Italy	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** unclear, insufficient information **Participant blinding:** no **Assessor blinding:** yes, endoscopist blinded **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and excluded patients with more than 1 petechia or area of haemorrhage or erosion; also excluded patients with history of peptic ulcer disease normal mucosa: a 28, b 28 Lanza score of 1: a 2, b 3 **Type and duration of arthritis (years):** Not applicable – cancer patients **Age:** a 59.8 (37–82), b 59.2 (21–80) **Sex:** M/F: a: 12/14, b 10/13 **Inclusion criteria:** patients who complained of cancer pain and who needed high-dose (200–300 mg/day) treatment with oral diclofenac; in good physical condition (Karnofsky performance status of 70 or more) **Exclusion criteria:** history of peptic ulcer disease, GI malignancy, GI surgery, bleeding diathesis, receiving treatment with other NSAIDs or gastric antisecretory drugs, baseline endoscopy score of more than 1 (1 petechia or area of haemorrhage or erosion)	**Comparison:** misoprostol plus diclofenac (b) vs ranitidine plus diclofenac (a) **Duration:** 4 weeks **Interventions:** b, misoprostol 400 μg /400–800 μg (200 μg ×2 daily); a, ranitidine 300 mg/150–300 mg (150 mg ×2 daily) **NSAIDs:** a+b: diclofenac 200–300 mg/75–150 mg diclofenac 200 mg: a 14, b 10 diclofenac 300 mg: a 12, b 13 **Endoscopy:** 4 weeks **Other medication:** chemotherapy, radiation, corticosteroids, antineoplastics allowed **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 5 (0, 1, 2, 3 and 4 weeks)	**Allocated:** a 31, b 30 **Completed:** a 26, b 23 **Drop-out:** a 5, b 7 **Assessed:** a 26, b 23 **Outcomes reported:** symptomatic ulcers, GI symptoms, endoscopic ulcers, GI drop-outs, total drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** history of ulcers: a 0, b 0 concomitant use of corticosteroids: a 4, b 4 >1 NSAID: a 0, b 0 **FUNDING** **Funded by:** unclear **Affiliation of contact author:** Centro di Riferimento Oncologico–Istituto Nazionale Tumori Centroeuropeo, Italy **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** unclear but at least 1 author employed by Searle Farmaceutici

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Raskin, 1996[142] **Location:** multicentre, USA	**Method of randomisation:** 'randomised' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and excluded patients with evidence of an ulcer of the gastric or duodenal mucosa, defined as a lesion of the mucosa of at least 3 mm in diameter with perceptible depth; also excluded patients with history of recurrent peptic ulcer disease (more than one episode in previous 12 months); had to be experiencing UGI pain thought to be related to their NSAID therapy **Baseline NSAID status:** mean duration NSAID use: a 9.2 months, b 9.8 months **Type of arthritis:** OA: a: 201, b 198; RA: a 40, b 48; both: a 13, b 7; other: a 13, b 16 **Age:** a: 60 (23–86), b 61 (23–85) **Sex:** M/F: a 116/153, b 126/143 **Inclusion criteria:** receiving daily doses of ibuprofen, piroxicam, naproxen, sulindac, tolmetin or indomethacin for one of the following conditions: osteoarthritis, rheumatoid arthritis, psoriatic arthritis, AS, or Reiters syndrome, and were expected to require at least 2 consecutive months of continued NSAID therapy; had to be experiencing UGI pain thought to be related to their NSAID therapy **Exclusion criteria:** patients with evidence of an ulcer of the gastric or duodenal mucosa, defined as a lesion of the mucosa of at least 3 mm in diameter with perceptible depth; patients with history of recurrent peptic ulcer disease (more than one episode in previous 12 months); any UGI tract malignancy or metastasis, pyloric or duodenal obstruction, acute hepatitis, pancreatitis, inflammatory bowel disease, bleeding diathesis; received misoprostol, H_2RA or any investigational drug or antineoplastic agent within 30 days prior to entry into study; renal impairment judged by investigator to be at risk of NSAID-induced renal failure; anticipated need for anti-ulcer medications other than study medication, antineoplastic drugs,	**Comparison:** misoprostol plus mixed NSAIDs (b) vs ranitidine plus mixed NSAIDs (a) **Duration:** 8 weeks **Interventions:** b, misoprostol 800 μg/400–800 μg (200 μg ×4 daily); a, ranitidine 300 mg/150–300 mg (150 mg ×2 daily), double dummy **NSAIDs:** ibuprofen: a 73, b 73 naproxen: a 78, b 65 piroxicam: a 54, b 56 sulindac: a 24, b 32 other: a 40, b 43 **Endoscopy:** 8 weeks **Other medication:** 28 × 600 mg antacid to be taken as required for relief of UGI pain were prescribed for first week only; anti-ulcer medications other than study medication, antineoplastic drugs, anticoagulants, prednisone greater than 7.5 mg/day, cyclophosphamide or methotrexate were excluded **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 3 (0, 4 and 8 weeks)	**Allocated:** a 269, b 269 **Completed:** a 219, b 206 **Drop-out:** a 50, b 63 **Assessed:** a 269, b 269 **Outcomes reported:** mortality, serious GI complications, serious cardiovascular or renal illness (extra data), GI symptoms, endoscopic ulcers, GI drop-outs, total drop-outs **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** history of ulcers: a 56, b 62 **FUNDING** **Funded by:** GD Searle **Affiliation of contact author:** university of Miami, USA **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 1 of 6

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Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
		anticoagulants, prednisone greater than 7.5 mg/day, cyclophosphamide or methotrexate during the course of the study			
Yildiz, 1996[143] **Location:** Turkey	**Method of randomisation:** 'divided randomly' **Allocation concealment:** unclear **Baseline comparability:** unclear **Participant blinding:** unclear **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and did not exclude any endoscopic score (1 person in each group had ulcer at baseline and excluded from analyses by reviewers) Type and duration of arthritis (years): 'rheumatic symptoms', no further details **Age:** a 39.2 (19–70) b 37.0 (20–55) **Sex:** M/F: a 1/15, b 4/12 **Inclusion criteria:** taking long-term NSAIDs for their primary rheumatic disease, any endoscopic score at baseline **Exclusion criteria:** no details	**Comparison:** famotidine plus naproxen sodium and indomethacin (b) vs misoprostol plus naproxen sodium and indomethacin (a) **Duration:** 2 months **Interventions:** b, famotidine 40 mg/20 mg (20 mg ×2 daily, a, misoprostol 400 μg/ 400–800 μg (200 μg ×2 daily) **NSAIDs:** a+b: naproxen sodium 1100 mg/500–1250 mg (550 mg ×2 daily) plus indomethacin suppositories 100 mg/100–200 mg (100 mg ×1 daily) **Endoscopy:** 1 and 2 months **Other medication:** no details **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 3 (0, 1 and 2 months)	**Allocated:** unclear **Completed:** a 16, b 16 **Drop-out:** unclear **Assessed:** a 15, b 15 **Outcomes reported:** endoscopy **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** no details **FUNDING** **Funded by:** unclear **Affiliation of contact author:** unclear **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** unclear **Other:** study in Turkish, only English abstract and endoscopy table extracted

(h) PPI plus NSAID versus misoprostol plus NSAID

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Hawkey, 1998b[62,65,160–164] OMNIUM **Location:** 93 centres in 14 countries including UK and USA	**Method of randomisation:** 'randomly assigned', randomisation phase not formally balanced according to treatment assignment in the healing phase **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** endoscopy performed and excluded participants without treatment success following 4–8-week healing phase (omeprazole 20 mg/day vs omeprazole 40 mg/day vs misoprostol 200 μg/day); treatment success defined as absence of ulcers in the stomach or duodenum and the presence of fewer than five gastric erosions, fewer than five duodenal erosions and not more than mild symptoms of dyspepsia (corresponded to a 2-point reduction in Lanza scale from grade 4 to grade 2) **Type of arthritis:** OA: a 70, b 129, c 142 RA: a 56, b 107, c 118 other: a 25, b 33, c 30 combination: a 5, b 5, c 6 **Age:** a 57 (20–80), b 58 (23–79), c 58 (23–85) **Sex:** M/F: a 48/107, b 101/173, c 118/178 **Inclusion criteria:** 18–85 years of age and who had any condition requiring continuous treatment with oral or rectal NSAIDs above a predetermined minimal dose (no maximum dose); treatment success defined as absence of ulcers in the stomach or duodenum and the presence of fewer than five gastric erosions, fewer than five duodenal erosions and not more than mild symptoms of dyspepsia (corresponded to a 2-point reduction in Lanza scale from grade 4 to grade 2) **Exclusion criteria:** concurrent reflux oesophagitis at stage 3 or 4 according to the Savary–Miller classification, clinically important GI bleeding, pyloric stenosis, history of gastric surgery or GI disorders that might impair the absorption of the study drugs	**Comparison:** misoprostol plus mixed NSAIDs (c) vs omeprazole plus mixed NSAIDs (b) vs placebo plus mixed NSAIDs (a) **Duration:** 6 months **Interventions:** c, misoprostol 400 μg/400–800 μg/day (200 μg ×2 daily; b, omeprazole 20 mg/20 mg (20 mg ×1 daily); a, identical placebo **Endoscopy:** 1, 3 and 6 months **NSAIDs:** (minimum and mean dose): diclofenac (50 mg, 129 mg/day) 23% total participants ketoprofen (100 mg, 137 mg) 16% total participants naproxen (500 mg, 844 mg) 22% total participants **Other medication:** patients could enter the study if they were taking glucocorticoids at a dose ≤10 mg of prednisolone (or its equivalent) **Aspirin allowed:** not stated **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 4 (0, 1, 3 and 6 months)	**Allocated:** a 155, b 274, c 296 (7 participants unaccounted for) **Completed:** a 139, b 242, c 247 **Drop-out**: a 16, b 33, c 50 **Assessed:** a 155, b 275, c 297 **Outcomes reported:** serious GI complications, QoL, endoscopic ulcers, total drop-out **How were adverse events assessed:** participants asked if had specific dyspeptic symptoms during the last 7 days and to describe any UGI symptoms on that day, symptoms graded, also symptom diary card used during initial 4 weeks **How was compliance assessed:** tablet count, result not reported	**Risk factors:** 63–64% of participants in each group had recent history of ulcers (remaining participants had recent history of more than 10 gastric or duodenal erosions) **FUNDING** **Funded by:** Astra Hassle, Sweden **Affiliation of contact author:** Nottingham Gastrointestinal Trials Service, University Hospital Nottingham, UK **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** One author serves as a consultant for Searle, Australia **Other:** participants were discontinued and excluded from analysis if developed more than 10 erosions or more than moderate dyspepsia or adverse events

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Graham, 2002[64,214] **Location:** 63 centres in North America	**Method of randomisation:** 'randomly assigned in blocks of 4', 'randomisation schedule was generated by a statistical specialist who was not involved in the trial design, the randomisation was coded and stored in sealed envelopes' **Allocation concealment:** adequate **Baseline comparability:** yes Participant blinding: yes for PPI and placebo groups, no for misoprostol group **Assessor blinding:** yes (statistician), endoscopist also blinded **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** low	**Baseline GI status:** baseline endoscopy performed, patients had to be without *H. pylori*, have history of endoscopically documented gastric ulcer with or without coexisting duodenal ulcer or GI bleeding (2/3 participants had previously completed participation in a healing trial for NSAID-associated gastric ulcer); excluded patients with gastric or duodenal ulcer crater at least 5 mm in diameter or more than 25 erosions or erosive reflux oesophagitis **Baseline NSAID status:** treatment with stable full therapeutic doses of an NSAID for at least the previous month (except nabumetone or aspirin at 1300 mg/day or more) **Type and duration of arthritis (years):** no details **Age:** a 60.5, b 59.4, c 61.6, d 60.2 **Sex:** M/F: a 46/87, b 43/91, c 50/86, d 48/84 **Inclusion criteria:** 18 years or older, history of endoscopically documented gastric ulcer with or without duodenal ulcer or GI bleeding, treatment with stable full therapeutic doses of an NSAID (with the exception of nabumetone or aspirin at 1300 mg/day or more; low-dose aspirin for cardiovascular protection was permitted) for at least the previous month **Exclusion criteria:** positive for *H. pylori*, gastric or duodenal ulcer crater of 5 mm or more or severe erosions defined as more than 25 erosions, erosive reflux oesophagitis, use of PPI, misoprostol or H_2RAs within 24 h of start of study	**Comparison:** lansoprazole (c, d) plus mixed NSAIDs vs misoprostol (b) plus mixed NSAIDs vs mixed NSAIDs (a) Duration: 12 weeks **Interventions:** d, lansoprazole 30 mg/15–30 mg (30 mg ×1 daily); c, lansoprazole 15 mg/15–30 mg (15 mg ×1 daily); b, misoprostol 800 μg/400–800 μg (200 μg ×4 daily); a, placebo **NSAID use:** ibuprofen: 40% naproxen: 35% diclofenac: 32% aspirin or aspirin combinations: 22% piroxicam: 17% other NSAIDs: 34% endoscopy: 1, 2 and 3 months **Other medication:** antacid provided for use as needed for symptom relief, instructed to avoid antiulcer medication other than study medication, ulcerogenic medication and agents that alter haemostasis **Aspirin allowed:** yes **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** ?4 (0, 4, 8 and 12 weeks)	**Allocated:** a 134, b 134, c 136, d 133 **Completed:** a 111, b 111, c 122, d:114 **Drop-out:** a 23, b 23, c 14, d 19 **Assessed:** a 133, b 134, c 136, d 132 **Outcomes reported:** mortality, serious GI complications, serious cardiovascular or renal illness, (extra data) endoscopic ulcers, total drop-outs **How were adverse events assessed:** participants kept diary of daily symptoms and asked direct questions at each visit **How was compliance assessed:** tablet count, 90% in groups a, c and d were compliant compared with 73% in group b (misoprostol)	**Risk factors:** history of ulcers: all participants **FUNDING** **Funded by:** TAP Pharmaceutical Products **Affiliation of contact author:** Veterans Affairs Medical Center, Houston, TX, USA **Affiliation of statistician:** Abbott Laboratories **Affiliation of study administrator:** TAP Pharmaceutical Products **No. of authors employed by sponsor:** 2 of 7

continued

(i) PPI plus NSAID versus Cox-2 coxib NSAID

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Chan, 2002[236] **Location:** Endoscopy centre, Prince of Wales Hospital, Hong Kong, China	**Method of randomisation:** 'randomly assigned', computer-generated list of random numbers, independent staff assigned treatments according to consecutive numbers in sealed envelopes' **Allocation concealment:** adequate **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** yes, blinded endoscopist and adjudication committee **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** low	**Baseline GI status:** baseline endoscopy performed, and patients excluded who did **not** present with ulcer bleeding, inclusion criteria were ulcer healing confirmed by follow up endoscopy, negative test for *H. pylori* (or successful eradication) **Type and duration of arthritis (years):** OA: a 127, b 123 RA: a 2, b 5 other: a 14, b 16 **Age:** a 68.8, b 66.5 **Sex:** M/F: a 65/78, b 61/83 **Inclusion criteria:** ulcer healing as confirmed by follow-up endoscopy, negative test for *H. pylori* or successful eradication of *H. pylori* according to histological findings, anticipated regular use of NSAIDs for the duration of the trial **Exclusion criteria:** concomitant use of anticoagulant agents or corticosteroids; history of gastric or duodenal surgery other than a patch repair; presence of erosive oesophagitis, gastric outlet obstruction, renal failure (defined by a serum creatinine level of more than 2.2 mg/dl), terminal illness or cancer	**Comparison:** celecoxib (b) vs diclofenac (extended release) plus omeprazole (a) **Duration:** 6 months **Interventions:** b, celecoxib 400 mg/200–400 mg (200 mg ×2 daily); a, diclofenac (extended release) 150 mg/75–150 mg (75 mg ×2 daily) + omeprazole 20 mg/20 mg (20 mg ×1 daily), diclofenac and celecoxib were identical-appearing red capsules, omeprazole and its placebo were identical-appearing green capsules **Other medication:** permitted to take antacids, non-NSAID analgesics, DMARDs; NSAIDs other than diclofenac, misoprostol, H_2RAs, sucralfate, PPIs other than omeprazole were prohibited **Aspirin allowed:** yes, 325 mg/day or less **Analgesic allowed:** yes, acetaminophen and non-NSAID analgesics **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 4 (telephone call at month 1, then visit at months 2, 4 and 6)	**Allocated:** a 143, b 144 **Completed:** a 124, b 123 **Drop-out:** a 19, b 21 **Assessed:** a 143, b 144 **Outcomes reported:** mortality, serious GI complications, symptomatic ulcers, serious cardiovascular or renal illness, GI symptoms, anaemia, GI drop-outs, total drop-outs **How were adverse events assessed:** observed or reported, direct telephone line for participants to report serious adverse events in between study visits **How was compliance assessed:** tablet count, 92% in each arm took at least 70% of study medication	**Risk factors:** history of bleeding ulcers: a 143, b 144 concomitant use of anticoagulants: a 0, b 0 corticosteroids: a 0, b 0 >1 NSAID: a 0, b 0 concurrent use of aspirin: a 18, b 9 **FUNDING** **Funded by:** Chinese University of Hong Kong and Health Services Research Centre of Hong Kong **Affiliation of contact author:** Prince of Wales Hospital, Hong Kong **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 0/12

(j) Misoprostol plus NSAID versus Cox-2 coxib NSAID

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Acevedo, 2001[144] **Location:** 21 investigative sites in Peru, Argentina, Canada, Columbia, Mexico, USA	**Method of randomisation:** 'randomised according to a computer-generated schedule and stratified according to history of ulcer or UGI bleeding' **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** yes ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** no baseline endoscopy performed, 7.1% (n = 17) arthrotec group (a) and 7.4% (n = 18) rofecoxib group (b) had prior history of UGI ulceration or bleeding **Type and duration of arthritis (years):** OA: a 8.5 (8.0), b 6.8 (6.0) **Age:** a 62.4, b 61.8 **Sex:** M/F: a 45/196, b 50/192 **Inclusion criteria:** at least 40 years of age, clinically established diagnosis of OA requiring regular NSAID treatment **Exclusion criteria:** inflammatory or post-traumatic arthritis; GI diseases associated with diarrhoea (such as irritable bowel disease); infectious disease; malabsorption; uncontrolled diabetes or other serious conditions (such as renal, cardiovascular, or hepatic disease); and/or a bleeding disorder; allergic to NSAIDs or paracetamol, had tested positive for faecal occult blood, had ever used misoprostol, were regular users of aspirin, had used corticosteroids in the previous month or had a history of sustained use of GI medication	**Comparison:** rofecoxib (b) vs arthrotec (a) **Duration:** 6 weeks **Interventions:** b, rofecoxib 12.5 mg/12.5–25 mg (12.5 mg ×1 daily); a, diclofenac 100 mg/75 mg–150 mg (50 mg ×2 daily) + misoprostol 400 μg/400 μg –800 μg (200 μg ×2 daily), matching placebo used **Other medication:** corticosteroids excluded **Aspirin allowed:** no **Analgesic allowed:** yes, paracetamol up to 2600 mg/day as required **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 4 (0, 2, 4 and 6 weeks)	**Allocated:** a 241, b 242 **Completed:** a 215, b 225 **Drop-out:** a 26, b 17 **Assessed:** a 241, b 242 **Outcomes reported:** GI symptoms, GI drop-outs, total drop-outs **How were adverse events assessed:** 'spontaneously reported' **How was compliance assessed:** no details	**Risk factors:** history of ulcers and/or bleeds: a 17, b 18 concomitant use of corticosteroids: a 0, b 0 CVD: a 0, b 0 Renal/hepatic disease: a: 0, b: 0 **FUNDING** **Funded by:** Merck Research Laboratories **Affiliation of contact author:** Merck **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 3 of 14

(k) Misoprostol plus NSAID versus Cox-2 preferential NSAID

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Roth, 1993[78] **Location:** 6 centres in the USA	**Method of randomisation:** 'randomised', participants assigned a treatment number that corresponded with treatment medication **Allocation concealment:** unclear **Baseline comparability:** no, misoprostol group contained younger participants and more with normal endoscopies **Participant blinding:** unclear **Assessor blinding:** yes **Intention-to-treat:** no ***A priori* sample size:** unclear **Summary risk of bias:** high	**Baseline GI status:** no more than 3 erosions at baseline endoscopy normal endoscopy: a 17, b 18, c 27 hyperemia: a 24, b 20, c 17 erosions: a 17, b 15, c 13 **Type and duration of arthritis:** OA: all participants, no other details **Age:** 60–64: a 15, b 17, c 22 65–74: a 34, b 32, c 35 ≥75: a 9, b 4, c 3 **Sex:** F/M: a 19/39, b 12/41, c 11/49 **Inclusion criteria:** OA aged 60 years or older, ACR functional class II or III, used an NSAID for at least 3 months before enrolment and expected to continue the use of this class of medication for at least 3 months **Exclusion criteria:** history of hypersensitivity reaction to any of the study drugs, inefficacy or intolerance to ibuprofen, history of MI within last 6 months, congestive heart failure, medically uncontrolled hypertension or arrhythmias, history of an ulcer or GI tract bleeding within 1 year of study entry, history of gastroduodenal or eosophageal surgery, significant lower bowel disease (including regional enteritis, ulcerative colitis, intestinal bypass surgery, frequently bleeding haemorrhoids), OA which required treatment with multiple NSAIDs within 3 months of enrolment, patients considered to be candidates for joint replacement during time of the study, patients who had received intra-articular steroid injections or oral steroids within 1 month of enrolment	**Comparison:** misoprostol plus ibuprofen (c) vs ibuprofen (b) vs nabumetone (a) **Duration:** 12 weeks **Interventions:** c, misoprostol 800 μg/400–800 μg (4× 200 μg daily) plus ibuprofen 2400 mg/600–2400 mg (4× 600 mg daily, administered concurrently with misoprostol); b, ibuprofen 2400 mg/600–2400 mg (4× 600 mg daily); a, nabumetone 1000 mg/500–2000 mg daily (no other details) **Endoscopy:** 0, 2, 6, 12 weeks and at early withdrawal **Other medication:** concomitant medication was allowed with the exception of anticoagulants, other anti-inflammatories, corticosteroids, immunosuppressant therapy, ulcer therapy (H_2RAs, sucralfate, long-term antacid therapy) **Aspirin allowed:** Not stated **Analgesic allowed:** paracetamol max. 12× 325 mg tablets in 24 h **Participant education:** not stated **Washout:** yes, 3–10 days during which administered placebo 3× daily **Number and frequency of visits:** 7 (0, 2, 4, 6, 8, 10 and 12 weeks)	**Allocated:** a 58, b 53, c 60 **Completed:** a 46, b 25, c 45 **Drop-out:** a 12, b 28, c 15 **Assessed for GI symptoms:** a 58, b 53, c 60 **Outcomes reported:** GI symptoms, endoscopic ulcers, anaemia, GI drop-outs **How were adverse events assessed:** participants asked if there had been any problems since last visit **How was compliance assessed:** tablet count	**Risk factors:** history of ulcers (1 year or more ago); a 10, b 14, c 14 all participants aged 60 years or more CVD: a 0, b 0 **FUNDING** **Funded by:** SmithKline Beecham Pharmaceuticals **Affiliation of contact author:** Arthritis Center, Phoenix, AZ, USA **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** unclear

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Agrawal, 1999[145] **Location:** Brazil, Canada, USA and Mexico	**Method of randomisation:** 'randomly assigned', stratified by *H. pylori* status **Allocation concealment:** unclear **Baseline comparability:** yes **Participant blinding:** yes **Assessor blinding:** unclear **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** baseline endoscopy performed and excluded patients with 10 or more gastric and/or duodenal erosions, participants had history of ulcers or erosions **Type and duration of arthritis (years):** OA: 10.3–11.0 years a 426, b 393 **Age:** a: 62.1 (32–90), b 61.8 (30–85) **Sex:** M/F a 132/294, b 138/255 **Inclusion criteria:** adults with OA hip or knee (ACR criteria) of at least 6 months duration, documented history of endoscopically confirmed gastric, pyloric-channel or duodenal ulcer of 10 or more erosions in the stomach or duodenum, experiencing OA symptoms ranked on a 5-point scale as fair, poor, very poor on both patient and physician global assessment of arthritis, as well as hip or knee pain on weight-bearing ranked as moderate, severe or very severe **Exclusion criteria:** active ulcer or more than 10 gastric and/or duodenal ulcers on baseline endoscopy, if participant had received NSAID or other analgesic within 3 days of enrolment, had taken corticosteroids (including intra-articular injections) or anticoagulants within 30 days of the first dose of any study medication or if they were expected to require corticosteroids or anticoagulants during the course of the study, any inflammatory arthritis other than OA, fibromylagia or acute joint trauma, anserina or trochanteric bursitis at the site of OA, if their alanine aminotransferase, aspartate aminotranferase or creatinine values were greater than 1.5 times the upper limit of normal, if they were scheduled to undergo arthroscopy or joint lavage of the index joint or joint	**Comparison:** arthrotec (b) vs nabumetone (a) **Duration:** 6 weeks **Interventions:** b, misoprostol 400 μg/400–800 μg (2× 200 μg daily) plus diclofenac 150 mg/75–150 mg (2× 75 mg daily) arthrotec 75; a, nabumetone 1500 mg/500–2000 mg (1× 1500 mg daily) **Other medication:** 6 × 600 mg aluminium hydroxide gel tablets per day for relief of UGI symptoms **Aspirin allowed:** yes, if dose no more than 325 mg per day and taken for 30 or more days before first dose of study medication **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** 3 days for NSAIDs, 30 days for corticosteroids or anticoagulants **Number and frequency of visits:** 2 (0 and 6 weeks) **Endoscopy:** (baseline and 6 weeks, or at earlier withdrawal)	**Allocated:** a 426, b 395 **Completed:** unclear **Drop-out:** unclear **Assessed for GI symptoms:** a 426, b 393 **Outcomes reported:** serious GI events, GI symptoms, endoscopic ulcers **How were adverse events assessed:** not stated **How was compliance assessed:** not stated	**Risk factors:** history of ulcers or erosions: all participants **FUNDING** **Funded by:** not stated **Affiliation of contact author:** Duke University Medical Center, USA **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 5/9 GD Searle **Other:** naproxen arm discontinued early owing to gastroduodenal ulcer rate. A further placebo arm is not reported here

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
		replacement surgery, if they had active GI disease (e.g. inflammatory bowel disease), if they had a history of gastric or duodenal surgery other than a simple oversew, if they had chronic or acute renal or hepatic disorder, a significant coagulation defect, a malignancy of any type, or a history of a malignancy or any other condition that precluded participation in the study			
Chan, 2001[146] **Location:** Endoscopy Centre, Prince of Wales Hospital, Hong Kong, China	**Method of randomisation:** 'randomly allocated, computer-generated list of random numbers, sealed packages of study medications in consecutive numbers dispensed by study nurse, medicines packed by local pharmacy so that neither patients nor investigators were aware of treatment assignment' **Allocation concealment:** adequate **Baseline comparability:** unclear **Participant blinding:** yes **Assessor blinding:** yes **Intention-to-treat:** no ***A priori* sample size:** yes **Summary risk of bias:** moderate	**Baseline GI status:** complete ulcer healing following 8 weeks of omeprazole 20 mg daily for bleeding peptic ulcers **Type and duration of arthritis (years):** OA: a 38, b 29; RA: a 1, b 3, no other details **Age:** a 74 (42–89), b 75 (43–92) **Sex:** M/F: a 15/30, b 17/28 **Inclusion criteria:** complete ulcer healing on endoscopy following 8 weeks of omeprazole 20 mg daily for bleeding peptic ulcers with NSAID treatment within 7 days before hospitalisation, had inadequate pain relief from simple analgesics before hospitalisations, negative for *h. pylori* **Exclusion criteria:** concomitant acid-suppressing drugs, steroids, anticoagulants or prophylactic low-dose aspirin, had undergone previous gastric surgery, had concurrent upper gastroduodenal diseases including erosive oesophagitis, grade II or above, oesophageal/gastric varices, gastric outlet obstruction, gastric cancer, had received *h. pylori* eradication therapy in the past, had renal impairment (serum creatinine >200 mmol/l) and were moribund, had underlying malignancy or were unable to return for follow-up	**Comparison:** naproxen plus misoprostol (b) vs nabumetone plus placebo misoprostol (a) **Duration:** 24 weeks **Interventions:** b, misoprostol 400 μg/400–800 μg (2 × 200 μg daily) plus naproxen 500–1000 mg/500–1250 mg (*n* = 12 took 1000 mg/day); a, placebo (2× daily) plus nabumetone 1000–1500 mg/500–2000 mg (*n* = 12 took 1500 mg/day) **Endoscopy:** baseline then repeated only if patients developed symptoms of recurrent ulcer bleeding or severe dyspepsia **Other medication:** not stated **Aspirin allowed:** no **Analgesic allowed:** not stated **Participant education:** not stated **Washout:** not stated **Number and frequency of visits:** 4 (0, 8, 16 and 24 weeks)	**Allocated:** unclear, 96 in total **Completed:** unclear **Drop-out:** unclear **Assessed for GI symptoms:** a 45, b 45 **Outcomes reported:** mortality, serious GI complications, symptomatic ulcers, serious cardiovascular or renal illness, GI symptoms **How were adverse events assessed:** not stated **How was compliance assessed:** tablet count, 80% or more (no more details) a 32/45, b 38/45	**Risk factors:** all had recent history of bleeding gastric and/or duodenal ulcers, major comorbid illness: a 27, b 29 **FUNDING** **Funded by:** Health Services Research Council Grant, Hong-Kong **Affiliation of contact author:** Chinese University of Hong Kong **Affiliation of statistician:** unclear **Affiliation of trial administrator:** unclear **No. of authors employed by sponsor:** 0/10?

(I) Cox-2 coxib NSAID versus Cox-2 preferential NSAID

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
Truitt, 2001[147] **Location:** 22 centres in Sweden, Denmark, Belgium, The Netherlands and Germany	**Method of randomisation:** 'randomised' by centralised computer-generated allocation schedule, stratified by low-dose aspirin use and study site **Allocation concealment:** unclear **Baseline comparability:** no, regarding duration of OA and history of ulcers or bleeds **Participant blinding:** yes **Assessor blinding:** yes, blinded investigator, laboratory testing at central laboratory **Intention-to-treat:** yes ***A priori* sample size:** yes **Summary risk of bias:** high	**Baseline GI status:** no baseline endoscopy performed but participants excluded if active GI bleeding in previous 3 months **Baseline NSAID status:** previous NSAID use: a 74.8%, b 75.4%, c 76.8% **Type and duration of arthritis (years):** OA: a 14.6, b 17.0, c 14.0 **Age:** a 83.1, b 83.3, c 83.8 **Sex:** M/F: a 41/74, b 41/77, c 24/31 **Inclusion criteria:** 80 years or more, clinical and radiographic criteria for the diagnosis of OA (knee or hip) (most painful joint designated as primary study joint), pain in the study joint to be present for at least 6 months, clinical symptoms had to be confirmed by the presence of radiographic findings (joint space narrowing in a hip, and joint space narrowing and osteophytes in a knee), ACR functional classes I, II or III, history of positive therapeutic benefit from NSAIDs (including salicylates) or acetaminophen, and to have taken therapy on 20 or more of the previous 30 days, required to score 24 or more on the 30-question (0–30) Mini–Mental Status Examination at screening, required to swallow a test dose of placebo without difficulty, flare following 3–5-day washout for those on previous NSAIDs, eligibility to enter washout required an initial Patient Global Assessment of Disease Status of less than 90 mm on a 100 mm VAS, from 0 = very well to 100 = very poor, eligibility for allocation required a post-washout Patient Global Assessment of Disease Status of 40mm or more; those who did not take pre-	**Comparison:** rofecoxib (b, c) vs nabumatone **Duration:** 6 weeks plus 7–10 days post-study assessment **Interventions:** b: rofecoxib 12.5 mg /12.5–25 mg (once daily); c, rofecoxib 25 mg/12.5–25 mg (once daily); a, nabumetone 1500 mg/500–2000 mg daily, double dummies used **Other medication:** not stated **Aspirin allowed:** yes, 325 mg daily or less permitted, a 32, b 38, c 23 **Analgesic allowed:** yes, acetaminophen 325 mg/day or less **Participant education:** not stated **Washout:** yes, 3–5 days for previous NSAIDs but not for those taking acetaminophen as NSAID **Number and frequency of visits:** 5 (0, 1, 2, 4 and 6 weeks)	**Allocated:** a 115, b 118, c 56 **Completed:** a 100, b 101. c 48 **Drop-out:** a 15, b 17, c 8 **Assessed:** a 115, b 118, c 56 **Outcomes reported:** serious GI complications, symptomatic ulcers, serious cardiovascular or renal illness, GI symptoms, occult bleeding, GI drop-outs **How were adverse events assessed:** participant interim histories, determination of adverse events was in the subjective opinion of the blinded investigator, events reviewed, rated by intensity and relationship to study treatment **How was compliance assessed:** not stated	**Risk factors:** history of PUBs: a 7, b 11, c 10 concomitant use of corticosteroids: a 0, b 0 history of angina: a 10, b 11, c 5 MI: a: 9, b 9. c 10 coronary artery disease: a 9, b 5, c:4 hypertension: a 56, b 55, c 27 **FUNDING** **Funded by:** Merck Research Laboratories **Affiliation of contact author:** Merck Research Laboratories **Affiliation of statistician:** unclear **Affiliation of study administrator:** unclear **No. of authors employed by sponsor:** 6 of 8 authors employed by Merck Research Laboratories **Other:** placebo group not data extracted

continued

Study identifier, location	Methods and validity	Participant characteristics	Intervention details	Outcome assessment	Risk factors, funding, other notes
		study NSAIDs but were taking pre-study acetaminophen were required to give consistent Patient Global Assessment of Disease Status (40 mm or more but less than 90 mm) at screening and baseline **Exclusion criteria:** prior history of inflammatory arthritis (including RA), acute ligamentous or meniscal injury to study joint within 18 months, or arthroscopy within 4 months, intra-articular or systemic corticosteroids within 3 months of study entry, other medical conditions or laboratory abnormalities which contraindicated use of NSAIDs or were potential confounders of safety evaluation, angina or congestive heart failure with symptoms at rest, serum creatinine more than 2.0 mg/dl or creatinine clearances 30 ml/minute or less, uncontrolled hypertension, active GI bleeding within 3 months, history of leukaemia, lymphoma or myeloproliferative disease, hypersensitivity to aspirin or NSAIDs, any one of three pre-allocation stool-guaiac tests being positive			

Appendix 7

Bias indicators

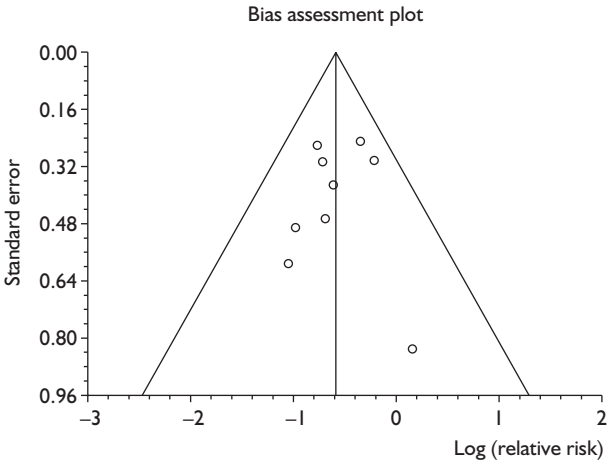
Funnel plots and related inferential methods were used to assess for evidence of small study effects, including publication bias.[34] These were carried out on StatsDirect software, using Egger and colleagues'[35] and Begg and Mazumdar's[36] tests. All of these methods have low power to detect small study effects (which may include bias) where there are few studies reporting the outcomes of interest.

(a) H_2RA versus placebo, endoscopic ulcers

Not enough studies reported symptomatic ulcers for this outcome to be used in assessment of bias.

Bias indicators

From regression of normalised effect versus precision (Egger and colleagues[35]): intercept (0 if unbiased) = –0.375 (approximate 95% CI = –2.429 to 1.680), $p = 0.679$. From Kendall's test on standardised effect versus variance (Begg and Mazumdar[36]): tau = –0.167, $p = 0.477$ (not robust, small sample).

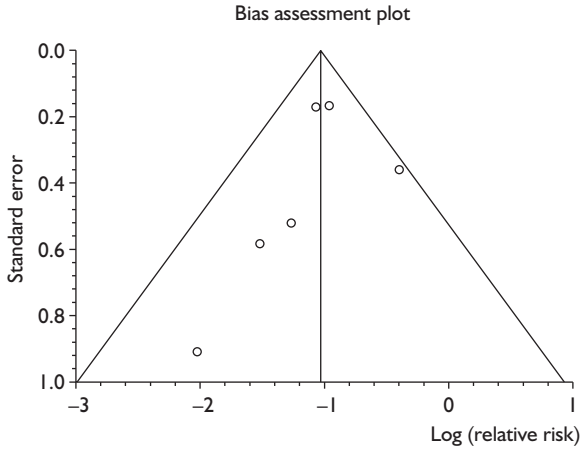


(b) PPI versus placebo, endoscopic ulcers

Not enough studies reported symptomatic ulcers for this outcome to be used in assessment of bias.

Bias indicators

From regression of normalised effect versus precision (Egger and colleagues[35]): intercept (0 if unbiased) = –0.619 (approximate 95% CI = –2.958 to 1.719) $p = 0.503$. From Kendall's test on standardised effect versus variance (Begg and Mazumdar[36]): tau = –0.733, $p = 0.0167$ (not robust, small sample).

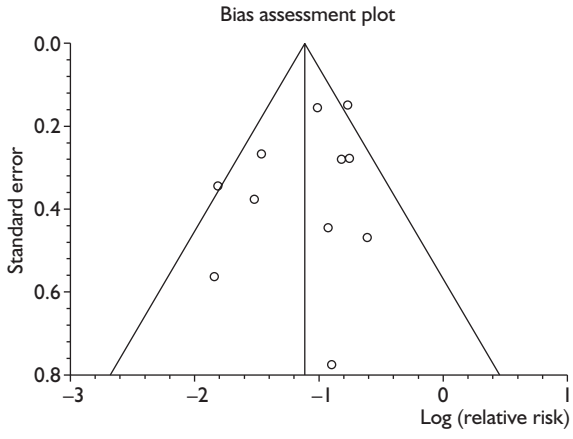


(c) Misoprostol versus placebo, endoscopic ulcers

Not enough studies reported symptomatic ulcers for this outcome to be used in assessment of bias.

Bias indicators

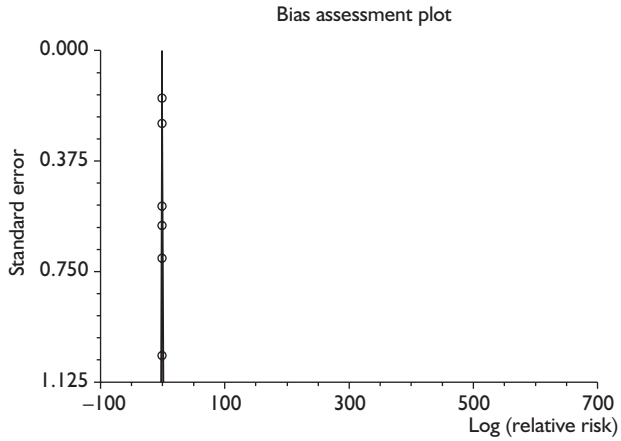
From regression of normalised effect versus precision (Egger and colleagues[35]): intercept (0 if unbiased) = –0.941699 (approximate 95% CI = –2.682789 to 0.799391), $p = 0.2559$. From Kendall's test on standardised effect versus variance (Begg and Mazumdar[36]): tau = –0.138462, $p = 0.5815$.



(d) Cox-2 coxibs NSAIDs versus Cox-1 NSAIDs, symptomatic ulcers

Bias indicators

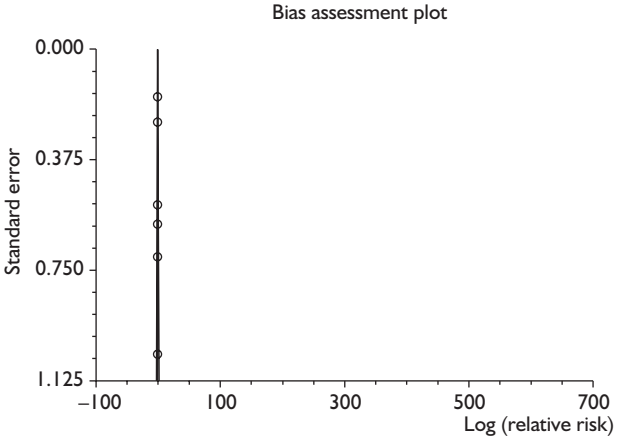
From regression of normalised effect versus precision (Egger and colleagues[35]): intercept (0 if unbiased) = 0.100571 (approximate 95% CI = –2.014181 to 2.215324), $p = 0.9013$. From Kendall's test on standardised effect versus variance (Begg and Mazumdar[36]): tau = 0.066667, $p > 0.9999$ (not robust, small sample).



(e) Cox-2 preferential NSAIDs versus Cox-1 NSAIDs, symptomatic ulcers

Bias indicators

From regression of normalised effect versus precision (Egger and colleagues[35]): intercept (0 if unbiased) = –0.966622 (approximate 95% CI = –2.596344 to 0.663099), $p = 0.1879$. From Kendall's test on standardised effect versus variance (Begg and Mazumdar[36]): tau = –0.142857, $p = 0.5619$ (not robust, small sample).



Appendix 8

Meta-regression results for direct comparisons

Comparison	Outcome	Covariate	No. of studies	Regression coefficient	95% CI of regression coefficient	*p*-Value
H_2RA vs placebo	Endoscopic ulcers	Study duration (weeks)	12	–0.011	–0.033 to 0.012	0.32
		% with history of ulcer or bleeds	8	–0.002	–0.009 to 0.005	0.60
		Mean age (years)	12	–0.023	–0.068 to 0.020	0.29
PPI vs placebo	Endoscopic ulcers	Study duration, (weeks)	6	–0.003	–0.033 to 0.026	0.82
		% with history of ulcer or bleeds	4	0.004	–0.006 to 0.014	0.40
		Mean age (years)	6	0.073	–0.087 to 0.233	0.37
Misoprostol vs placebo	Endoscopic ulcers	Study duration (weeks)	19	0.014	0.001 to 0.027	0.03
		% with history of ulcer or bleeds	11	0.002	–0.005 to 0.010	0.56
		Mean age (years)	18	–0.002	–0.053 to 0.049	0.94
Cox-2 coxibs vs Cox-1	Symptomatic ulcers	Study duration (weeks)	12	0.011	–0.010 to 0.032	0.32
		% with history of ulcer or bleeds	7	0.025	–0.061 to 0.110	0.57
		Mean age (years)	12	0.014	–0.032 to 0.060	0.56
Cox-2 preferentials vs Cox-1	Symptomatic ulcers	Study duration (weeks)	14	–0.016	–0.053 to 0.020	0.39
		% with history of ulcer or bleeds	5	0.047	–0.273 to 0.368	0.77
		Mean age (years)	12	0.013	-0.053 to 0.078	0.71

Appendix 9

Absolute risk reductions (risk differences)

Absolute risk reduction (ARR) or risk difference is the risk in the intervention group minus the risk in the control group.

(a) Overall ARRs for direct comparisons

Outcome	Events intervention	*N* intervention	Events control	*N* control	ARR	95% CI, lower limit	95% CI, upper limit	Hetero-geneity *p*-value
H_2RA vs placebo								
Serious GI events	0	497	1	397	–0.004	–0.011	0.003	
Symptomatic ulcers	1	221	0	122	0.005	–0.005	0.015	
Serious CV or renal events	2	440	3	341	–0.007	–0.017	0.003	
Deaths	1	364	0	357	0.0002	–0.007	0.008	
GI symptoms	84	695	117	690	–0.037	–0.069	–0.006	
Endoscopic ulcers	105	987	145	760	–0.09	–0.13	–0.05	
Drop-outs, total	176	994	166	878	–0.002	–0.03	0.02	
Drop-outs, GI symptoms	25	668	32	557	–0.005	–0.04	0.03	
PPI vs placebo								
Serious GI events	1	677	2	431	–0.001	–0.01	0.008	
Symptomatic ulcers	1	168	17	175	–0.09	–0.13	–0.04	
Serious CV or renal events	2	333	1	163	0.002	–0.015	0.019	
Deaths	0	268	1	133	–0.008	–0.022	0.007	
GI symptoms	13	85	32	90	–0.2	–0.33	–0.08	
Endoscopic ulcers	108	816	173	542	–0.18	–0.26	–0.11	
Drop-outs, total	73	600	43	346	0.001	–0.05	0.06	
Drop-outs, GI symptoms	15	155	33	124	–0.098	–0.378	0.182	
Misoprostol vs placebo								
Serious GI events	26	5780	49	5727	–0.003	–0.006	–0.0001	0.46
Symptomatic ulcers	14	4436	40	4477	–0.005	–0.008	–0.002	0.55
Serious CV or renal events	3	1581	1	725	0.0002	–0.003	0.003	0.38
Deaths	17	6452	18	5616	–0.0005	–0.002	0.001	1.0
GI symptoms	863	1338	355	635	–0.0017	–0.11	0.11	0.004
Endoscopic ulcers	220	3407	438	2675	–0.119	–0.135	–0.103	<0.0001
Drop-outs, total	2655	8120	2117	7155	0.026	0.003	0.049	0.008
Drop-outs, GI symptoms	1366	6373	966	5922	0.024	–0.006	0.054	<0.0001
Cox-2 coxibs vs Cox-1								
Serious GI events	41	11661	74	10082	–0.003	–0.005	–0.001	0.90
Symptomatic ulcers	97	11896	184	10115	–0.007	–0.011	–0.002	0.03
Serious CV or renal events	134	10181	108	9403	0.002	–0.002	0.006	0.22
Deaths	40	9292	36	8821	–0.0002	–0.003	0.002	0.24
GI symptoms	2554	6883	2630	5855	–0.06	–0.08	–0.04	0.70
Endoscopic ulcers	162	2184	360	1159	–0.23	–0.34	–0.12	<0.0001
Drop-outs, total	4967	13877	4583	11379	–0.055	–0.090	–0.021	<0.0001
Drop-outs, GI symptoms	990	12912	1201	10883	–0.019	–0.032	–0.006	0.0002

continued

Outcome	Events intervention	N intervention	events control	*N* control	ARR	95% CI, lower limit	95% CI, upper limit	Hetero-geneity *p*-value
Cox-2 preferentials vs Cox-1								
Serious GI events	17	11797	26	10928	–0.0004	–0.0013	0.0006	0.55
Symptomatic ulcers	23	10980	59	10391	–0.0033	–0.0074	0.0008	0.0004
Serious CV or renal events	23	9824	25	9732	0.0002	–0.0012	0.0015	0.89
Deaths	7	10510	12	10072	–0.0001	–0.0008	0.0006	0.48
GI symptoms	1724	12263	2170	11396	–0.054	–0.068	–0.040	0.29
Endoscopic ulcers	6	185	18	182	–0.06	–0.11	–0.002	0.29
Drop-outs, total	2179	13920	2095	13047	–0.013	–0.022	–0.003	0.42
Drop-outs, GI symptoms	455	12049	719	11727	–0.021	–0.029	–0.013	0.24

(b) Update April 2005, subgrouping RRs for direct comparisons by baseline GI risk and by age

Comparison	Outcome	Factor for subgrouping	Events/ participants in intervention	Events/ participants in control group	Limits	RR[a]	95% CI[a]	Hetero-geneity *p*-value
H_2RA vs placebo	Serious GI events	Baseline GI risk			No usable data for subgrouping			
		Baseline age			No usable data for subgrouping			
	Symptomatic ulcers	Baseline GI risk			No usable data for subgrouping			
		Baseline age			No usable data for subgrouping			
	Endoscopic ulcers	Baseline GI risk[b]	16/197	27/176	1	0.52	0.29 to 0.94	0.90
			76/709	86/509	2	0.61	0.46 to 0.82	0.48
			0/33	3/26	3	0.19	0.02 to 1.65	0.93
			13/48	29/49	4	0.45	0.27 to 0.76	0.66
		Baseline age	94/883	121/658	<65 years	0.57	0.45 to 0.74	0.62
			9/92	22/88	≥ 65 years	0.39	0.20 to 0.77	0.90
PPI vs placebo	Serious GI events	Baseline GI risk			No usable data for subgrouping			
		Baseline age			No usable data for subgrouping			
	Symptomatic ulcers	Baseline GI risk			No usable data for subgrouping			
		Baseline age			No usable data for subgrouping			
	Endoscopic ulcers	Baseline GI risk[b]	1/50	8/53	1	0.13	0.02 to 1.02	Not relevant
			16/139	23/111	2	0.42	0.14 to 1.31	0.10
					3	No relevant studies		
			87/542	127/288	4	0.36	0.29 to 0.46	0.69
		Baseline age			<65 years	No included studies have a mean age over 65 years or appropriate subgrouping		
					≥65 years			
Misoprostol vs placebo	Serious GI events	Baseline GI risk[b]			1	One study only, no events		
			0/349	6/547	2	0.25	0.03 to 2.15	0.72
					3	No studies		
			0/431	1/288	4	0.17	0.01 to 4.26	Not relevant
		Baseline age	1/1305	6/1209	<65 years	0.34	0.06 to 2.03	0.56
			25/4444	42/4482	≥65 years	0.60	0.37 to 0.98	Not relevant

continued

Comparison	Outcome	Factor for subgrouping	Events/ participants in intervention	Events/ participants in control group	Limits	RR*	95% CI*	Hetero-geneity *p*-value
	Symptomatic ulcers	Baseline GI risk[b]			1	No studies		
					2	No studies		
					3	No studies		
					4	No studies		
		Baseline age			<65 years	No studies		
			14/4436	40/4477	≥65 years	0.36	0.20 to 0.67	0.52
	Endoscopic ulcers	Baseline GI risk[b]r	0/45	5/45	1	0.09	0.01 to 1.60	Not relevant
			47/1670	159/1739	2	0.31	0.23 to 0.44	0.62
			85/948	106/427	3	0.39	0.30 to 0.50	0.42
			73/430	127/288	4	0.34	0.17 to 0.67	0.02
		Baseline age	215/3318	419/2584	<65 years	0.33	0.27 to 0.41	0.19
			5/32	11/38	≥65 years	0.54	0.21 to 1.39	Not relevant
Cox-2 coxibs vs Cox-1	Serious GI events	Baseline GI risk[b]			1	No studies		
			23/5699	30/4846	2	0.72	0.42 to 1.22	0.51
					3	No studies		
					4	No studies		
		Baseline age	41/11487	73/9967	<65 years	0.55	0.38 to 0.80	0.75
					≥65 years	No studies		
	Symptomatic ulcers	Baseline GI risk[b]			1	No studies		
			38/5877	56/4842	2	0.56	0.36 to 0.85	0.39
					3	No studies		
					4	No studies		
		Baseline age	97/11722	184/10000	<65 years	0.49	0.38 to 0.62	0.78
					≥65 years	No studies		
	Endoscopic ulcers	Baseline GI risk[b]		1	No studies			
			154/1972	327/941	2	0.25	0.21 to 0.30	0.52
					3	No studies		
					4	No studies		
		Baseline age	162/2184	360/1159	<65 years	0.25	0.21 to 0.30	0.66
					≥65 years	No studies		
Cox-2 preferentials vs Cox-1	Serious GI events	Baseline GI risk[b]			1	No studies		
			0/36	0/36	2	One study, no events		
					3	No studies		
					4	No studies		
		Baseline age	14/10891	22/10195	<65 years	0.59	0.31 to 1.12	0.98
			3/707	4/553	≥65 years	0.73	0.17 to 3.09	0.60
	Symptomatic ulcers	Baseline GI risk[b]			1	No studies		
			2/78	7/77	2	0.28	0.06 to 1.33	0.87
					3	No studies		
					4	No studies		
		Baseline age	21/10321	48/9751	<65 years	0.43	0.26 to 0.71	0.88
			1/418	6/419	≥65 years	0.34	0.08 to 1.42	1.00
	Endoscopic ulcers	Baseline GI risk[b]			1	No studies		
			4/161	16/153	2	0.29	0.10 to 0.86	0.61
					3	No studies		
					4	No studies		
		Baseline age	2/61	5/59	<65 years	0.47	0.10 to 2.18	0.48
			2/24	2/29	≥ 65 years	1.21	0.18 to 7.95	Not relevant

[a] Using random effects meta-analysis.
[b] By baseline risk of GI problems: 1, normal gut on endoscopy for all participants; 2, some participants normal, others have some erosions and/or haemorrhages on endoscopy, but no frank ulcers; 3, all abnormal gut at baseline endoscopy (no ulcers or up to 50% recently healed ulcers). 4, all recently healed from ulcers (at least 50% recently healed ulcers).

Appendix 10

Quality of life data

(a) Omeprazole versus misoprostol versus placebo

Study	Interventions	Measure of QoL used[a]	Baseline QoL	Change in QoL	Final QoL
Hawkey, 1998[62] (OMNIUM), (reported in Yeomans, 2001[65])	Omeprazole 20 mg/day (n = 274) Misoprostol 400 μg /day (n = 297) Placebo (n = 155)	Nottingham Health Profile (NHP)	Baseline was before ulcer healing. Only reported by type of arthritis, not treatment group, and includes those in misoprostol, placebo and omeprazole arms: Total score part 1: RA n = 220 mean score 32.3 (SD 19.5), OA n = 313, mean score 32.2 (SD 21.1) Total score part 2: RA n = 220 mean score 93.8 (SD 18.1), OA n = 313, mean score 92.3 (SD 19.0)	After healing there was a slight improvement on all dimensions of the NHP, in particular regarding arthritis pain relief (15%), improved sleep (6%), vitality (7%) and ability to look after the home (8%)	6 months: 'During prevention the health-related QoL assessed by the NHP was preserved.' No further data, or data by intervention group, were presented
		Psychological General Well-Being Index (PGWB)	Mean score of 93 in the study compared with 103 in the general population, indicating that their well-being was severely compromised. Worst dimensions were general health and vitality	After healing the mean PGWB score improved from 93 to 98, a clinically relevant improvement	The PGWB index was maintained at 'the same level' as after healing

[a] Nottingham Health Profile: the NHP is a generic questionnaire that measures the perceived impact of chronic disease. Part 1 consists of 38 yes/no questions about distress and dysfunction in six dimensions (energy, sleep, social isolation, pain, emotions, physical mobility). Part 2 has seven yes/no statements about health-related problems in employment, housework, social life, home life, sex life, hobbies and holidays. The higher the score the worse is the QoL; an improvement in QoL is indicated by a decreased score. Psychological General Well-Being Index: the PGWB measures subjective well-being or distress in terms of anxiety, depressed mood, positive well-being, self-control and general health and vitality on a six-point Likert scale. The worst possible score is 22 and the best is 132.

(b) Cox-2 coxib NSAIDs versus Cox-1 NSAIDs

Study	Interventions	Measure of QoL used	Baseline QoL	Change in QoL
Simon 1999,[86] (reported in Zhao, 2000[240])	Cox-2: b celecoxib 200 mg/day (n = 240) c celecoxib 400 mg/day (n = 235) d celecoxib 800 mg/day (n = 218) Cox-1: a naproxen 1000 mg/day (n = 225)	Stanford Health Assessment Questionnaire (HAQ) Disability Index	Total functional disability index: b 1.40 (SD 0.65) c 1.50 (SD 0.73) d 1.40 (SD 0.72) a 1.50 (SD 0.67)	12 weeks: Total functional disability index b –0.17 c –0.29 d –0.28 a –0.22
		Medical Outcomes Study Short Form with 36 Items (SF-36)	Physical component score: b 29.7 (SD 8.0) c 29.5 (SD 7.9) d 29.5 (SD 8.3) a 29.9 (SD 8.9) Mental component score b 47.6 (SD 11.1) c 45.3 (SD 12.3) d 47.5 (SD 11.6) a 46.2 (SD 11.6)	12 weeks: Physical component score: b 2.5 c 4.3 d 4.4 a 2.7 Mental component score: b 1.8 c 2.8 d 1.8 a 2.1

The Medical Outcomes Study Short Form with 36 Items (SF-36) is a general health measure. Measures health across three dimensions (functional status, well-being, overall evaluation of health) using eight domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, mental health, plus health transition). Can be self-administered in 5–10 minutes. Higher scores indicate better QoL.

[a] The Stanford Health Assessment Questionnaire (HAQ) Disability Index (the 20-item core instrument of the HAQ) is a disease-specific instrument. Can be self-administered in less than 5 minutes and evaluates eight categories of daily functioning: dressing, arising, eating, walking, hygiene, reach, grip, activities. A lower score represents better functional status.

(c) Cox-2 preferential NSAIDs versus Cox-1 NSAID

Study	Interventions	Measure of QoL used[a]	Baseline QoL	Change in QoL
Hosie, 1996[123]	Cox-2: b meloxicam 7.5mg/day (*n* = 169) Cox-1: a diclofenac 100 mg/day (*n* = 166)	Modified Nottingham Health Profile	b score 7.2 (SD 4.3) a score 7.0 (SD 4.3)	6 months: b mean –2.3 (SD 3.7) a mean –2.2 (SD 4.2)
Hosie, 1997[126]	Cox-2: b meloxicam 15 mg/day (*n* = 306) Cox-1 a piroxicam 20 mg/day (*n* = 149)	Modified Nottingham Health Profile	No data provided	6 months: b median –1 (Interquartile range –2 to 0) a median –1 (Interquartile range –3 to 0)
Furst, 2002[139]	Cox-2: b meloxicam 7.5 mg/day (*n* = 175) c meloxicam 15 mg/day (*n* = 184) d meloxicam 22.5 mg/day (*n* = 177) Cox-1: a diclofenac 150mg/day (*n* = 181)	Modified Health Assessment Questionnaire (mHAQ)	At flare b 1.02 (SD 0.59) c 1.06 (SD 0.66) d 1.09 (SD 0.61) a 1.02 (SD 0.60)	12 weeks: b –0.32 c –0.37 d –0.42 a –0.33

[a] The Modified Nottingham Health Profile has 22 questions from 3 of 6 sections in part 1 and 3 of 6 sections from part 2 covering physical mobility, social isolation, energy levels and influences on various aspects of life. An improvement in QoL is indicated by a decreased score. The Modified Health Assessment Questionnaire (mHAQ) for patient assessment of physical function has maximum score = +3. This is more a measure of efficacy than of QoL.

Appendix 11

Direct comparisons, meta-analysis and sensitivity analysis details

(a) H_2RA versus PPI meta-analysis (MA) and sensitivity analysis (SA) results

Outcome	Analysis	No. of included RCTs	No. of participants	No. of events	RR (random effects)	95% CI	Heterogeneity *p*-value
Serious GI events	MA	1	425	1	0.33	0.01 to 7.95	NR
	SA quality	1	425		0.33	0.01 to 7.95	NR
	SA dosage	1	425		0.33	0.01 to 7.95	NR
Symptomatic ulcers	MA	1	425	1	0.33	0.01 to 7.95	NR
	SA quality	1	425		0.33	0.01 to 7.95	NR
	SA dosage	1	425		0.33	0.01 to 7.95	NR
Serious CV or renal events	MA	0					
QoL	MA	0					
Deaths	MA	0					
GI symptoms	MA	0					
Endoscopic ulcers	MA	1	425	46	3.11	1.62 to 5.95	NR
	SA quality	1	425		3.11	1.62 to 5.95	NR
	SA dosage	1	425		3.11	1.62 to 5.95	NR
Anaemia	MA	0					
Occult bleed	MA	0					
Total drop-outs	MA	1	425	59	0.94	0.59 to 1.52	NR
	SA quality	1	425		0.94	0.59 to 1.52	NR
	SA dosage	1	425		0.94	0.59 to 1.52	NR
Drop-outs due to GI symptoms	MA	0					

NR, not relevant (e.g. tests of heterogeneity when only one study is included in the analysis).

(b) H_2RA vs misoprostol meta-analysis (MA) and sensitivity analysis (SA)

Outcome	Analysis	No. of included RCTs	No. of participants	No. of events	RR (random effects)	95% CI	Heterogeneity *p*-value
Serious GI events	MA	1	538	0	NE	NE	NR
	SA quality	1	538		NE	NE	NR
	SA dosage	1	538		NE	NE	NR
Symptomatic ulcers	MA	1	49	1	2.67	0.11 to 62.42	NR
	SA quality	1	49		2.67	0.11 to 62.42	NR
	SA dosage	0					
Serious CV or renal events	MA	1	538	0	NE	NE	NR
	SA quality	1	538		NE	NE	NR
	SA dosage	1	538		NE	NE	NR
	SA naproxen	0					
QoL		0					
Deaths	MA	1	538	0	NE	NE	NR
	SA quality	1	538		NE	NE	NR
	SA dosage	1	538		NE	NE	NR
	SA Naproxen	0					
GI symptoms	MA	2	587	345	0.85	0.74 to 0.97	0.46
	SA quality	2	587		0.85	0.74 to 0.97	0.46
	SA dosage	1	538		0.84	0.73 to 0.96	
Endoscopic ulcers	MA	3	454	23	4.35	1.51 to 12.55	0.82
	SA quality	3	454		4.35	1.51 to 12.55	0.82
	SA dosage	1	375		4.04	1.17 to 13.96	NR
Anaemia	MA	0					
Occult bleed	MA	0					
Total drop-outs	MA	2	599	125	0.78	0.57 to 1.07	0.8
	SA quality	2	599		0.78	0.57 to 1.07	0.8
	SA dosage	1	538		0.79	0.57 to 1.10	NR
Drop-outs due to GI symptoms	MA	2	599	46	0.40	0.22 to 0.74	0.89
	SA quality	2	599		0.40	0.22 to 0.74	0.89
	SA dosage	1	538		0.41	0.22 to 0.76	NR

NE, no events, and so no data; NR, not relevant (e.g. tests of heterogeneity when only one study is included in the analysis).

(c) PPI versus misoprostol meta-analysis (MA) and sensitivity analysis (SA)

Outcome	Analysis	No. of included RCTs	No. of participants	No. of events	RR (random effects)	95% CI	Heterogeneity *p*-value
Serious GI events	MA	2	972	1	1.51	0.06 to 36.71	NR
	SA quality	2	972		1.51	0.06 to 36.71	NR
	SA dosage	2	972		1.51	0.06 to 36.71	NR
Symptomatic ulcers	MA	0					
Serious CV or renal events	MA	1	402	4	0.50	0.07 to 3.51	NR
	SA quality	1	402		0.50	0.07 to 3.51	NR
	SA dosage	1	402		0.50	0.07 to 3.51	NR
	SA naproxen	0					
QoL		0					
Deaths	MA	1	402	1	0.17	0.01 to 4.08	NR
	SA quality	1	402		0.17	0.01 to 4.08	NR
	SA dosage	1	402		0.17	0.01 to 4.08	NR
	SA naproxen	0					
GI symptoms	MA	0					
Endoscopic ulcers	MA	2	972	160	1.08	0.50 to 2.32	0.021
	SA quality	2	972		1.08	0.50 to 2.32	0.021
	SA dosage	2	972		1.08	0.50 to 2.32	0.021
Anaemia	MA	0					
Occult bleed	MA	0					
Total drop-outs	MA	2	972	139	0.71	0.52 to 0.98	0.99
	SA quality	2	972		0.71	0.52 to 0.98	0.99
	SA dosage	2	972		0.71	0.52 to 0.98	0.99
Drop-outs due to GI symptoms	MA	0					

NR, not relevant (e.g. tests of heterogeneity when only one study is included in the analysis).

(d) PPI vs Cox-2 coxib meta-analysis (MA) and sensitivity analysis (SA) results

Outcome	Analysis	No. of included RCTs	No. of participants	No. of events	RR (random effects)	95% CI	Heterogeneity *p*-value
Serious GI events	MA	1	287	21	2.01	0.84 to 4.84	NR
	SA quality	1	287		2.01	0.84 to 4.84	NR
	SA dosage	1	287		2.01	0.84 to 4.84	NR
Symptomatic ulcers	MA	1	287	16	1.29	0.50 to 3.38	NR
	SA quality	1	287		1.29	0.50 to 3.38	NR
	SA dosage	1	287		1.29	0.50 to 3.38	NR
Serious CV or renal events	MA	1	287	21	1.11	0.49 to 2.53	NR
	SA quality	1	287		1.11	0.49 to 2.53	NR
	SA dosage	1	287		1.11	0.49 to 2.53	NR
	SA naproxen	1	287		1.11	0.49 to 2.53	NR
QoL		0					
Deaths	MA	1	287	2	1.01	0.06 to 15.95	NR
	SA quality	1	287		1.01	0.06 to 15.95	NR
	SA dosage	1	287		1.01	0.06 to 15.95	NR
	SA naproxen	1	287		1.01	0.06 to 15.95	NR
GI symptoms	MA	1	287	37	0.61	0.33 to 1.14	NR
	SA quality	1	287		0.61	0.33 to 1.14	NR
	SA dosage	1	287		0.61	0.33 to 1.14	NR
Endoscopic ulcers	MA	0					
Anaemia	MA	1	287	4	9.06	0.49 to 166.81	NR
	SA quality	1	287		9.06	0.49 to 166.81	NR
	SA dosage	1	287		9.06	0.49 to 166.81	NR
Occult bleeds	MA	0					
Total drop-outs	MA	1	287	40	0.91	0.51 to 1.62	NR
	SA quality	1	287		0.91	0.51 to 1.62	NR
	SA dosage	1	287		0.91	0.51 to 1.62	NR
Drop-outs due to GI symptoms	MA	1	287	11	0.84	0.26 to 2.69	NR
	SA quality	1	287		0.84	0.26 to 2.69	NR
	SA dosage	1	287		0.84	0.26 to 2.69	NR

NR, not relevant (e.g. tests of heterogeneity when only one study is included in the analysis).

(e) Misoprostol versus Cox-2 coxib meta-analysis (MA) and sensitivity analysis (SA) results

Outcome	Analysis	No. of included RCTs	No. of participants	No. of events	RR (random effects)	95% CI	Heterogeneity *p*-value
Serious GI events	MA	0					
Symptomatic ulcers	MA	0					
Serious CV or renal events	MA	1	483	24	0.72	0.32 to 1.58	NR
	SA quality	1	483	24	0.72	0.32 to 1.58	NR
	SA dosage	1	483	24	0.72	0.32 to 1.58	NR
	SA naproxen	1	483	24	0.72	0.32 to 1.58	NR
QoL		0					
Deaths	MA	0					
GI symptoms	MA	1	483	187	1.68	1.32 to 2.13	NR
	SA quality	1	483	187	1.68	1.32 to 2.13	NR
	SA dosage	1	483	187	1.68	1.32 to 2.13	NR
Endoscopic ulcers	MA	0					
Anaemia	MA	0					
Occult bleed	MA	0					
Total drop-outs	MA	1	483	43	1.54	0.86 to 2.76	NR
	SA quality	1	483	43	1.54	0.86 to 2.76	NR
	SA dosage	1	483	43	1.54	0.86 to 2.76	NR
Drop-outs due to GI symptoms	MA	1	483	10	9.04	1.15 to 70.78	NR
	SA quality	1	483	10	9.04	1.15 to 70.8	NR
	SA dosage	1	483	10	9.04	1.15 to 70.8	NR

NR, not relevant (e.g. tests of heterogeneity when only one study is included in the analysis).

(f) Misoprostol versus Cox-2 preferential meta-analysis (MA) and sensitivity analysis (SA) results

Outcome	Analysis	No. of included RCTs	No. of participants	No. of events	RR (random effects)	95% CI	Heterogeneity *p*-value
Serious GI events	MA	2	909	16	3.05	1.03 to 9.06	0.75
	SA quality	2	909	16	3.05	1.03 to 9.06	0.75
	SA dosage	2	909	16	3.05	1.03 to 9.06	0.75
Symptomatic ulcers	MA	1	90	5	0.25	0.03 to 2.15	NR
	SA quality	1	90	5	0.25	0.03 to 2.15	NR
	SA dosage	1	90	5	0.25	0.03 to 2.15	NR
Serious CV or renal events	MA	1	90	2	1.00	0.06 to 15.50	NR
	SA quality	1	90	2	1.00	0.06 to 15.50	NR
	SA dosage	1	90	2	1.00	0.06 to 15.50	NR
	SA naproxen	0					
QoL		0					
Deaths	MA	1	90	4	1.00	0.15 to 6.79	NR
	SA quality	1	90	4	1.00	0.15 to 6.79	NR
	SA dosage	1	90	4	1.00	0.15 to 6.79	NR
	SA naproxen	0					
GI symptoms	MA	1	90	12	0.50	0.16 to 1.54	NR
	SA quality	1	90	12	0.50	0.16 to 1.54	NR
	SA dosage	1	90	12	0.50	0.16 to 1.54	NR
Endoscopic ulcers	MA	2	934	60	0.37	0.21 to 0.65	0.96
	SA quality	1	819	59	0.37	0.21 to 0.65	NR
	SA dosage	2	934	60	0.37	0.21 to 0.65	0.96
Anaemia	MA	1	118	1	2.90	0.12 to 69.8	NR
	SA quality	0					
	SA dosage	1	118	1	2.90	0.12 to 69.8	NR
Occult bleed	MA	0					
Total drop-outs	MA	2	208	63	1.00	0.67 to 1.50	0.48
	SA quality	1	90	36	0.89	0.54 to 1.49	NR
	SA dosage	2	208	63	1.00	0.67 to 1.50	0.48
Drop-outs due to GI symptoms	MA	0					

NR, not relevant (e.g. tests of heterogeneity when only one study is included in the analysis).

(g) Cox-2 (pooled coxib and preferential) NSAIDs versus Cox-1 NSAID meta-analysis (MA) and sensitivity analysis (SA) results

Outcome	Analysis	No. of included RCTs	No. of participants	No. of events	RR (random effects)	95% CI	Heterogeneity *p*-value
Serious GI events	MA	31	44468	158	0.56	0.41,0.77	0.99
	SA quality	24	42547		0.56	0.41,0.78	0.96
	SA dosage	28	27369		0.55	0.33,0.92	1.00
	SA Cox-2 preferentials	11	21454		0.55	0.38,0.80	0.75
Symptomatic ulcers	MA	28	43194	363	0.47	0.38,0.59	1
	SA quality	22	41576		0.48	0.38,0.60	0.99
	SA dosage	26	26445		0.44	0.30,0.63	1
	SA Cox-2 preferentials	11	21534		0.49	0.39,0.63	0.83
Serious CV or renal events	MA	20	39140	290	1.09	0.86,1.37	0.64
	SA quality	14	37874		1.11	0.88,1.40	0.57
	SA dosage	18	23096		0.93	0.62,1.41	0.78
	SA Cox-2 preferentials	8	19295		1.19	0.80,1.75	0.27
	SA naproxen	18	30525		0.98	0.76,1.26	0.89
QoL		1	335		WMD –0.10	–0.95,0.75	NR
Deaths	MA	20	38695	97	0.99	0.66,1.48	0.56
	SA quality	14	37688		1.06	0.70,1.60	0.49
	SA dosage	18	22474		0.60	0.27,1.32	0.59
	SA Cox-2 preferentials	6	18113		1.02	0.55,1.92	0.26
	SA naproxen	17	30050		0.93	0.55,1.56	0.48
GI symptoms	MA	38	36045	8996	0.77	0.72,0.84	<0.001
	SA quality	27	34108		0.77	0.71, 0.84	<0.001
	SA dosage	35	27330		0.73	0.69, 0.77	0.61
	SA Cox-2 preferentials	9	12446		0.85	0.79, 0.91	0.32
Endoscopic ulcers	MA	11	3411	531	0.25	0.21,0.30	0.58
	SA quality	7	2861		0.25	0.21, 0.31	0.38
	SA dosage	10	2903		0.24	0.19, 0.29	0.64
	SA Cox-2 preferentials	7	3173		0.25	0.21, 0.30	0.45
Anaemia	MA	8	10218	470	0.61	0.51,0.73	0.87
	SA quality	6	9506		0.61	0.51, 0.73	0.72
	SA dosage	7	2250		0.26	0.09, 0.74	1.00
	SA Cox-2 preferentials	4	9191		0.62	0.51, 0.74	0.54
Occult bleed	MA	5	1328	18	0.92	0.37,2.31	0.89
	SA quality	4	1039		0.86	0.33, 2.24	0.83
	SA dosage	5	1151		0.92	0.37, 2.31	0.88
	SA Cox-2 preferentials	0					
Total drop-outs	MA	59	51739	13706	0.69	0.61,0.77	0.048
	SA quality	43	49134		0.88	0.83, 0.95	<0.001
	SA dosage	52	33562		0.88	0.81, 0.96	<0.001
	SA Cox-2 preferentials	18	24848		0.83	0.74, 0.92	<0.001

continued

Outcome	Analysis	No. of included RCTs	No. of participants	No. of events	RR (random effects)	95% CI	Heterogeneity *p*-value
Drop-outs due to GI symptoms	MA	47	47383	3365	0.89	0.84,0.95	<0.001
	SA quality	33	44866		0.69	0.61, 0.78	0.07
	SA dosage	44	30924		0.66	0.57, 0.77	0.16
	SA Cox-2 preferentials	19	32867		0.71	0.60, 0.85	0.006

WMD, weighted mean difference.

Appendix 12

Economic evaluations

(a) Economic evaluations of Cox-1 NSAIDS versus Cox-1 NSAIDS plus misoprostol

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Hillman, 1989[149] USA (healthcare provider)	To compare the economic effects (direct medical costs) of the use of misoprostol prophylaxis against no prophylaxis in the treatment of osteoarthritis patients taking NSAIDs	A decision-analytic (decision-tree) model was used to compare the economic effects of the two treatment options One-way SA was used to test for uncertainty	Clinical: synthesis of previously published studies Direct costs = included: source = misoprostol = based on the price of alternative medication (cimetidine) Inpatient = epidemiological risk study[257] Indirect costs = not included Resource use = epidemiological risk study;[237] Expert opinion. (US dollars, 1987)	3 months	Cost of therapy per patient (3 months) at different prices of misoprostol: Misoprostol price $1.70/day: Misoprostol prophylaxis = $298.91 No prophylaxis = $301.65 (cost saving = $2.74) Misoprostol price $1.93/day: Misoprostol prophylaxis = $315.63 No prophylaxis = $301.65 Misoprostol price $2.10/day: Misoprostol prophylaxis = $327.58 No prophylaxis = $301.65 The authors reported misoprostol was cost saving at any price below $1.74/day in their base-case 3-month analysis	The authors conclude that the use of misoprostol in the treatment of patients with osteoarthritis is potentially cost saving, depending on the price of medication, the silent ulcer rate and the rate of patient compliance. In relation to the medication price, the authors report that misoprostol is cost saving at any price below $2.74/day

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Carrin, 1990[150] Belgium (hospital)	To analyse the cost-effectiveness of misoprostol for prevention of gastric ulcers in OA patients treated with NSAIDs To compare the costs of prophylaxis with misoprostol with the costs of the present standard treatment	A decision-analytic model was used SA was used to investigate uncertainty	Clinical: basic clinical data were derived from Graham *et al*.[66] Data on incidence of gastric ulcer disease were derived from an epidemiological survey (1984) by the Institute of Hygiene and Epidemiology of Belgian Ministry of Public Health Economic: Closon,[238] expert opinion and a databank prepared for this study containing data from 42,510 patients from three Belgian University Hospitals. (Belgian francs, June 1985–8)	Societal	In a university hospital scenario the use of misoprostol would entail net savings per patient of 1999 BEF In a general hospital scenario the use of misoprostol would entail a saving for society	Preventative treatment with misoprostol entails net savings for society as a whole; however, the size of the net saving is sensitive to parameters such as the presence of asymptomatic ulcers and the cost of misoprostol

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Edelson, 1990[151] USA Healthcare provider	To compare the cost-effectiveness of primary and secondary prophylaxis with misoprostol against no prophylaxis in the prevention of NSAID-induced GI tract bleeding The two health technologies were compared in three populations of NSAID users: (i) the general population (all users); (ii) users aged 60 years or older; (iii) users with RA	A decision-analytic (decision-tree) model was used to derive the cost-effectiveness of the two treatment strategies. This was calculated in relation to the cost per additional year of life saved, the cost per additional bleed prevented and the cost per fatal bleed prevented. One-way SA was used to test uncertainty	Clinical: synthesis of previously published studies Economic: direct costs = included: source: hospital charge data indirect costs = not included Resource use = hospital billing (US dollars, 1989)	1 year	The average net cost per 100,000 patients treated with misoprostol prophylaxis compared with no prophylaxis, by population group: general population (all users) = $53,879,000; users aged ≥60 years = $49,814,000; users with RA = $36,920,000 Incremental/net cost per year of life saved, by population group: General population (all users) = $667,400 Users aged ≥60 years = $186,700 Users with RA = $95,600 Cost-effectiveness of misoprostol as a secondary prevention: ICERs of less than $40,00 per life-year saved were reported in all patient groups	The authors conclude that misoprostol was costly as a primary prevention for NSAID-induced GI bleeding, but state that misoprostol may be cost-effective as a secondary prevention in patients with a history of GI tract bleeding

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Knill-Jones, 1990[15] UK (NHS)	To compare the costs of misoprostol prophylaxis against no misoprostol in the treatment of osteoarthritis receiving NSAIDs	A decision-analytic (decision-tree) model was used to compare the costs of misoprostol against no misoprostol in patients with OA One-way SA was used to test for uncertainty	Clinical: Epidemiological data from England and Scotland; CCT (Graham *et al.*, 1988)[66] Direct costs = included: source = national unit costs; MIMS Indirect costs = not included Resource use = Scottish Morbidity Records (SMR1); Health Activity Analysis (HAA) (West Midlands); expert opinion (GPs) (UK pounds sterling, 1988)	3 months	The authors report that the net savings per patient to the NHS over the expected 3 months of care were £6.10 in Scotland and £8.40 in England In relation to the SA the authors report that increasing the dose of misoprostol to 800 µg would result in a net cost of £25.0 in Scotland and £22.70 in England The other variables tested showed that under many assumptions, misoprostol prophylaxis generates a net saving to the NHS or a small net cost	The authors conclude that using conservative assumptions and a daily dose of 400 µg of misoprostol results in cost savings per patient to the NHS of £5–8 over a 3-month period. The authors also report that a daily dose of 800 µg misoprostol prophylaxis results in a net cost of £23–25 per patient to the NHS

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Jonsson, 1992[152] Sweden (societal)	To compare the cost-effectiveness of prophylaxis with misoprostol against no prophylaxis in the treatment of patients with osteoarthritis and NSAID-associated abdominal pain	A decision-analytic (decision-tree) model was used to derive the cost-effectiveness of the two treatment strategies. This was calculated in terms of the cost per episode of gastric ulcer disease avoided One-way SA was used to test for uncertainty	Clinical: synthesis of previously published studies. Direct costs = included: source = Swedish hospitals (secondary) and primary care Indirect costs = included: source = sick leave/days based on average income statistics in Sweden Resource use = Swedish hospitals, and Medical Index Sweden (Swedish kroner, 1988)	3 months	Base case analysis Cost per patient (indirect costs not included): Prophylaxis with misoprostol = 969 SEK No prophylaxis = 1090 SEK (Difference = 121 SEK) Cost per patient (indirect costs included): Prophylaxis with misoprostol = 1016 SEK No prophylaxis = 1202 SEK (Difference = 186 SEK) The authors reported the cost-effectiveness of prophylaxis with misoprostol at different risk levels of ulcer disease (35–5%) and different effectiveness assumptions (100–50%). The maximum cost per episode of gastric ulcer avoided within this analysis = 38,000 SEK (probability of ulcer = 5%, effectiveness = 100%)	The authors conclude that in patients with osteoarthritis and NSAID-associated abdominal pain, prophylaxis with misoprostol is cost-effective in Sweden

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Knill-Jones, 1992[153] UK (NHS)	To compare the iatrogenic cost factors of 10 NSAIDs in the UK NHS against those of the French national health insurance system (Assurance Maladie) The ten NSAIDs were diclofenac, naproxen, sulindac, ibuprofen, indomethacin, piroxicam, flurbiprofen, etodolac, ketoprofen and diclofenac/ misoprostol	The author reports that the iatrogenic cost factor of NSAIDs for the UK NHS were calculated using the model of De Pouvourville and Bader[239]	Clinical: synthesis of previously published studies Direct costs = included: source = monthly Index of Medical Specialities (MIMS), August 1991 Indirect costs = not included Resource use: not reported (UK pounds, sterling)	6 months	Iatrogenic cost factor range by NSAID: Diclofenac = 1.42–1.47 Naproxen = 1.40–1.44 Sulindac = 1.57–1.63 Ibuprofen = 2.38–2.53 Indomethacin = 1.80–1.88 Piroxicam = 184–1.93 Flurbiprofen = 1.90–2.00 Etodolac = 1.84–1.93 Ketoprofen = 1.71–1.79 Diclofenac/misoprostol = 1.08–1.09 (Iatrogenic cost factor = ratio of the shadow price to the NHS price)	The authors conclude that NHS iatrogenic cost factors of the 10 NSAIDs were similar to those calculated by De Pouvourville and Bader for the French Assurance Maladie, and ranged from 1.08 for diclofenac/misoprostol to 2.38 for ibuprofen

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Gabriel, 1993[154] Canada (hospital)	To assess the cost-effectiveness of misoprostol prophylaxis in the prevention of NSAID-associated GI adverse events in OA patients in three different populations: (i) prophylaxis for all patients taking NSAIDs; (ii) prophylaxis for no patients taking NSAIDs; (iii) prophylaxis for elderly persons (age ≥ 60 years) taking NSAIDs	A decision-analytic (decision-tree) model was used to derive the cost-effectiveness of misoprostol prophylaxis in the three different populations. This was calculated in terms of the cost per GI event averted One- and two-way SA was used to test for uncertainty	Clinical: synthesis of previously published studies Direct costs: included source: medical ward at Wellesley Hospital, Ontario Indirect costs = not included Resource use = Wellesley Hospital, Ontario: medical records of patients (Canadian dollars, 1990)	3 months	Baseline costs: Hypothetical cohort of 100 patients: No prophylaxis = $25,662 Elderly prophylaxis = $28,971 All users prophylaxis = $32,396 Cost per GI event averted: No prophylaxis = $297.9 Elderly prophylaxis = $317.7 All users prophylaxis = $338.0	The authors conclude that their results show misoprostol prophylaxis to be highly cost-effective in the Canadian healthcare setting
Peacock, 1993[155] UK (NHS)	To compare the total cost of treating a hypothetical cohort of 1000 patients with a month's supply of one of the following three interventions: (i) an oral NSAID; (ii) Traxam (topical NSAID); (iii) Arthrotec (diclofenac/misoprostol)	A decision-analytic (decision-tree) model was used to calculate the drug cost, the shadow cost and total cost of treating a hypothetical cohort of 1000 patients with the three different interventions One-way SA was used to test for uncertainty	Clinical: synthesis of previously completed studies Direct costs = included: source = Drug Tariff (October 1993); MIMS (September 1993) Indirect costs = not included Resource use = hospital and ambulatory (UK pounds sterling, 1993)	1 year	Total cost of treating 1000 patients for 1 month: An oral NSAID = £39,678–58,858 Traxam = £7,139 Arthrotec = £17,924 (Although the authors report that the study was a cost-effectiveness analysis, no summary measure of health benefit was reported and no synthesis of costs and benefits was undertaken. The study should therefore be classified as a cost–consequences analysis)	The authors conclude that prescription of the topical NSAID, in place of an oral preparation, would result in cost savings to both GP and hospital budgets, because of the reduced cost of treating side-effects

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Gabriel, 1994[156] USA Healthcare provider	To compare the cost-effectiveness/utility of strategies for the treatment of patients with OA The three treatment strategies were (i) prophylaxis for all NSAID users, (ii) prophylaxis for elderly NSAID users and (iii) no prophylaxis for NSAID users	A decision-analytic (decision-tree) model was used to derive the cost–utility of the treatment options. This was calculated in terms of the cost per QALY saved One-way, two-way and probabilistic SA was undertaken to test for uncertainty	Clinical: synthesis of previously published studies Direct costs = included: source = Healthcare = Local data, Minnesota Misoprostol = average wholesale price Indirect costs = not included Resource use = medical records of patients (US dollars, 1992)	3 months	Average cost of treatment: (I) Base case: No prophylaxis for NSAID users = $142 Prophylaxis for elderly NSAID users = $170 Prophylaxis for all NSAID users = $202 (ii) Worst case: No prophylaxis for NSAID users = $142 Prophylaxis for elderly NSAID users = $170 Prophylaxis for all NSAID users = $202 (iii) Best case: No prophylaxis for NSAID users = $142 Prophylaxis for elderly NSAID users = $170 Prophylaxis for all NSAID users = $202 Incremental cost–utility ratio: Best case: Prophylaxis for all NSAID users vs prophylaxis for the elderly = $10,666 per QALY saved	The authors conclude that their results show that misoprostol prophylaxis results in modest additional costs, but provides no additional QoL. The authors state that even for those patients demonstrating a marked positive utility for prophylaxis, the incremental cost per QALY gained was relatively high and highly sensitive to changes in preference scores

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Al, 1996[157] The Netherlands (societal)	To compare the cost-effectiveness of a fixed dose combination (FDC) of diclofenac and misoprostol with diclofenac monotherapy in the prevention of NSAID-induced ulcers in patients with RA	A decision-analytic model was used to derive the cost-effectiveness of the two treatment strategies. This was calculated as the cost per symptomatic ulcer-free period gained Univariate and multivariate SA was undertaken to test for uncertainty	Clinical: synthesis of previously published studies Direct costs = hospital costs and tariffs Indirect costs = not included Resource use = expert opinion, previously published literature and 2 general hospitals in The Netherlands. (Dutch guilders, 1995)	3 months	Baseline results – total costs for 100 patients receiving 3 months' treatment: diclofenac monotherapy = NLG 19,825 FDC diclofenac–misoprostol = NLG 20,598 (Incremental cost of FDC diclofenac–misoprostol = NLG 773) Incremental cost per symptomatic ulcer-free period gained using FDC diclofenac–misoprostol compared with diclofenac monotherapy = NLG 949 Incremental cost per additional survivor using FDC diclofenac–misoprostol compared with diclofenac monotherapy = NLG 41,790	The authors conclude that treatment with diclofenac–misoprostol is cost saving in RA patients at high risk of NSAID-induced ulcers, and that for RA patients in general this intervention compares favourably with other prophylactic treatments in terms of cost-effectiveness

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Maetzel, 1998[11] Canada (provincial health care plan)	To re-examine the cost-effectiveness of misoprostol using data form a recently published placebo-controlled trial in patients with rheumatoid arthritis taking NSAIDs (MUCOSA study)[87] The treatment regimens were (1) NSAID and placebo and (2) NSAID and misoprostol (up to 800 μg daily)	A decision tree was used to model the clinical and major resource use events in the two arms of the study Approximate CIs for the cost-effectiveness estimates were calculated using Monte Carlo simulations The study population patients was a hypothetical cohort of patients with rheumatoid arthritis over the age of 52 years and taking NSAID for more than 6 months The model allowed for separate analyses to be performed for patients with different levels of baseline risk	Clinical: synthesis of previously published studies Direct costs = drugs costs, use of GI-related procedures including number of hospitalisations; number of endoscopies/UGI radiographic series; number of surgical procedures Source: Ontario Case Cost Project (OCCP) database Indirect costs = not included Resource use = collected from patients' charts and study monitor logs. (Canadian dollars, 1994)	6 months	The unit costs were: misoprostol = Can$0.51 per tablet; gastric ulcer with haemorrhage and perforation = Can$6514; duodenal ulcer with haemorrhage and perforation = Can$9578; gastric ulcer with haemorrhage but no perforation = Can$3580; gastric ulcer without haemorrhage = Can$2807; duodenal ulcer without haemorrhage = Can$2573 In the baseline analysis, the cost of averting one serious GI complication by prescribing misoprostol was estimated to be Can$94,766 (95% CI: 60,286 to 137,146) In patients with a medium risk (previous peptic ulcer disease), the cost of averting one serious GI complication by prescribing misoprostol was estimated to be Can$14,943 (95% CI: 10,912 to 332,157) In patients with a high risk (previous peptic ulcer disease and over 75 years old), the cost of averting one serious GI complication by prescribing misoprostol was estimated to be Can$4101 (95% CI: –220 to 18,146)	The authors concluded that prescribing misoprostol for all patients with RA at least 52 years of age costs $95,766 for each additional GI event averted. When patients are at a higher risk the cost per GI event averted is markedly reduced. The authors suggest that these results provide a better estimate of the true cost-effectiveness of misoprostol based on endoscopic data and modelling of resource use

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Kristiansen, 1999[12] Norway (societal)	To compare the cost-effectiveness of a fixed combination of diclofenac and misoprostol against diclofenac in the treatment of patients with RA	A deterministic decision-analytic (decision-tree) model was used to derive the cost-effectiveness of the treatment options. This was calculated in terms of the cost per LYG and cost per QALY gain	Clinical: synthesis of previously published clinical studies. Direct costs = included: source = inpatient care = diagnosis-related group charges (DRG) Drugs = market prices Indirect costs = not included (although the authors report that the study was undertaken from a societal perspective) Resource use = not reported (US dollars, 1996)	6 months	Average cost per patient for females with a risk of complications similar to that in the MUCOSA study (some patients having risk factors, some not): Diclofenac–misoprostol combination = $327 Diclofenac = $298 The authors reported the incremental cost per LYG and the cost per QALY gained of replacing diclofenac with a diclofenac–misoprostol combination across a range of risk factors for RA: RA – no risk factors: cost per QALY, males = $95,900, females = $72,700 RA + history of GI bleeding, males = $4900, females = $4100 RA + 2 risk factors, males = cost saving, females = cost saving	The authors conclude that replacing diclofenac with fixed diclofenac–misoprostol in the treatment of patients with RA is cost-effective when restricted to RA patients at increased risk of serious GI events

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Davey, 2000[158] Australia (healthcare system perspective)	To compare the cost-effectiveness of misoprostol for NSAID-induced GI damage against no misoprostol (placebo) The two treatment options were compared in three populations: (i) the population in the MUCOSA trial (8843 patients);[88] (ii) patients with a history of peptic ulcer disease; (iii) patients >65 years of age	A decision-analytic model was used to derive the cost-effectiveness of the two treatment options. This was calculated in terms of the cost per life-year saved and the cost per definite serious GI event averted One-way SA was used to test for uncertainty	Clinical: MUCOSA trial and synthesis of previously published studies Direct costs = included: source = misoprostol = price for a 90-tablet packet; inpatient and outpatient = charge data (hospital, GP) Indirect costs = not included Resource use = expert opinion (Australian dollars, 1996/97)	1 year	Cost-effectiveness: (i) Cost per life-year saved: Total trial population (MUCOSA): misoprostol = $181 (117), no misoprostol = $33 (22), Patients with a history of peptic ulcer: misoprostol = $192 (125), no misoprostol = $90 (58) Patients >65 years of age: misoprostol = $186 (121), no misoprostol = $40 (26), incremental cost = $40,322 (26,208) (ii) Cost per definite serious GI event averted: Total trial population (MUCOSA): misoprostol = $181 (117), no misoprostol = $33 (22) Patients with a history of peptic ulcer: misoprostol = $192 (125), no misoprostol = $90 (58) Patients >65 years of age: misoprostol = $186 (121), no misoprostol = $40 (26)	The authors conclude that misoprostol represents a cost-effective treatment option in their setting

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Rahme, 2001[159] Canada (Provincial Government of Quebec, Canada)	To compare the GI healthcare resource use (HCRU) and associated costs for inpatients taking a fixed combination of diclofenac and misoprostol against other NSAIDs The study population comprised a cohort of 12,087 patients aged 66 years and over selected from the Government of Quebec and Health Insurance Agency Database	The authors used a 3-stage model to determine the factors that influenced the direct medical costs of GI HCRU: (i) a logistic regression model to estimate the risk of GI HCRU; (ii) a linear regression model to estimate the direct costs of GI HCRU for those who had such events; (iii) multiplication of the estimated risks from model 1 by the costs from model 2 to give the estimated direct costs of GI HCRU for all patients	Clinical: cohort study from RAMQ data Direct costs = included: source = reimbursement costs from RAMQ; Canadian Institute for Health Information Indirect costs = not included Resource use = cohort study (Canadian dollars, 1997)	2 years	Average direct medical costs of the GI HCRU per patient during the 2-year follow-up: Diclofenac–misoprostol Group = $310.52 NSAID group = $231.19	The authors conclude that their results showed no significant differences in GI HCRU in patients taking diclofenac–misoprostol compared with those taking NSAIDs

ACCES, arthritis cost consequence evaluation system; b.d., twice daily; BEF, Belgian francs; BNF, British National Formulary; CEAC, cost-effectiveness acceptability curve; DRG, diagnosis-related groups; ECR, extra-contractual referrals; €, euros; FDC, fixed dose combination; GI, gastrointestinal; HAA, health activity analysis; Hb, haemoglobin; HCRU, healthcare resource use; HK$, Hong Kong dollars; ICF, iatrogenic cost factor; MEMO: Medicines Monitoring Unit; MIMS, Monthly Index of Medical Specialities; MPCI, minimum perceptible clinical improvement; MUCOSA, Misoprostol Ulcer Complications Outcome Safety Assessment; NLG, Dutch guilders; NOK, Norwegian krone; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; OCCP, Ontario Case Cost Project; PUB, peptic ulcer bleed; QALY, quality-adjusted life-year; RA, rheumatoid arthritis; RAMQ, Régie d'Assurance Maladie du Québec; SEK: Swedish kroner; SMR, Scottish morbidity records; SwF, Swiss francs; t.d.s., three times daily.

(b) Economic evaluations of Cox-1 NSAIDS versus Cox-2 Coxibs or Cox-2 preferentials

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Jansen, 1996[160] UK (UK NHS)	To compare the economic impact of meloxicam 7.5 mg against diclofenac 100 mg retard in the treatment of patients with OA in the UK	A decision-analytic (decision-tree) model was used to compare the expected cost of meloxicam 7.5 mg against diclofenac 100 mg retard in OA patients One-way SA was used to test for uncertainty	Clinical: double-blind randomised clinical trials. Direct costs = included: source = BNF, Benefit Costing database, Medicines Monitoring Unit database (MEMO) database Indirect costs = not included Resource use = Tayeside MEMO database, expert opinion (UK pounds sterling, 1995)	30 days	Cost per patient (direct medical costs): Meloxicam 7.5 mg = £28.18 Diclofenac 100 mg retard = £37.14 Cost saving of meloxicam 7.5 mg compared with diclofenac 100 mg retard = £8.96 per patient	The authors conclude that the cost analyses showed a saving of £8.96 per patient (£28.18 vs £37.14) in favour of meloxicam for a 30-day treatment period of OA when compared with diclofenac retard

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Jansen, 1997[161] France, Italy and the UK. (France = French Statutory Health Insurance; Italy = Italian NHS; UK = UK NHS)	To compare the economic impact of meloxicam (7.5 mg) against sustained-release diclofenac (100 mg) in the treatment of patients with OA in France, Italy and the UK	A decision-analytic (decision-tree) model was used to compare the costs of meloxicam against sustained-release diclofenac in France, Italy and the UK One-way SA was used to test for uncertainty	Clinical: double-blind RCTs Direct costs = included: source = France = Official French Tariffs Italy = Italian DRGs, National Tariffs, Italian National Formulatory UK = City University cost database, benefit costing database, BNF. Indirect costs = not included Resource use: expert opinion (French francs, Italian lira, UK pounds sterling, US dollars, 1995)	30 days	Average cost per patient: France: Meloxicam = $37.99 Diclofenac = $56.15 Incremental cost = $18.16 (Cost saving of meloxicam = 32%) Italy: Meloxicam = $86.80 Diclofenac = $91.14 Incremental cost = $4.34 (Cost saving of meloxicam = 5%) UK: Meloxicam = $43.69 Diclofenac = $57.58 Incremental cost = $13.89 (Cost saving of meloxicam = 24%)	The authors conclude that compared with sustained diclofenac, meloxicam resulted in cost savings in France ($18.16 = 32%), Italy ($4.34 = 5%) and the UK ($13.89 = 24%)

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
McCabe, 1998[13,161] UK (NHS)	To compare the costs and outcomes of prescribing alternative NSAIDs for the treatment of RA and OA, and more specifically to test the hypothesis that NSAIDs with lower risks of major adverse events are cost saving and more effective The 5 NSAIDs were nabumetone, diclofenac, ibuprofen, piroxicam and naproxen (N.B. Only results for nabumetone and ibuprofen were reported)	Two different decision-analytic (decision-tree) models were used to compare the relative costs and outcomes associated with the 5 alternative NSAIDs. The cost-effectiveness of the alternative NSAIDs was calculated in terms of the cost per LYG The two separate models (Coprescription and Switching) reflected different approaches to the management of minor adverse events One-way SA used to test for uncertainty	Clinical: data from a multi-centred RCT (Eversmeyer *et al.*[19]) Direct costs = included: source: NSAID treatment = Drug Tariff, Chemist, Druggist Monthly Price List Adverse effects = ECR prices – Trent Region of UK NHS Indirect costs = not included Resource use = ECRs (UK pounds sterling, 1995)	3 months	Cost per patient of 3 months' prescription for NSAIDs: Nabumetone = £68.45 Piroxicam = £13.70 Naproxen = £14.95 Ibuprofen = £12.78 Diclofenac = £37.77 Cost of care for a hypothetical cohort of 100,000 patients receiving nabumetone or ibuprofen (in parentheses: per patient cost): 1. Coprescription model: Nabumetone – all patients = £7,597,908 (75.99) Ibuprofen – All patients = £3,517,032 (35.17) 2). Switching model: Nabumetone – all patients = £6,314,234 (64.20) Ibuprofen – all patients = £3,754,295 (41.67) Cost per LYG using nabumetone rather the Ibuprofen: Coprescription model = £2517 Switching model = £1880	The authors conclude that prescribing newer, more expensive NSAIDs will not necessarily result in cost savings. The management of adverse events can have a significant impact on costs which may be justifiable in relation to mortality and morbidity gains associated with new, lower risk NSAIDs

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Liaropoulos, 1999[162] Greece (social security system perspective)	To compare the total costs of 15 days' treatment with nimesulide against diclofenac in the treatment of patients with OA (Cost-minimisation analysis)	The authors did not explicitly report the use of a model. However, the authors do state that a model was used to assess the management of GI adverse events treated on an ambulatory basis and for the calculation of the actual cost of these adverse events for the two drugs One-way SA was used to test for uncertainty	Clinical: MA of previously published studies (RCTs) Direct costs = included: source = Social Security Funds – ministry of Health (Greece) Indirect costs = not included Resource use = expert opinion (panel of physicians) (US dollars, price year not reported)	15 days	Total cost per patient of 15 days' treatment: Nimesulide = $37.44 Diclofenac = $58.42 (nimesulide results in a cost saving of $20.98 per patient compared with diclofenac)	The authors conclude that their cost-minimisation analysis showed that the incremental cost of 15 days' treatment with nimesulide is $20.98 lower per patient than treatment with diclofenac
Svarvar, 2000[163] Norway (societal)	To compare the cost-effectiveness of celecoxib against NSAID monotherapy and base-case scenarios for OA and RA	The Arthritis Cost Consequence Evaluation System (ACCES) model was used to derive the cost-effectiveness of the alternative treatment options. This was calculated in terms of the incremental cost per GI event averted and the incremental cost per LYG One-way SA was used to test for uncertainty	Clinical: synthesis of data from previously published studies Direct costs = included: source = Norwegian authorities Indirect costs = not included Resource use = expert opinion (clinicians in Norway) (Norwegian krone, 1999)	1 year	Total costs per year per patient (NOK): NSAID monotherapy: OA = 2705, RA = 4243 Celecoxib: OA = 2125, RA = 3729 Base-case: OA = 3223, RA = 5191 In relation to the incremental cost-effectiveness of celecoxib against (i) NSAID alone, and (ii) base case, the results were as follows: incremental cost-effectiveness: GI events averted: NSAID alone: OA = dominant, RA = dominant Base case: OA = dominant, RA = dominant LYG: NSAID alone: OA = dominant, RA = dominant. Base case: OA = dominant, RA = dominant	The authors conclude that the introduction of celecoxib into the Norwegian NSAID market and its use as a first-line agent will result in improved healthcare at a reduced cost in patients with OA and RA

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Marshall, 2001[164] Canada (Ontario Ministry of Health)	To compare the incremental cost-effectiveness of rofecoxib against non-selective NSAIDs in the treatment of patients with osteoarthritis aged >65 years in Ontario, Canada	A decision-analytic (decision-tree) model was used to derive the cost-effectiveness of the two drugs. This was calculated in terms of the cost per additional PUB avoided One- and two-way SA was used to test for uncertainty	Clinical = pooled analysis from 8 clinical trials Direct costs = included: source = drug costs = Ontario Public Claims Data Hospital = Ontario case costing Project and Ontario Schedule of Benefits Indirect costs = not included Resource use = Ontario Ministry of Health (Canadian dollars, 1999)	1 year	Average annual direct medical cost per patient: Non-selective NSAID = $584.91 Rofecoxib = $609.36 (Incremental cost = $24.25) The incremental cost to avoid 1 additional PUB by substituting rofecoxib for non-selective NSAIDs = $2247	The authors conclude that the replacement of non-selective NSAIDs with rofecoxib for treatment of OA would reduce the incidence of serious GI events at a modest incremental cost to Canadian provincial governments

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Moore, 2001[167] UK (NHS)	To examine the economic implications of switching all OA patients currently treated with conventional NSAIDs to rofecoxib The treatment regimens were (1) rofecoxib and (2) conventional NSAIDs (represented by a composite of NSAID on the UK market)	A decision tree was developed to model the expected GI healthcare-related resource use associated with patients taking rofecoxib or NSAID. The incidence rates of GI events was determined using Kaplan–Meier estimation Three baseline analyses and extensive sensitivity analyses (cost of NSAID and model health states) were presented The study population comprised patients with OA taking on of the two treatments continuously for up to 1 year. Cohort of 10,000 patients	Clinical: synthesis of previously published studies Direct costs = drug treatment, physician encounters (primary care and specialists), laboratory and tests, endoscopy, Hb testing, hospital, surgery Source: finance staff at NHS trusts (3) and the literature and Mediplus (IMS, UK) database Indirect costs = not included Resource use = expert opinion and published sources (UK pounds sterling, 1999)	1 year	The costs for 6 model health states were estimated: minor GI problem leading to treatment = £39; outpatient investigation for PUB and treatment = £376; inpatient investigation for PUB and treatment = £818; outpatient treatment for PUB = £675; surgery for PUB = £3838 The expected costs per day based on observed PUB were £0.91 for rofecoxib and £0.59 for conventional NSAID The expected costs per day based on endoscopic data with an 85% silent ulcer adjustment were £1.03 for rofecoxib and £1.13 for conventional NSAID The expected costs per day based on endoscopic ulcer data with a 40% silent ulcer adjustment were £1.36 for rofecoxib and £2.52 for conventional NSAID	The authors concluded that the introduction of rofecoxib represents an important therapeutic advantage for patients, and a substantial reduction in the risk of GI complications compared with patients on conventional NSAID comes at only a modest additional cost to the NHS

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Pellissier, 2001[168] USA (third-party payer)	To assess the cost-effectiveness of rofecoxib against non-selective NSAIDs in the treatment of patients with OA	A decision-analytic (decision-tree) model was used to derive the cost-effectiveness of the two health technologies. This was calculated in terms of the cost per year of life saved and the cost per PUB avoided One-way SA was used to test for uncertainty	Clinical: data synthesised from 8 double-blind RCTs trials Direct costs = included: source = drug costs = average wholesale prices Indirect costs = not included Resource use = published reports and expert opinion (US dollars, 1998)	1 year	Base-case analysis: expected cost per day: Rofecoxib = $2.86 NSAIDs = $2.73 Rofecoxib versus NSAIDs: expected cost per year of life saved = $18,614	The authors conclude that the study showed that drug cost differences between rofecoxib and NSAIDs were markedly offset by expected cost savings in GI problems averted with rofecoxib. The expected cost per year of life saved, $18,614, was well within the reported threshold of $50,00 per year

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Peris, 2001[166] Spain (healthcare system)	To undertake a modelled economic comparison of aceclofenac against alternative NSAIDs used in the treatment of common arthritic disorders including RA and OA The alternative NSAIDs were diclofenac, naproxen, piroxicam, ketoprofen, tenoxicam, and indomethacin	A decision-analytic (decision-tree) model was used to compare the costs and effectiveness of the alternative treatment strategies Foldback analysis and bootstrap methods were undertaken to test the robustness of the results	Clinical: 12 randomised double-blinded clinical trials Direct costs = included: source = local unit cost data, hospital accounting datasets, market prices (Spain) Indirect costs = not included Resource use = expert panel of rheumatologists (US dollars, 1996)	3 months	Total cost per patient (NSAID cost + iatrogenic cost) by study, mean value: 1. Diclofenac = $106.5; aceclofenac = $108.6 2. Indomethacin = $87.9; aceclofenac = $110.5 3. Naproxen = $78.2; aceclofenac = $100.3 4. Tenoxicam = $86.7; aceclofenac = $87.9 5. Ketoprofen = $94.8; aceclofenac = $108.7 6. Piroxicam = $63.4; aceclofenac = $87.4 Iatrogenic cost factor (ICF): 1. Diclofenac = 1.88; aceclofenac = 1.53 2. Indomethacin = 2.23; aceclofenac = 1.52 3. Naproxen = 1.55; aceclofenac = 1.38; 4. Tenoxicam = 1.63; aceclofenac = 1.38 5. Ketoprofen = 2.26; aceclofenac = 1.30 6. Piroxicam = 1.17; aceclofenac = 1.32	The authors conclude that the results showed that aceclofenac had a better ICF than the other NSAIDs used in the analysis, which in turn resulted in very similar overall costs, despite the higher overall acquisition cost of aceclofenac

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Tarricone, 2001[165] France, Italy, Spain (healthcare providers)	To compare the cost of 15 days' treatment with nimesulide against diclofenac in the treatment of patients with OA in France, Italy and Spain (Cost-minimisation analysis)	A decision-analytic (decision-tree) was used to compare the total costs (direct) of nimesulide against diclofenac Two-way SA was undertaken to test for uncertainty	Clinical: MA of three RCTs. Direct costs = included: source = National Tariffs; expert panel Indirect costs = not included Resource use = expert panel of GPs in France, Spain and Italy. (Euros, 1999)	15 days	15-day cost of treatment per case: Nimesulide: France = €7, Italy = €10, Spain = €17 Diclofenac: France = €8, Italy = €12, Spain = €21	The authors conclude that their cost-minimisation analysis showed nimesulide to be cost saving compared with diclofenac in all three countries considered. The authors report that projecting their results to the estimated OA prevalence in the entire population of the three countries would result in cost savings to the NHS ranging from a minimum of €17,500,000 in France to a maximum of € 30,000,000 in Spain

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Fendrick, 2002[169] USA (payer perspective)	To compare the economic and clinical effects of two different NSAID treatment strategies in the prevention of NSAID gastropathy Strategy 1: generic NSAID used initially, with safer, more expensive NSAID reserved for patients experiencing a GI adverse events or for patients intolerant of the generic NSAID Strategy 2: safer, more expensive NSAID used in all patients	A Markov decision analysis was used to derive the cost-effectiveness of the two treatment strategies. This was calculated in terms of the incremental cost per symptomatic and complicated ulcer avoided SA was used to test for uncertainty	Clinical: synthesis of previously published studies Direct costs = included: source = payments made by medical services by large private Insurer Indirect costs = not included Resource use =not reported (US dollars, price year no reported)	1 year	Cost per patient treated per year: Strategy 1 = $239 Strategy 2 = $831 Strategy 2 prevented an additional symptomatic ulcer at an incremental cost of $31,900 and a complicated ulcer at a cost of $56,700	The authors conclude that the unrestricted use of safer NSAIDs that reduce the risk of symptomatic ulcer has the potential to produce clinical benefits at incremental cost
Spiegel, 2003[170] USA (third-party payer)	To compare the costs and outcomes of a coxib (once daily) against naproxen (twice daily) in the treatment of patients' chronic arthritis, in order to determine if the degree of risk reduction in GI complications by coxibs offsets their increased cost	A decision-analytic (decision-tree) model was used to estimate the cost-effectiveness of the alternative treatment strategies. This was calculated in terms of the incremental cost per QALY gained One-way and multivariate SA was undertaken to test for uncertainty	Clinical: systematic review of MEDLINE and published abstracts Direct costs = included: source = 2002 American Medical Association Current Procedural Terminology Codebook, 2002 Medicare Free Schedule, Red Book Indirect costs = not included Resource use = not reported (US dollars, price year not reported)	Lifetime	Cost per patient (base case analysis – 3% discount rate): Naproxen = $4859 Coxib = $16,433 The use of a coxib instead of naproxen resulted in an incremental cost of $275,809 per QALY gained	The authors conclude that the risk reduction associated with coxibs does not offset their increased cost compared with non-selective NSAIDs such as naproxen in the management of average-risk patients with chronic RA

For abbreviations, see the footnote to Apendix 12a.

(c) Economic evaluations of head-to-head comparisons of Cox-1 NSAID plus GPA versus Cox-2 inhibitor or Cox-2 preferential

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Bentkover, 1994[171] USA (healthcare payer)	To compare the direct medical costs of three NSAID treatment regimens in a population of elderly patients (≥ 60 years old) with OA The three treatment regimens compared were (i) nabumetone (1 g/day), (ii) ibuprofen alone (2.4 g/day), and (iii) ibuprofen (2.4 g/day) plus misoprostol (800 µg/day)	A decision-analytic model was used to estimate the direct medical costs per patient treated for each of the three treatment regimens One-way SA was used to test for uncertainty	Clinical: data from a single-blind clinical trial Direct costs = included: source = prescription drugs = wholesale drug costs; non-prescription drugs = Red Book (1992); direct medical resource costs = DRG reimbursement amounts (1992) Resource use = single-blind clinical trial (Roth *et al.* 1993)[78] Indirect costs = not Included (US dollars, 1992)	3 months	Total direct medical costs per patient treated: Nabumetone = $183 Ibuprofen = $252 Ibuprofen + misoprostol = $270	The authors conclude that nabumetone is cost saving when compared with ibuprofen only and ibuprofen + misoprostol. Differences in costs resulted from higher costs of the treatment of drug-related adverse events with ibuprofen and higher drug acquisition costs with ibuprofen + misoprostol
Brixner, 1994[172] USA (healthcare provider)	To compare the economic effects (direct medical costs) of nabumetone against NSAIDs alone and NSAID/anti-ulcer therapy in the treatment of patients with OA and RA	A decision-analytic model was used to compare the direct medical costs of the three treatment options	Clinical: synthesis of previously published studies. Direct costs = drugs = wholesale acquisition cost; average weighted costs; Medicare claims Indirect costs = not included Resource use = clinical study (US dollars, price year not reported)	3 months	Direct medical costs (3 months' treatment) Nabumetone = $186.08 NSAIDs alone = $259.89 NSAID/anti-ulcer therapy = $230.24	The authors conclude that in elderly patients with OA or RA treatment with nabumetone would result in cost savings compared with NSAIDs alone and NSAID/anti-ulcer therapy

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Goldstein, 1997[173] USA (healthcare provider)	To compare the costs and consequences of five different treatment regimens for the prevention and management NSAID-induced gastropathy The treatment regimens were: (i) NSAID alone (ii) NSAID with H_2RA (iii) NSAID with misoprostol (iv) diclofenac 50 mg b.d – misoprostol 200 μg t.d.s. (v) diclofenac 75 mg b.d. – misoprostol 200 μg b.d.	A decision-analytic model was used to compare the direct medical costs of the five treatment options	Clinical: synthesis of previously published studies Direct costs = included: source = drugs, average wholesale charges; hospitalisation, mean hospital charges Indirect costs = not included Resource use = expert opinion (US dollars, 1996)	6 months	Treatment costs per patient (6 months): Overall: NSAID regimens = $1153.00 Diclofenac – misoprostol = $939.00 (Cost reduction of $214.00) By individual regimen: NSAID alone = $1017.00 NSAID with H_2RA = $1583 NSAID with misoprostol = $1353.00 Diclofenac (50 mg b.d.) – misoprostol (200 μg/t.d.s.) $921.00 Diclofenac (75 mg b.d.) – misoprostol (200 μg b.d.) = $957.00	The authors conclude that in the base case the diclofenac–misoprostol regimens represented the least costly treatment options, resulting in costs per patient of $214 when compared with the NSAID regimens over the 6-month treatment period

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Ko, 2000[174] USA (third-party payer)	To compare the relative cost-effectiveness of 6 prophylactic strategies against no prophylaxis in the primary prevention of NSAID-induced ulcers in patients aged 65 years commencing NSAID treatment The prophylactic strategies compared were: (i) *H. pylori* testing and selective treatment (ii) treat all empirically for *H. pylori* (iii) conventional dose H_2RA (iv) high-dose H_2RA (v) misoprostol (vi) omeprazole	A decision-analytic (decision-tree) model was used to compare the cost-effectiveness of the alternative treatment strategies. This was calculated in terms of the cost per year of life saved One and two-way SA was undertaken to test for uncertainty	Clinical: synthesis of previously published studies (MEDLINE 1966–88) Direct costs = included: source = Medicare Fee Schedule, 1997, Drug Topics Red Book, American Medical Association Current Procedural Terminology Code Book Indirect costs = not included Resource Use = Medicare (US dollars, 1997)	3 months	Cost per year of life saved: (i) *H. pylori* testing and selective treatment = $23,800 (ii) Treat all empirically for *H. pylori* = cost saving (iii) conventional/low-dose H_2RA = $78,800 (iv) high-dose H_2RA = $78,700 (v) misoprostol = $46,100 (vi) omeprazole = $34,400	The authors conclude that in the baseline analysis the cost-effectiveness of each of the prophylactic strategies for the primary prevention of NSAID-induced ulcers was less than $78,800 per year of life saved, and that empirically treating all patients for *H. pylori* was cost saving

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Zabinski, 2001[175] Canada (Provincial Ministry of Health)	To compare the costs and consequences of treating patients with six different treatment regimens for the management of OA and RA The treatment regimens were: (i) celecoxib (ii) NSAID alone (iii) diclofenac – misoprostol (iv) NSAID + PPI (v) NSAID + H_2RA (vi) NSAID + misoprostol	A decision-analytic (decision-tree) model was used to compare the costs and clinical consequences of the six different treatment regimens One-way SA was used to test for uncertainty	Clinical: pooled analysis of 8 clinical trials. Direct costs = included: source = physician fees and procedures = Ontario Schedule of Benefits; Hospitalisation = acute care in Ontario; drug = Ontario Drug Benefit Data from Brogan Inc. Indirect costs = not included Resource use = expert opinion (physicians practising in Canada) (Canadian dollars, 1998)	6 months	Weighted average cost per patient per 6 months: Celecoxib = Can$273 NSAID alone = Can$262 NSAID + H_2RA = Can$423 Diclofenac – misoprostol = $365 NSAID + misoprostol = Can$421 NSAID + PPI = Can$731	The authors conclude that the results of the study show that the use of celecoxib could result in the avoidance of a significant number of GI adverse events. They also state that the incremental cost of using celecoxib in place of current treatment alternatives in Canada would not impose an excessive incremental cost on the Canadian healthcare budget

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Chancellor, 2001[176] Switzerland (public health insurers)	To estimate the cost-effectiveness of celecoxib in the treatment of OA The costs and consequences in the treatment of OA with celecoxib were compared against five treatment options: (i) NSAIDs alone (ii) NSAID + PPI (iii) NSAID + H_2RA (iv) NSAID + misoprostol (v) diclofenac–misoprostol	A decision-analytic model with Monte Carlo simulation was used to compare the costs and consequences of the six treatment options The authors calculated the cost-effectiveness of celecoxib compared with NSAIDs alone in terms of the cost per adverse event avoided. This was estimated in a stochastic version of the decision-analytic model using Monte Carlo simulation One-way SA was used to test for uncertainty	Clinical = pooled analysis from clinical trials; MA of published literature Direct costs = included: source = hospital = official price list published by Health Insurance Agency; drug costs = Health Insurance Office Indirect costs = not included Resource use = expert opinion (Clinicians in Switzerland) (Swiss francs, price year – not reported)	6 months	Per patient costs of 6 months' treatment (SwF) (figures in parentheses = incremental cost to celecoxib) Celecoxib = 435 NSAID alone = 509.94 (74.88) Diclofenac – misoprostol = 521.95 (86.89), NSAID + misoprostol = 1033.63 (598.57) NSAID + H_2RA = 1201.09 (766.03) NSAID + PPI = 1414.72 (979.66) In relation to the cost-effectiveness analysis using Monte Carlo simulation, the authors report that in 95% of 500 iterations, celecoxib was predicted to save both costs and adverse events, thus dominating NSAIDs alone; the maximum cost per adverse event avoided was SwF4400	The authors conclude that celecoxib is the most cost-effective of the options considered for the treatment of arthritis patients in Switzerland. The estimate that celecoxib will result in cost savings for healthcare budgets if patients are switched from NSAID-based regimens

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
You, 2002[177] Hong Kong (public health organisation)	To analyse the cost of celecoxib and conventional NSAID regimens for the treatment of OA and RA The treatment regimens were: 1. celecoxib 2. NSAID only (naproxen, diclofenac, ibuprofen) 3. NSAID plus H_2RA (150 mg ranitidine twice daily, 20 mg famotidine twice daily, nizatidine 150 mg twice daily or cimetidine 400 mg twice daily) 4. NSAID plus misoprostol (200 μg two to four times daily) 5. NSAID plus PPI (20–40 mg omeprazole daily or 15–30 mg lansoprazole daily)	A decision tree was used to simulate the clinical outcomes and cost of 5 treatment regimens One-way SA was included on patients' GI risk scores and all clinical probabilities and costs The study population was a hypothetical cohort of patients with OA and RA	Clinical: synthesis of previously published studies Direct costs: drugs, GPAs and medicines involved with management of GI events, hospitalisation, clinic visits, laboratory tests, oesophago-gastro-duodenoscopy and surgery Source: drugs – from hospital authority. Other costs: charges for itemised healthcare services posted in the Hong Kong Gazette. Indirect costs: not included Resource use: medical records of 144 patients admitted to a public teaching hospital in Hong Kong (HK$, where US$1 = HK$7.8, price year not reported)	6 months	The expected costs for the base-case analysis were: 1. Celecoxib = HK$1545 2. NSAID only = HK$1610 3. NSAID plus H_2RA = HK$1404 4. NSAID plus misoprostol = HK$2213 5. NSAID plus PPI = HK$2857	The authors concluded that celecoxib appeared to be the least costly alternative in patients with intermediate to high GI risk for the treatment of OA and RA in Hong Kong

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
El-Serag, 2002[178] USA (third-party payer)	To determine the most cost-effective strategy for reducing the risk of clinical UGI events (symptomatic ulcer, perforation, bleeding and obstruction) in NSAID users. The results were presented using a nomogram The treatment regimens were: 1. conventional NSAID (800 mg ibuprofen t.d.s.) 2. conventional NSAID plus a single dose of regular-strength PPI (30 mg lansoprazole daily) 3. conventional NSAID plus 200 μg misoprostol daily 4. coxib (100 mg celecoxib twice daily) 5–8. bismuth subsalicylate – metronidazole – tetracycline combination and PPI treatment for *H. pylori* twice daily for 2 weeks followed by each of the first 4 treatment strategies	A decision-analytic (decision-tree) model was used to evaluate the cost-effectiveness of 8 strategies for reducing the risk of GI events The SA included 3 variables: baseline risk of GI events with conventional NSAID alone, risk of GI events with other strategies of NSAID and cost of the drugs. One-, two- and three-way SAs were conducted The model was applied assuming that the patient was a 55-year-old person with OA who requires NSAID therapy for 1 year	Clinical: synthesis of previously published studies Direct costs: costs of drugs alone and costs of drugs plus cost of clinical GI events Source: not reported for the unit costs of drugs The assumed cost of a UGI event was fixed at $28,000 Indirect costs: not included Resource use: not reported (US dollars, price year not reported)	1 year	Cost of drugs per patient per year (US$): Strategy 1 = $239; strategy 2 = $1632; strategy 3 = $1209; strategy 4 = $1029; strategy 5 = $423; strategy 6 = $1816; strategy 7 = $1393; strategy 8 = $1213 Cost of strategy per patient per year (cost of drugs plus cost of clinical GI event) assuming baseline risk of 6.5% for GI event with conventional NSAID: strategy 1 = $2059; strategy 2 = $2445; strategy 3 = $2301; strategy 4 = $1939; strategy 5 = $2061; strategy 6 = $2538; strategy 7 = $2375; strategy 8 = $2032 ICER using costs of drugs alone compared with strategy 1 assuming a risk of 6.5% for UGI: strategy 2 = $11877; strategy 3 = $9308; strategy 4 = dominant; strategy 5 = $308; strategy 6 = $16,112; strategy 7 = $10,595; strategy 8 = dominant	The authors concluded that it is cost-effective to use relatively expensive medicines such as coxibs or to add a PPI to regimens for patients with a high risk for GI events

continued

Study (perspective)	Study aim	Modelling methods	Sources of data	Time horizon	Results	Conclusion
Kamath, 2003[179] USA (third-party payer)	To conduct an economic evaluation of rofecoxib and celecoxib compared with high-dose acetaminophen (paracetamol) or ibuprofen with and without misoprostol for patients with symptomatic knee OA The treatment regimens were: 1. acetaminophen (1 g four times daily) 2. ibuprofen (800 mg t.d.s.) 3. ibuprofen (800 mg tds) plus misoprostol 200 μg t.d.s 4. celecoxib (200 mg b.d.) 5. rofecoxib (25 mg b.d.)	A decision-analytic (decision-tree) model was used to evaluate the cost-effectiveness of 5 strategies for knee OA The SA included every variable in the model One, two and probabilistic SAs were conducted The model was applied assuming that the patient population typically included those over 50 years of age, who had radiographically identified knee OA, for whom the above drugs were indicated for pain relief	Clinical: synthesis of previously published studies Direct costs: costs of drugs, monitoring and treating adverse events, which included hospitalisation, surgery, outpatient procedures, consultations and co-prescription of GPAs Source: Red Book per prescribed dose of drugs. Mayo Clinic billing data over 5 years. Medicare Fee Schedule Indirect costs: not included Resource use: actual resource use of OA patients from two published studies[87] (US dollars, 2000)	6 months	The costs for a cohort of 1000 patients were: (1) $63,000 for acetaminophen, (2) $112,000 for ibuprofen, (3) $471,000 for ibuprofen plus misoprostol; (4) $474,000 for celecoxib and (5) $556,000 for rofecoxib ICER using adverse events averted (all patients): (1) not applicable; (2) dominated; (3) dominated; (4) dominated; (5) dominated ICER using patients achieving MPCI response (all patients): (1) not applicable; (2) $610.77; (3) $11,977.25; (4) dominated; (5) dominated	The authors concluded that for OA patients with average risk, acetaminophen dominates the other therapies in terms of cost per GI event averted, supporting the current guidelines for OA drug therapy. In terms of pain relief, CEACs indicate that if one values pain relief below $275 per patient achieving MPCI, acetaminophen is the therapy most likely to be optimal

For abbreviations, see the footnote to Appendix 12a.

Appendix 13

Defined daily doses (DDDs) and average daily quantity (ADQ) for non-steroidal anti-inflammatory drugs (BNF sub-section 10.1.1)

Administration route	BNF name	DDD	ADQ	Unit	Notes
Oral	Aceclofenac[a,b,c]	200	200	mg	
Oral	Acemetacin[a]		120	mg	New July 2000
Oral	Azapropazone[c]	750	900	mg	
Oral	Benorylate[a]	3	3	g	=
Oral	Celecoxib[a,b]	200	200	mg	New July 2000
Oral	Dexketoprofen[d]	75	50	mg	New November 1999
Oral, rectal	Diclofenac sodium[a]	100	100	mg	
Oral	Diclofenac sodium and misoprostol 50 mg/200 µg	100 mg	4	Tablets	New July 2000; DDD corresponds to diclofenac; ADQ is 2 tablets of each drug
Oral	Diclofenac sodium and misoprostol; 75 mg/200 µg	100 mg	4	Tablets	New July 2000 2 tablets of each drug
Oral	Diflunisal[a,d]	750	750	mg	
Oral	Etodolac[a,b]	400	600	mg	
Oral	Fenbufen[a]	600	900	mg	
Oral	Fenoprofen[a]	1.2	1.2	g	
Oral	Flurbiprofen[a,d]	200	200	mg	
Oral, rectal	Ibuprofen[a,d]	1.2	1.2	g	
Oral	Ibuprofen and codeine 300 mg/20 mg		4	Tablets	New July 2000
Oral, rectal	Indomethacin[a,b]	100	100	mg	Rectal ADQ; new July 2000
Oral, rectal	Ketoprofen[a,d]	150	150	mg	
Oral	Mefenamic Acid[a,b,d]	1	1	g	
Oral	Meloxicam[a,b,c]	15	7.5	mg	New November 1999
Rectal	Meloxicam[a,b,c]	15	15	mg	New November 1999
Oral	Nabumetone[a,b]	1	1	g	
Oral, rectal	Naproxen[a,d]	500	750	mg	
Oral	Naproxen and misoprostol 500 mg/200 µg		4	Tablets	New July 2000 2 tablets of each drug
Oral, rectal	Piroxicam[a]	20	20	mg	
Oral	Rofecoxib[b]		25	mg	New November 1999
Oral	Sodium Salicylate[a]	3	3	g	
Oral	Sulindac[a]	400	400	mg	
Oral	Tenoxicam[a]	20	20	mg	
Oral	Tiaprofenic Acid[a]	600	600	mg	
Oral	Tolmetin[a,b,c]	700	800	mg	

Indications:
[a] Pain and inflammation in rheumatic disease and other musculoskeletal disorders.
[b] Osteoarthritis.
[c] Ankylosing spondylitis.
[d] Mild to moderate pain including dysmenorrhoea.

Appendix 14

References to excluded studies

Study reference	Reason for exclusion code[a]
Multicenter study with nimesulide in rheumatology. [Portuguese]. *Arq Bras Med* 1992;**66**:363–7.	B
Aabakken L, Larsen S, Osnes M. Cimetidine tablets or suspension for the prevention of gastrointestinal mucosal lesions caused by non-steroidal, anti-inflammatory drugs. *Scand J Rheumatol* 1989;**18**:369–75.	B
Aenishanslin W, Barlocher C, Bernoulli R. Misoprostol and cimetidine in treatment of duodenal ulcer. [German]. *Schweiz Med Wochenschr* 1985;**115**:1225–31.	C
Agrawal N, Roth S, Graham D, White R, Germain B, Brown J, *et al*. Misoprostol compared with sucralfate in the prevention of nonsteroidal anti-inflammatory drug induced gastric ulcer: a randomised, controlled trial. *Ann Intern Med* 1991;**115**:195–200.	G
Agrawal NM, Campbell DR, Safdi MA, Lukasik NL, Huang B, Haber MM. Superiority of lansoprazole vs ranitidine in healing nonsteroidal anti-inflammatory drug-associated gastric ulcers: results of a double-blind, randomized, multicenter study. *Arch Intern Med* 2000;**160**:1455–61.	F (healing, no non-GI outcomes)
Agrifoglio E, Bartolozzi P, Campailla P, Cherubino P, Di Leo P, Fusilli DCF *et al*. Multicentric study on efficacy and tolerance of misoprostol in gastropathy due to NSAIDs. [Italian]. *Ortop Traumatol Oggi* 1993;**13**:147–55.	A
Agus GB, De Angelis R, Mondani P, Moia R. Double-blind comparison of nimesulide and diclofenac in the treatment of superficial thrombophlebitis with telethermographic assessment. *Drugs* 1993;**46**:200–3.	B
Ahmed WU, Kirmani SR, Qureshi H, Alam SE, Zuberi SJ. Misoprostol in the treatment of NSAID-induced gastroduodenal lesions. *Indian J Gastroenterol* 1991;**10**:135–6.	F
Alberdi FJ, Guemes DF, Perez MA. A double-blind study of trithiozine in peptic ulcers. *Clinical Ther* 1978;**1**:251–9.	C (healing, not on NSAIDs)
Bach GL, Stock K-P, Hudepohl M. Treatment of NSAID-induced gastrointestinal lesions with misoprostol. [German]. *Z Rheumatol* 1991;**50**:175–80.	F
Barbier JP, Haccoun P, Bergmann JF, Arnould B, Hamelin B. Prognostic factors influencing healing of reflux esophagitis. A controlled trial of omeprazole versus ranitidine. Study group Omega [French]. *Ann Gastroenterol Hepatol* 1993;**29**:213–18.	C
Berkowitz JM, Rogenes PR, Sharp JT, Warner CW. Ranitidine protects against gastroduodenal mucosal damage associated with chronic aspirin therapy. *Arch Intern Med* 1987;**147**:2137–9.	G
Bianchi Porro G, Caruso I, Petrillo M, Montrone F, Ardizzone S . A double-blind gastroscopic evaluation of the effects of etodolac and naproxen on the gastrointestinal mucosa of rheumatic patients. *J Intern Med* 1991;**229**:5–8.	E
Bijlsma JW. Treatment of endoscopy-negative NSAID-induced upper gastrointestinal symptoms with cimetidine: an international multicentre collaborative study. *Aliment Pharmacol Ther* 1988;**2**:Suppl: 83.	A
Blardi P, Gatti F, Auteri A, Di Perri T. Effectiveness and tolerability of nimesulide in the treatment of osteoarthritic elderly patients. *Int J Tissue React* 1992;**14**:263–8.	C
Bocca M, Giordano M, Del Pizzo M, Nelken A, Ghiggia M, Pomatto E. The use of misoprostol in prevention of gastric disease from nonsteroidal anti-inflammatory drugs in oral–maxillofacial surgery. [Italian]. *Minerva Ortognatodontica* 1990;**8**:139–41.	B
Boers M, Dijkmans BAC, Breedveld FC, Camps JAJ, Chang PC, Van Brummelen P, *et al*. No effect of Misoprostol on renal function of rheumatoid patients treated with diclofenac. *Br J Rheumatol* 1991;**30**:56–9.	B
Bolten W, Lemmel EM, Distel M, Bluhmki E, Hanft G, Degner FL. Treatment of rheumatoid arthritis (RA) with meloxicam: controlled double-blind clinical test with placebo. *Z Rheumatol*. 1996;**55** Suppl 1:112.	B

continued

Study reference	Reason for exclusion code[a]
Bontoux D. Lumbo-radiculalgia: efficacy, safety and therapeutic benefit of etodolac (600 mg daily) versus diclofenac (150 mg daily and placebo). *Rhumatologie* 1990;**42**:201–6.	B
Briancon D, Peterschmitt J, Laviec G. Double-blind parallel-group evaluation of the safety and efficacy of etodolac capsules compared with piroxicam capsules in patients with rheumatoid arthritis. *Acta Therapeutica* 1991;**17**:35–47.	E
Cantarelli A, Giannunzio D, Ligorio L, Mapelli A, Veca G, Gallucci M, *et al*. Comparison of nimesulide and naproxen sodium in the control of cancer pain. [Italian]. *Minerva Anestesiol* 1991;**57**:1103–4.	B
Carabba M, Galanti A, Paresce E, Angelini M, Re K, Torchiana E, *et al*. Gastrointestinal effects of meloxicam versus piroxicam by means of gastroduodenoscopy in patients with rheumatoid arthritis. *Scand J Rheumatol Suppl* 1996;**106**:55.	B
Chikanza IC, Clarke B, Hopkins R, MacFarlane DG, Bird H, Grahame R. A comparative study of the efficacy and toxicity of etodolac and naproxen in the treatment of osteoarthritis. *Br J Clin Prac* 1994;**48**:67–9.	D
Cohen de Lara A, Gompel H, Baranes C, Bornstein U, Brajer S, Cambray S, *et al*. Two comparative studies of dosmalfate vs. misoprostol in the prevention of NSAID-induced gastric ulcers in rheumatic patients. *Drugs Today* 2000;**36**:73–8.	C
Copley-Merriman C, Egbuonu-Davis L, Kotsanos JG, Conforti P, Franson T, Gordon G. Clinical economics: a method for prospective health resource data collection. *Pharmacoeconomics* 1992;**1**:370–6.	B
Czarnobilski Z, Bem S, Czarnobilski K, Konturek SJ. Carprofen and the therapy of gastroduodenal ulcerations by ranitidine. *Hepato-Gastroenterology* 1985;**32**:20–3.	C
Dammann HG, Simon-Schultz J, Dreyer M, Simon B, Muller P. Effective prophylaxis of piroxicam-induced gastroduodenal lesions with nizatidine. [German]. *Z Gastroenterol* 1990;**28**:94–6.	B
Davies J, Collins AJ, Dixon SA. The influence of cimetidine on peptic ulcer in patients with arthritis taking anti-inflammatory drugs. *Br J Rheumatol* 1986;**25**:54–8.	F (healing, no non-GI outcomes)
De Oliveira D. The treatment of upper respiratory tract and ear inflammatory non-infectious conditions with NSAID. A comparative randomized trial with nimesulide and potassium diclofenac. [Portuguese]. *Folha Med* 1991;**102**:87–91.	B
de Queiros MF. Double-blind comparison of etodolac and naproxen in the treatment of rheumatoid arthritis. *Clin Ther* 1991;**13**:38–46.	E
Delcambre B. Rheumatoid arthritis: efficacy, safety and therapeutic benefit of etodolac (600 mg daily) versus indomethacin (100 mg daily). *Rhumatologie* 1990;**42**:213–18.	D
Di Leo S, Meli MT, Scaricabarozzi I, Bedoschi D. Sicilian multicenter study of the efficacy and tolerability of nimesulide in gyneacological inflammatory diseases. [Italian]. *Minerva Ginecol* 1990;**42**:277–81.	A
Dick WC, Franchimont P, Veys E. Double-blind comparison of etodolac and piroxicam in the treatment of rheumatoid arthritis. *Clin Ther* 1993;**15**:148–59.	E
Durakovic Z, Vrhovac B, Falisevac V, Gjurasin M. Therapeutic trial of cimetidine in erosive gastritis. [Serbocroatian]. *Lijecnicki Vjesnik* 1979;**101**:289–93.	A
Edworthy SM, Devins GM. Improving medication adherence through patient education distinguishing between appropriate and inappropriate utilization. Patient Education Study Group. *J Rheumatol* 1999;**26**:1793–801.	C
Elta GH, Appelman HD, Behler EM, Wilson JA, Nostrant TJ. A study of the correlation between endoscopic and histological diagnoses in gastroduodenitis. *Am J Gastroenterol* 1987;**82**:749–53.	C
Famaey JP, Bruhwyler J, Geczy J, Vandekerckhove K, Appelboom T. Open controlled randomized multicenter comparison of nimesulide and diclofenac in the treatment of subacute and chronic low back pain. *J Clin Res* 1998;**1**:219–38.	D
Farini R, Di Mario F, Scalabrin G. Cimetidine vs. trithiozine in the treatment of benign gastric ulcer. *Ital J Gastroenterol* 1982;**14**:55.	C

continued

Study reference	Reason for exclusion code[a]
Ferrari E, Pratesi C, Scaricabarozzi I, Trezzani R. A clinical study of efficacy and tolerability of nimesulide compared with diclofenac sodium in the treatment of acute superficial thrombophlebitis. [Italian]. *Minerva Cardioangiol* 1992;**40**:455–60.	B
Ferrari E, Pratesi C, Scaricabarozzi I. A comparison of nimesulide and diclofenac in the treatment of acute superficial thrombophlebitis. *Drugs* 1993;**46**:197–9.	B
Frank WO, Wallin BA, Berkowitz JM, Kimmey MB, Palmer RH, Rockhold F, *et al*. Reduction of indomethacin induced gastroduodenal mucosal injury and gastrointestinal symptoms with cimetidine in normal subjects. *J Rheumatol* 1989;**16**:1249–52.	B
Gabryelewicz S, *et al*. Preventive effect of ranitidine against gastrointestinal disorders in rheumatic patients treated with non-steroidal anti-inflammatory drugs (NSAID). *Gastroenterology* 1987;**92**:1398.	A
Gallucci M, Toscani F, Mapelli A, Cantarelli A, Veca G, Scaricabarozzi I. Nimesulide in the treatment of advanced cancer pain. Double-blind comparison with naproxen. *Arzneim-Forsch* 1992;**42**:1028–30.	B
Georg KJ, Mertens D, and Mons GV. Lansoprazole versus misoprostol in the prevention of indomethacin-induced gastro-duodenal lesions. A prospective randomized single-blind study in women undergoing hip joint endoprostesis [abstract]. *Gut* 1997;**41** (Suppl 3):A7.	D
Gottesdiener K, Mehlisch DR, Huntington M, Yuan W-Y, Brown P, Gertz B, *et al*. Efficacy and tolerability of the specific cyclooxygenase-2 inhibitor DFP compared with naproxen sodium in patients with postoperative dental pain. *Clin Ther* 1999;**21**:1301–12.	B
Habibullah CM, Singh SP, Phaterpekar SJ. Misoprostol (Cytotec) in NSAID gastropathy. *J Assoc Physicians India* 1993;**41**:770.	A
Hannequin J-R. Efficacy of Arthrotec(TM) in the treatment of rheumatoid arthritis. *Scand J Rheumat Suppl* 1992;**21**:7–14.	D
Hunt RH, Bowen B, Mortensen ER, Simon TJ, James C, Cagliola A, *et al.* A randomized trial measuring fecal blood loss after treatment with rofecoxib, ibuprofen, or placebo in healthy subjects. *Am J Med* 2000;**109**:201–6.	F (healthy adults)
Huskisson EC, Narjes H, Bluhmki E. Efficacy and tolerance of meloxicam, a new NSAID, in daily oral doses of 15, 30 and 60 mg in comparison to 20 mg piroxicam in patients with rheumatoid arthritis. *Scand J Rheumatol Suppl* 1994;**98**:115.	D
Jallad NS, Sanda M, Salom IL, Perdomo CS, Garg DC, Mullane JF, *et al*. Gastrointestinal blood loss in arthritic patients receiving chronic dosing with etodolac and piroxicam. *Am J Med Sci* 1986;**292**:272–6.	D
Jaszewski R, Graham DY, Stromatt SC. Treatment of nonsteroidal antiinflammatory drug-induced gastric ulcers with misoprostol: a double-blind multicenter study. *Dig Dise Sci*1992;**37**:1820–4.	B
Jenoure P, Gorschewsky O, Ryf C, Steigbugel M, Wetzel C, Frey W, *et al*. Randomised, double-blind, multicentre study of nimesulide vs. diclofenac in adults with acute sport injuries. *J Drug Assess* 1998;**1** (Part 3):495–508.	B
Jensen DM, Ho S, Hamamah S, Frankl H, Faigel D, DeMarco D, *et al*. A randomised study of Omeprazole compared to misoprostol for prevention of recurrent ulcers and ulcer hemorrhage in high risk patients injesting aspirin or NSAIDs. *Gastroenterol* 2000;**118** (4, Suppl 2):AS92.	E (unclear what proportion on aspirin rather than NSAIDs)
Jones AC, Coulson L, Muir K, Tolley K, Lophatananon A, Everitt L, *et al*. A nurse-delivered advice intervention can reduce chronic non-steroidal anti-inflammatory drug use in general practice: a randomized controlled trial. *Rheumatology* 2002;**41**:14–21.	C
Karateev AE, Murav'ev I, Nasonova VA. The endoscopic assessment of the effect of ranitidine and pirenzepine on the manifestations of the gastropathy induced by nonsteroidal anti-inflammatory preparations. [Russian]. *Terapevticheskii Arkhiv* 1997;**69**:67–9.	C
Klumb EM, Pinheiro GRC, Ferrari A, Albuquerque EMN. The treatment of acute gout arthritis. Double-blind randomized comparative study between nimesulid and indomethacin. [Portuguese]. *Rev Bras Med* 1996;**53**:540–6.	B

continued

Study reference	Reason for exclusion code[a]
Laine L, Cominelli F, Sloane R, Casini-Raggi V, Marin-Sorensen M, Weinstein WM. Interaction of NSAIDs and *Helicobacter pylori* on gastrointestinal injury and prostaglandin production: a controlled double-blind trial. *Aliment Pharmacol Ther* 1995;**9**:127–35.	F (healthy volunteers)
Laine L, Sloane R, Ferretti M, Cominelli F. A randomized double-blind comparison of placebo, etodolac, and naproxen on gastrointestinal injury and prostaglandin production. *Gastrointest Endosc* 1995;**42**:428–33.	F
Lanza FL, Royer GL. NSAID-induced gastric ulceration is dose-related by weight: an endoscopic study with flurbiprofen. *Am.J Gastroenterol* 1993;**88**:683–6.	B
Lauritsen K, Rutgersson K, Bolling E, Brunner G, Eriksson S, Galmiche JP, *et al*. Omeprazole and ranitidine in the prevention of relapse in patients with duodenal ulcer disease. *Can J Gastroenterol* 1999;**13**:806–13.	C
Lei-Munhoz MS, Malavasi GM, Munhoz MLGS, Gananca HHC, Gananca FF. Comparative study with nimesulide vs potassium diclofenac in ent disease. *Rev Bras Med* 1990;**47**:591–4.	B
Lemmel EM, Bolten W, Vargas R, Platt PN, NissilS M, and SD. A double-blind placebo controlled study of 7.5 mg and 15 mg of meloxicam in patients with rheumatoid arthritis (RA). *Scand J Rheumatol Suppl* 1994;**98**:111	B
Lipscomb GR, Wallis N, Armstrong G, Rees WDW. Gastrointestinal tolerability of meloxicam and piroxicam: A double-blind placebo-controlled study. *Br J Clin Pharmacol* 1998;**46**:133–7.	F (healthy volunteers)
Lonauer G, Tisscher JR, Lim HG, Bijlsma JW. Double-blind comparison of etodolac and diclofenac in patients with rheumatoid arthritis. *Curr Med Res Opin* 1993;**13**:70–7.	E
Lucker PW, Pawlowski C, Friederich I, Faiella F, Magni E. Double-blind, randomised, multi-centre clinical study evaluating the efficacy and tolerability of nimesulide in comparison with etodalac in patients suffering from osteoarthritis of the knee. *Eur J Rheumatol Inflamm* 1994;**14**:29–38.	C
Macciocchi A. Results of a Swiss phase IV study. Nimesulide in the daily practice. [German]. *Ther Schweiz* 1997;**13**:270–5.	A
Maeda A. Clinical efficacy of lansoprazole in treatment of gastric ulcer induced by NSAIDs. [Japanese]. *Jpn Pharmacol Ther* 1998;**26**:225–30.	F (Healing, no non-GI outcomes)
Malavasi GM, Lei Munhoz MS, Caovilla HH, Munhoz ML, Freitas GF. Comparative study of nimesulide versus potassium diclofenac in acute otitis media. [Portuguese]. *Rev Bra Medi* 1990;**47**:373–6.	B
Manniche C, Malchow-Moller A . The influence of non-steroid anti-inflammatory drugs (NSAID) on the treatment of peptic ulceration. A prospective randomized investigation. [Danish]. *Ugeskr Laeger* 1987;**149**:2143–4.	C
Marcon V, Cannizeuro R, Valentini M, Cressani B, Costan BF, Angonese C, *et al*. Sucralfate, ranitidine and no treatment in gastric ulcer management – a multicenter, prospective, randomized, 24-month follow-up with a study of risk factors of relapse. *Digestion* 1992;**53**:72–8.	C
Marques Neto JF, Samara AM. Double-blind crossover study. Cimetidine/placebo in patients with rheumatoid arthritis treated with indomethacin. [Portuguese]. *Folha Medica* 1982;**85**:885–6.	D
Martinez RO, Casas H, Mazure PA, Leczycki H, Cosen JN, Canievsky L, *et al*. Gastroduodenal lesions in rheumatoid arthritis. Evaluation and treatment. [Spanish]. *Acta Gastroenterol Latinoam* 1988;**18**:87–96.	F
McKenna F. Efficacy of diclofenac/misoprostol vs diclofenac in the treatment of ankylosing spondylitis. *Drugs* 1993;**45**:24–30.	D
McKenna F, Weaver A, Fiechtner JJ, Bello AE, Fort JG. COX-2 specific inhibitors in the management of osteoarthritis of the knee: a placebo-controlled, randomized, double-blind study. *JCR J Clin Rheumatol* 2001;**7**:151–9.	C
Medina Santillan R, Reyes GG, Mateos GE. Prevention of gastroduodenal injury induced by NSAIDs with low-dose Misoprostol. *Proc West Pharmacol Soc* 1999;**42**:33–4.	B
Menkes CJ. Scapulo-humeral periarthritis: efficacy, safety and therapeutic benefit of etodolac (600 mg daily) versus piroxicam (40/20 mg daily). *Rhumatologie* 1990;**42**:195–200.	B

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Study reference	Reason for exclusion code[a]
Metzenroth H, Publig W, Knahr K, Zandl C, Kuchner G, Carda C. Indomethacin as a prophylactic against ossification following total hip-joint replacement and its effect on the gastric mucosa. [German]. *Z Orthop Ihre Grenzgeb* 1991;**129**:178–82.	B
Milvio C, Borellini P, Milvio E. Tolerability of nimesulide. A long-term clinical trial. *Arch Med Interna* 1983;**35**:127–36.	A
Miniti AM. Comparative study of nimesulide versus naproxen in patients with pharyngo-tonsillitis. *Arq Brasde Med* 1991;**65**:511–14.	B
Monette J, Mogun H, Bohn RL, Avorn J. Concurrent use of antiulcerative agents. *J Clin Gastroenterol* 1997;**24**:207–13.	A
Montoneri C, Garofalo A, Lurato S, Scaricabarozzi I, Trezzani R. Clinical study of the efficacy and tolerability of nimesulide in suppository formulation compared to flurbiprofen in gynecology. [Italian]. *Minerva Ginecol* 1990;**42**:413–19.	B
Murray FE, Shah AA, Thjodleifsson B, *et al*. Comparison of the effects of naproxen and the COX-2 selective NSAID, nimesulide, on prostanoid formation in man [abstract]. *Gut* 1998;**42**:A6.	B
Musi AO, Morgante P, Porrini A. Ranitidine protective activity on esophageal–gastroduodenal mucosa of rheumatic patients receiving antiinflammatory non-steroidal drugs. [Spanish]. *Prensa Med Argent* 1984;**71**:803–8.	C
Orti E, Canelles P, Quiles F, Zapater R, Cuquerella J, Ariete V, *et al.* Is upper gastrointestinal bleeding evolution influenced by the used antisecretory? [Spanish]. *Rev Esp Enferm Dig* 1995;**87**:427–30.	B
Patoia L, Santucci L, Furno P, Dionisi MS, Dell'Orso S, Romagnoli M, *et al*. A 4-week, double-blind, parallel-group study to compare the gastrointestinal effects of meloxicam 7.5 mg, meloxicam 15 mg, piroxicam 20 mg and placebo by means of faecal blood loss, endoscopy and symptom evaluation in healthy volunteers. *Br J Rheumatol* 1996;**35**:61–7.	F (healing, no non-GI outcomes)
Pattin S. Ankylosing spondylitis: efficacy, safety and therapeutic benefit of etodolac (600 mg daily) versus piroxicam (20 mg daily). *Rhumatologie* 1990;**42**:207–12.	D
Penston JG, Dixon JS, Boyd EJ, Wormsley KG. A placebo-controlled investigation of duodenal ulcer recurrence after withdrawal of long-term treatment with ranitidine. *Aliment Pharmacol Ther* 1993;**7**:259–65.	C
Peris F, *et al*. Treatment compliance and safety of aceclofenac versus standard NSAIDs in patients with common arthritic disorders: a meta-analysis. *Eur J Rheumatol Inflamm* 1996;**16**:37–45.	A
Piotrowski J, Gabryelewicz A , Konturek S. Ranitidine effect of gastric mucosa damage in patients with rheumatoid diseases on long-term treatment with non-steroid anti-inflammatory drugs. *Mater Med Pol* 1986;**18**:170–6.	F (healing, no non-GI outcomes)
Pitkala KH, Strandberg TE, Tilvis RS. Worsening heart failure associated with COX-2 inhibitors [2]. *Am J Med* 2002;**112**:424–6.	A
Puscas I, Fillat O, Herrero E, *et al*. Effectiveness and safety of ebrotidine versus ranitidine in the prevention of piroxicam-induced gastroduodenal lesions. *Revista Espa±ola.de Reumatologfa*. 1996;**23**:182.	B
Ramella G, Costagli V, Vetere M, Capra C, Casella G, Sogni A, *et al*. Comparison of nimesulide and diclofenac in the prevention and treatment of painful inflammatory postoperative complications of general surgery. *Drugs* 1993;**46**:159–61.	B
Reginster JY, Distel M, Bluhmki E. A double-blind, three-week study to compare the efficacy and safety of meloxicam 7.5 mg and meloxicam 15 mg in patients with rheumatoid arthritis. *Br J Rheumatol* 1996;**35**:17–21.	C
Reitblat T, *et al*. The different patterns of blood pressure elevation by rofecoxib and nabumetone. *Journal of Human Hypertension* 2002;**16**:431–4.	D
Reynolds JC, Schoen RE, Maislin G, Zangari GG. Risk factors for delayed healing of duodenal ulcers treated with famotidine and ranitidine. A*m J Gastroenterol* 1994;**89**:571–80.	C
Reynoso SG, Gallardo FM. Cimetidine, 800 mg nocte, in gastritis resulting from prolonged use of non-steroid antiinflammatories. [Spanish]. *Invest Med Int* 1988;**14**:254–7.	A

continued

Study reference	Reason for exclusion code[a]
Rovinski A, Cavalheiro Neto AR, Gattas C. The treatment of acute back pain. Single blind randomic and comparative trial among nimesulide and diclofenac potassium. [Portuguese]. *Rev Bras Med* 1995;**52**:784–9.	B
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continued

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[a] A, not an RCT; B, not of at least 3 weeks duration; C, not a relevant comparison; D, no usable outcome data; E, not at least minimum dose of NSAIDs or gastroprotectors; F, other (e.g. participants were healthy volunteers, or this was a healing study that did not report non-GI outcomes or more than 20% of participants were on aspirin rather than NSAIDs); G, Rostom reference not appropriate to this review.

Appendix 15

References to studies awaiting translation

Study reference	Original language
Shiokawa Y, Nobunaga M, Saito T, Sakita T, Miwa T, Nakamura K, *et al*. [Evaluation of misoprostol's clinical utility for gastric/duodenal ulcers seen under long-term use of non-steroidal anti-inflammatory drugs (NSAID) – I. Evaluation of mucosal prophylactic effects by a placebo-controlled double blind comparative study]. *Ryumachi* 1991;**31**:554–71.	Japanese
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Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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ISSN 1366-5278