

Comparative Effectiveness and Safety of Analgesics for Osteoarthritis- An Update of the 2006 Report

Appendixes

Appendix A. Comparable NSAID Dose Levels

Nonselective NSAIDs	Low Dose	Medium Dose	High or Max Dose
Diclofenac potassium	50mg bid	50mg tid	50mg qid (in OA/RA only)
Diclofenac sodium	50mg bid	75mg bid	50mg qid or 100mg SR bid (in RA only)
Fenoprofen	200-300mg qid	600mg tid-qid	800mg qid
Flurbiprofen	50mg bid	50mg tid-qid	100mg tid
Ibuprofen	400mg tid	600mg tid-qid	800mg qid**
Ketoprofen	25-50mg tid	75mg tid	IR =300mg/day (divide), SR =200mg/day
Naproxen	250mg tid	500mg bid	1250mg/day (divided)
Naproxen sodium	275mg tid	550mg bid	1375mg/day (divided)
Oxaprozin	600mg qd	1200mg qd	1200mg qd
Sulindac	150mg bid	200mg bid	200g bid
Piroxicam	10mg qd	20mg qd	40mg per day (not indicated for OA or RA)
Partially-selective NSAIDs	Low Dose	Medium Dose	High or Max Dose
Etodolac	200mg tid	400mg bid	1200mg max (IR or SR divided doses)
Meloxicam/Mobic	7.5mg qd	7.5mg qd	15mg qd
Nabumetone	1000mg qd	1000mg bid	2000mg/day (qd or divided bid)
Cox-2 inhibitors	Low Dose	Medium Dose	High or Max Dose
Celecoxib/Celebrex	200mg qd	200mg bid	200mg bid

Abbreviations: COX= Cyclo-oxygenase; IR= Immediate release; NSAID= Nonsteroidal antiinflammatory drug; OA= Osteoarthritis; RA= Rheumatoid arthritis; SR= Sustained release

**This table does not represent exact or equivalent dosing conversions. It is based on FDA approved dosing ranges and comparative doses from clinical trials.*

Source: <http://www.ashp.org/emplibrary/NSAIDsConversiontools.pdf>

Appendix B. Cyclooxygenase Selectivity of NSAIDs

NSAID	Ratio*
Flurbiprofen	10.27
Ketoprofen	8.16
Fenoprofen	5.14
Tolmetin	3.93
Aspirin	3.12
Oxaprozin	2.52
Naproxen	1.79
Indomethacin	1.78
Ibuprofen	1.69
Ketorolac	1.64
Piroxicam	0.79
Nabumetone	0.64
Etodolac	0.11
Celecoxib	0.11
Meloxicam	0.09
Mefenamic acid	0.08
Diclofenac	0.05

Abbreviation: NSAID= Nonsteroidal antiinflammatory drug

*Expressed as the ratio of the 50% inhibitory concentration of cyclooxygenase-2 to the 50% inhibitory concentration of cyclooxygenase-1 in whole blood. NSAIDs with a ratio of <1 indicate selectivity for cyclooxygenase-2.

Adapted from: Feldman M, McMahon AT. Do cyclooxygenase-2 inhibitors provide benefits similar to those of traditional nonsteroidal anti-inflammatory drugs, with less gastrointestinal toxicity? *Annals of Internal Medicine* 2000;132:134-43.

Appendix C. Exact Search Strings

Original Report

Ovid MEDLINE® searches (1966 to July Week 3 2005)

I. Search Strategy: NSAIDs, focus on efficacy (OA)

- 1 exp OSTEOARTHRITIS/ (26153)
- 2 limit 1 to (humans and english language) (18162)
- 3 celecoxib.mp. (1545)
- 4 choline magnesium trisalicylate.mp. (38)
- 5 DICLOFENAC/ (3399)
- 6 DIFLUNISAL/ (380)
- 7 ETODOLAC/ (284)
- 8 FENOPROFEN/ (257)
- 9 FLURBIPROFEN/ (1184)
- 10 IBUPROFEN/ (4177)
- 11 INDOMETHACIN/ (23527)
- 12 KETOPROFEN/ (1443)
- 13 KETOROLAC/ (723)
- 14 meclofenamate sodium.mp. (51)
- 15 Mefenamic Acid/ (764)
- 16 meloxicam.mp. (522)
- 17 nabumetone.mp. (350)
- 18 NAPROXEN/ (2378)
- 19 oxaprozin.mp. (121)
- 20 PIROXICAM/ (1920)
- 21 salsalate.mp. (74)
- 22 SULINDAC/ (923)
- 23 TOLMETIN/ (1255)
- 24 valdecoxib.mp. (183)
- 25 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 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (40472)
- 26 limit 25 to (humans and english language) (17770)
- 27 2 and 26 (1094)
- 28 Comparative Study/ (1202473)
- 29 Cohort Studies/ (57012)
- 30 Randomized Controlled Trials/ (38090)
- 31 27 and (28 or 29 or 30) (532)
- 32 from 31 keep 1-532 (532)

II. Search Strategy: NSAIDs, focus on adverse events (OA & RA)

- 1 Arthritis, Rheumatoid/ (53548)
- 2 limit 1 to (humans and english language) (37493)
- 3 celecoxib.mp. (1545)
- 4 choline magnesium trisalicylate.mp. (38)
- 5 *DICLOFENAC/ae [Adverse Effects] (374)
- 6 *DIFLUNISAL/ae [Adverse Effects] (27)

- 7 *ETODOLAC/ae [Adverse Effects] (19)
- 8 *FENOPROFEN/ae [Adverse Effects] (41)
- 9 *FLURBIPROFEN/ae [Adverse Effects] (41)
- 10 *IBUPROFEN/ae [Adverse Effects] (356)
- 11 *INDOMETHACIN/ae [Adverse Effects] (678)
- 12 *KETOPROFEN/ae [Adverse Effects] (109)
- 13 *KETOROLAC/ae [Adverse Effects] (16)
- 14 meclofenamate sodium.mp. (51)
- 15 *Mefenamic Acid/ae [Adverse Effects] (67)
- 16 meloxicam.mp. (522)
- 17 nabumetone.mp. (350)
- 18 *NAPROXEN/ae [Adverse Effects] (269)
- 19 oxaprozin.mp. (121)
- 20 *PIROXICAM/ae [Adverse Effects] (130)
- 21 salsalate.mp. (74)
- 22 *SULINDAC/ae [Adverse Effects] (116)
- 23 *TOLMETIN/ae [Adverse Effects] (74)
- 24 valdecoxib.mp. (183)
- 25 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 or 16 or 17 or 18 or 19
or 20 or 21 or 22 or 23 or 24 (4875)
- 26 limit 25 to (humans and english language) (3433)
- 27 2 and 26 (357)
- 28 Cohort Studies/ (57012)
- 29 Comparative Study/ (1202473)
- 30 Randomized Controlled Trials/ (38090)
- 31 27 and (28 or 29 or 30) (128)
- 32 from 31 keep 1-128 (128)

III. Search Strategy: Aspirin/acetaminophen

- 1 exp OSTEOARTHRITIS/ (26153)
- 2 limit 1 to (humans and english language) (18162)
- 3 ASPIRIN/ (26642)
- 4 ACETAMINOPHEN/ (8992)
- 5 2 and (3 or 4) (323)
- 6 exp Arthritis, Rheumatoid/ (71858)
- 7 limit 6 to (humans and english language) (50057)
- 8 *ASPIRIN/ae [Adverse Effects] (2386)
- 9 *ACETAMINOPHEN/ae [Adverse Effects] (719)
- 10 7 and (8 or 9) (81)
- 11 5 or 10 (400)
- 12 Cohort Studies/ (57012)
- 13 Comparative Study/ (1202473)
- 14 Randomized Controlled Trials/ (38090)
- 15 11 and (12 or 13 or 14) (158)
- 16 from 15 keep 1-158 (158)

IV. Search Strategy: Topical analgesics

- 1 exp OSTEOARTHRITIS/ (26153)
- 2 limit 1 to (humans and english language) (18162)
- 3 (topical and capsaicin).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (614)
- 4 (topical and diclofenac).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (356)
- 5 (topical and ibuprofen).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (137)
- 6 (topical and ketoprofen).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (114)
- 7 (topical and salicylate).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (160)
- 8 2 and (3 or 4 or 5 or 6 or 7) (40)
- 9 exp Arthritis, Rheumatoid/ (71858)
- 10 9 and (3 or 4 or 5 or 6 or 7) (11)
- 11 8 or 10 (49)
- 12 from 11 keep 1-49 (49)

CDSR/CRCT searches (through 3rd Quarter 2005)

I. Search Strategy: NSAIDs, focus on efficacy (OA)

- 1 exp OSTEOARTHRITIS/ (1546)
- 2 limit 1 to (humans and english language) (1546)
- 3 celecoxib.mp. (219)
- 4 choline magnesium trisalicylate.mp. (29)
- 5 DICLOFENAC/ (878)
- 6 DIFLUNISAL/ (90)
- 7 ETODOLAC/ (70)
- 8 FENOPROFEN/ (35)
- 9 FLURBIPROFEN/ (272)
- 10 IBUPROFEN/ (776)
- 11 INDOMETHACIN/ (1224)
- 12 KETOPROFEN/ (299)
- 13 KETOROLAC/ (279)
- 14 meclufenamate sodium.mp. (37)
- 15 Mefenamic Acid/ (92)
- 16 meloxicam.mp. (133)
- 17 nabumetone.mp. (141)
- 18 NAPROXEN/ (645)
- 19 oxaprozin.mp. (47)
- 20 PIROXICAM/ (447)
- 21 salsalate.mp. (31)
- 22 SULINDAC/ (119)
- 23 TOLMETIN/ (360)
- 24 valdecoxib.mp. (56)

- 25 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 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (5040)
- 26 limit 25 to (humans and english language)(5040)
- 27 2 and 26 (555)
- 28 Comparative Study/ (96540)
- 29 Cohort Studies/ (2139)
- 30 Randomized Controlled Trials/ (4538)
- 31 27 and (28 or 29 or 30) (402)

II. Search Strategy: NSAIDs, focus on adverse events (OA & RA)

- 1 Arthritis, Rheumatoid/ (2385)
- 2 limit 1 to (humans and english language) (2385)
- 3 celecoxib.mp. (219)
- 4 choline magnesium trisalicylate.mp. (29)
- 5 *DICLOFENAC/ae [Adverse Effects] (39)
- 6 *DIFLUNISAL/ae [Adverse Effects] (6)
- 7 *ETODOLAC/ae [Adverse Effects] (3)
- 8 *FENOPROFEN/ae [Adverse Effects] (2)
- 9 *FLURBIPROFEN/ae [Adverse Effects] (5)
- 10 *IBUPROFEN/ae [Adverse Effects] (40)
- 11 *INDOMETHACIN/ae [Adverse Effects] (61)
- 12 *KETOPROFEN/ae [Adverse Effects] (9)
- 13 *KETOROLAC/ae [Adverse Effects] (6)
- 14 meclofenamate sodium.mp. (37)
- 15 *Mefenamic Acid/ae [Adverse Effects] (0)
- 16 meloxicam.mp. (133)
- 17 nabumetone.mp. (141)
- 18 *NAPROXEN/ae [Adverse Effects] (62)
- 19 oxaprozin.mp. (47)
- 20 *PIROXICAM/ae [Adverse Effects] (19)
- 21 salsalate.mp. (31)
- 22 *SULINDAC/ae [Adverse Effects] (11)
- 23 *TOLMETIN/ae [Adverse Effects] (0)
- 24 valdecoxib.mp. (56)
- 25 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 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (846)
- 26 limit 25 to (humans and english language) [Limit not valid in: CDSR,ACP Journal Club,DARE,CCTR; records were retained] (846)
- 27 2 and 26 (98)
- 28 Cohort Studies/ (2139)
- 29 Comparative Study/ (96540)
- 30 Randomized Controlled Trials/ (4538)
- 31 27 and (28 or 29 or 30) (73)

III. Search Strategy: Aspirin/acetaminophen

- 1 exp OSTEOARTHRITIS/ (1546)

- 2 limit 1 to (humans and english language) (1546)
- 3 ASPIRIN/ (3028)
- 4 ACETAMINOPHEN/ (1128)
- 5 2 and (3 or 4) (115)
- 6 exp Arthritis, Rheumatoid/ (2730)
- 7 limit 6 to (humans and english language) (2730)
- 8 *ASPIRIN/ae [Adverse Effects] (271)
- 9 *ACETAMINOPHEN/ae [Adverse Effects] (32)
- 10 7 and (8 or 9) (10)
- 11 5 or 10 (124)
- 12 Cohort Studies/ (2139)
- 13 Comparative Study/ (96540)
- 14 Randomized Controlled Trials/ (4538)
- 15 11 and (12 or 13 or 14) (90)

IV. Search Strategy: Topicals

- 1 exp OSTEOARTHRITIS/ (1546)
- 2 limit 1 to (humans and english language) (1546)
- 3 (topical and capsaicin).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (123)
- 4 (topical and diclofenac).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (199)
- 5 (topical and ibuprofen).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (69)
- 6 (topical and ketoprofen).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (46)
- 7 (topical and salicylate).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw] (44)
- 8 2 and (3 or 4 or 5 or 6 or 7) (18)
- 9 exp Arthritis, Rheumatoid/ (2730)
- 10 9 and (3 or 4 or 5 or 6 or 7) (6)
- 11 8 or 10 (22)

Current CER Update Search Strings

Database: Ovid MEDLINE® 1996 to March Week 1 2010

RCTs

- 1 exp OSTEOARTHRITIS/ (18286)
- 2 osteoarthriti\$.mp. (23317)
- 3 1 or 2 (23317)
- 4 Aspirin/ or aspirin.mp. (20844)
- 5 acetaminophen.mp. or Acetaminophen/ (7386)
- 6 Cyclooxygenase 2 Inhibitors/ or celecoxib.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (7518)
- 7 capsaicin.mp. or Capsaicin/ (6135)
- 8 Chondroitin/ or chondroitin.mp. (5835)
- 9 diclofenac.mp. or Diclofenac/ (4611)
- 10 diflunisal.mp. or Diflunisal/ (162)
- 11 etodolac.mp. or Etodolac/ (295)
- 12 fenoprofen.mp. or Fenoprofen/ (106)
- 13 flurbiprofen.mp. or Flurbiprofen/ (813)
- 14 Glucosamine/ or glucosamine.mp. (4146)

- 15 ibuprofen.mp. or Ibuprofen/ (4484)
- 16 indomethacin.mp. or Indomethacin/ (11590)
- 17 ketoprofen.mp. or Ketoprofen/ (1574)
- 18 Ketorolac/ or ketorolac.mp. (1209)
- 19 meclufenamate.mp. (157)
- 20 mefenamic acid.mp. or Mefenamic Acid/ (362)
- 21 meloxicam.mp. (881)
- 22 nabumetone.mp. (218)
- 23 naproxen.mp. or Naproxen/ (2158)
- 24 oxaprozin.mp. (59)
- 25 piroxicam.mp. or Piroxicam/ (1288)
- 26 salsalate.mp. (27)
- 27 sulindac.mp. or Sulindac/ (878)
- 28 tolmetin.mp. or Tolmetin/ (410)
- 29 or/4-28 (71421)
- 30 randomized controlled trial.mp. or exp Randomized Controlled Trial/ (189494)
- 31 randomized controlled trial.pt. (186325)
- 32 controlled clinical trial.mp. or exp Controlled Clinical Trial/ (38495)
- 33 controlled clinical trial.pt. (34791)
- 34 clinical trial.mp. or exp Clinical Trial/ (404159)
- 35 clinical trial.pt. (252913)
- 36 or/30-35 (406908)
- 37 limit 36 to humans (397588)
- 38 3 and 29 and 37 (542)
- 39 38 and (200507\$ or 200508\$ or 200509\$ or 20051\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$).ed. (211)
- 40 limit 39 to english language (189)
- 41 limit 39 to abstracts (202)
- 42 40 or 41 (210)

Systematic reviews

- 1 exp OSTEOARTHRITIS/ (18286)
- 2 osteoarthriti\$.mp. (23317)
- 3 1 or 2 (23317)
- 4 Aspirin/ or aspirin.mp. (20844)
- 5 acetaminophen.mp. or Acetaminophen/ (7386)
- 6 Cyclooxygenase 2 Inhibitors/ or celecoxib.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (7518)
- 7 capsaicin.mp. or Capsaicin/ (6135)
- 8 Chondroitin/ or chondroitin.mp. (5835)
- 9 diclofenac.mp. or Diclofenac/ (4611)
- 10 diflunisal.mp. or Diflunisal/ (162)
- 11 etodolac.mp. or Etodolac/ (295)
- 12 fenoprofen.mp. or Fenoprofen/ (106)
- 13 flurbiprofen.mp. or Flurbiprofen/ (813)
- 14 Glucosamine/ or glucosamine.mp. (4146)

- 15 ibuprofen.mp. or Ibuprofen/ (4484)
- 16 indomethacin.mp. or Indomethacin/ (11590)
- 17 ketoprofen.mp. or Ketoprofen/ (1574)
- 18 Ketorolac/ or ketorolac.mp. (1209)
- 19 meclufenamate.mp. (157)
- 20 mefenamic acid.mp. or Mefenamic Acid/ (362)
- 21 meloxicam.mp. (881)
- 22 nabumetone.mp. (218)
- 23 naproxen.mp. or Naproxen/ (2158)
- 24 oxaprozin.mp. (59)
- 25 piroxicam.mp. or Piroxicam/ (1288)
- 26 salsalate.mp. (27)
- 27 sulindac.mp. or Sulindac/ (878)
- 28 tolmetin.mp. or Tolmetin/ (410)
- 29 or/4-28 (71421)
- 30 meta-analysis.mp. or exp Meta-Analysis/ (33804)
- 31 (cochrane or medline).tw. (33065)
- 32 search\$.tw. (112106)
- 33 30 or 31 or 32 (139975)
- 34 "Review Literature as Topic"/ or systematic review.mp. (19084)
- 35 33 or 34 (146484)
- 36 3 and 29 and 35 (163)
- 37 36 and (200507\$ or 200508\$ or 200509\$ or 20051\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$.ed. (77)
- 38 limit 37 to humans (75)
- 39 limit 38 to english language (72)
- 40 limit 38 to abstracts (66)

Harms

- 1 Aspirin/ or aspirin.mp. (20844)
- 2 acetaminophen.mp. or Acetaminophen/ (7386)
- 3 Cyclooxygenase 2 Inhibitors/ or celecoxib.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (7518)
- 4 capsaicin.mp. or Capsaicin/ (6135)
- 5 Chondroitin/ or chondroitin.mp. (5835)
- 6 diclofenac.mp. or Diclofenac/ (4611)
- 7 diflunisal.mp. or Diflunisal/ (162)
- 8 etodolac.mp. or Etodolac/ (295)
- 9 fenoprofen.mp. or Fenoprofen/ (106)
- 10 flurbiprofen.mp. or Flurbiprofen/ (813)
- 11 Glucosamine/ or glucosamine.mp. (4146)
- 12 ibuprofen.mp. or Ibuprofen/ (4484)
- 13 indomethacin.mp. or Indomethacin/ (11590)
- 14 ketoprofen.mp. or Ketoprofen/ (1574)
- 15 Ketorolac/ or ketorolac.mp. (1209)
- 16 meclufenamate.mp. (157)
- 17 mefenamic acid.mp. or Mefenamic Acid/ (362)

- 18 meloxicam.mp. (881)
- 19 nabumetone.mp. (218)
- 20 naproxen.mp. or Naproxen/ (2158)
- 21 oxaprozin.mp. (59)
- 22 piroxicam.mp. or Piroxicam/ (1288)
- 23 salsalate.mp. (27)
- 24 sulindac.mp. or Sulindac/ (878)
- 25 tolmetin.mp. or Tolmetin/ (410)
- 26 or/1-25 (71421)
- 27 (ae or co or de).fs. (1917797)
- 28 (adverse effect\$ or adverse event\$ or harm\$).mp. (125151)
- 29 27 or 28 (1980478)
- 30 rheumatoid arthritis.mp. or Arthritis, Rheumatoid/ (34754)
- 31 Alzheimer Disease/pc [Prevention & Control] (1442)
- 32 (alzheimer\$ adj2 prevent\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (267)
- 33 31 or 32 (1566)
- 34 Neoplasms/pc [Prevention & Control] (6517)
- 35 (cancer adj1 prevent\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (6643)
- 36 34 or 35 (11729)
- 37 30 or 33 or 36 (47989)
- 38 26 and 29 and 37 (1011)
- 39 38 and (200507\$ or 200508\$ or 200509\$ or 20051\$ or 2006\$ or 2007\$ or 2008\$ or 2009\$ or 2010\$.ed. (332)
- 40 limit 39 to humans (290)
- 41 limit 40 to english language (264)
- 42 limit 40 to abstracts (252)
- 43 41 or 42 (278)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2010

- 1 exp OSTEOARTHRITIS/ (2149)
- 2 osteoarthriti\$.mp. (3327)
- 3 1 or 2 (3327)
- 4 Aspirin/ or aspirin.mp. (6044)
- 5 acetaminophen.mp. or Acetaminophen/ (2083)
- 6 Cyclooxygenase 2 Inhibitors/ or celecoxib.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (639)
- 7 capsaicin.mp. or Capsaicin/ (427)
- 8 Chondroitin/ or chondroitin.mp. (212)
- 9 diclofenac.mp. or Diclofenac/ (2245)
- 10 diflunisal.mp. or Diflunisal/ (207)
- 11 etodolac.mp. or Etodolac/ (154)
- 12 fenoprofen.mp. or Fenoprofen/ (83)
- 13 flurbiprofen.mp. or Flurbiprofen/ (499)

- 14 Glucosamine/ or glucosamine.mp. (171)
- 15 ibuprofen.mp. or Ibuprofen/ (1769)
- 16 indomethacin.mp. or Indomethacin/ (2174)
- 17 ketoprofen.mp. or Ketoprofen/ (687)
- 18 Ketorolac/ or ketorolac.mp. (909)
- 19 meclofenamate.mp. (69)
- 20 mefenamic acid.mp. or Mefenamic Acid/ (196)
- 21 meloxicam.mp. (160)
- 22 nabumetone.mp. (137)
- 23 naproxen.mp. or Naproxen/ (1268)
- 24 oxaprozin.mp. (48)
- 25 piroxicam.mp. or Piroxicam/ (900)
- 26 salsalate.mp. (31)
- 27 sulindac.mp. or Sulindac/ (249)
- 28 tolmetin.mp. or Tolmetin/ (421)
- 29 or/4-28 (17609)
- 30 3 and 29 (1357)
- 31 limit 30 to yr="2005 -Current" (192)

Database: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to January 2010

- 1 osteoarthritis.mp. (203)
- 2 Aspirin/ or aspirin.mp. (303)
- 3 acetaminophen.mp. or Acetaminophen/ (86)
- 4 Cyclooxygenase 2 Inhibitors/ or celecoxib.mp. [mp=title, abstract, full text, keywords, caption text] (58)
- 5 capsaicin.mp. or Capsaicin/ (37)
- 6 Chondroitin/ or chondroitin.mp. (10)
- 7 diclofenac.mp. or Diclofenac/ (99)
- 8 diflunisal.mp. or Diflunisal/ (17)
- 9 etodolac.mp. or Etodolac/ (17)
- 10 fenoprofen.mp. or Fenoprofen/ (14)
- 11 flurbiprofen.mp. or Flurbiprofen/ (24)
- 12 Glucosamine/ or glucosamine.mp. (17)
- 13 ibuprofen.mp. or Ibuprofen/ (126)
- 14 indomethacin.mp. or Indomethacin/ (92)
- 15 ketoprofen.mp. or Ketoprofen/ (40)
- 16 Ketorolac/ or ketorolac.mp. (43)
- 17 meclofenamate.mp. (8)
- 18 mefenamic acid.mp. or Mefenamic Acid/ (27)
- 19 meloxicam.mp. (14)
- 20 nabumetone.mp. (9)
- 21 naproxen.mp. or Naproxen/ (90)
- 22 oxaprozin.mp. (5)
- 23 piroxicam.mp. or Piroxicam/ (33)
- 24 salsalate.mp. (2)
- 25 sulindac.mp. or Sulindac/ (21)

- 26 tolmetin.mp. or Tolmetin/ (8)
- 27 or/2-26 (536)
- 28 1 and 27 (60)
- 29 limit 28 to full systematic reviews (49)

Appendix D. Inclusion and Exclusion Criteria

Abstract level Eligibility Criteria

<u>Study Characteristic</u>	<u>Inclusion/Exclusion</u>
Population	<p>Include: all ages >18; patients with osteoarthritis, rheumatoid arthritis; patients with Alzheimer's or enrolled in cancer prevention trials (for studies reporting Adverse events)</p> <p>Exclude: Juvenile populations; Post- surgical pain patients</p>
Interventions	<p>Include: acetaminophen, aspirin, celecoxib, chondroitin, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, glucosamine, ibuprofen, indomethacin, ketoprofen, ketorolac, meclufenamate sodium, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, salsalate, sulindac, tolmetin</p> <p>Exclude: all other medications, including COX-2 and other drugs included in previous report but no longer FDA approved for use in the United States</p>
Comparators	<p>Include: any above medication, placebo</p> <p>Exclude: drugs not included in this review</p>
Outcomes	<p>Include: Improvements in osteoarthritis symptoms; Adverse events: any cardiovascular, gastrointestinal, renal toxicity, hepatic toxicity; quality of life; sudden death</p>
Timing/Duration	<p>Include any study duration (no minimum exposure)</p>
Setting	<p>Include primary care or specialty setting</p>
Study Design	<p>Include: RCT, cohort, case control, systematic review, meta-analysis</p>

Full Text Eligibility Criteria

<u>Study Characteristic</u>	<u>Inclusion/Exclusion</u>
Population	<p>Include: all ages >18; patients with osteoarthritis, rheumatoid arthritis; patients with Alzheimer's or enrolled in cancer prevention trials (for studies reporting Adverse events)</p> <p>Exclude: Juvenile populations; Post- surgical pain patients</p>
Interventions	<p>Include: acetaminophen, aspirin, celecoxib, chondroitin, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, glucosamine, ibuprofen, indomethacin, ketoprofen, ketorolac, meclufenamate sodium, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, salsalate, sulindac, tolmetin</p> <p>Exclude: all other medications, including COX-2 and other drugs included in previous report but no longer FDA approved for use in the United States; combination therapies of multiple NSAIDs</p>
Comparators	<p>Include: any above medication, placebo</p> <p>Exclude: drugs not included in this review</p>
Outcomes	<p>Include: Improvements in osteoarthritis symptoms; Adverse events: any cardiovascular, gastrointestinal, renal toxicity, hepatic toxicity; quality of life; sudden death</p>
Timing/Duration	<p>Include any study duration (no minimum exposure)</p>
Setting	<p>Include primary care or specialty setting</p>
Study Design	<p>Include: RCT, cohort, case control, systematic review, meta-analysis</p> <p>Exclude: cohort or case control study with <1000 patients, dose-ranging study, pharmacokinetics, single-dose study, drug interaction, case report, non-systematic review</p>

Appendix E. Excluded Studies*

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Appendix F. Quality Assessment Methods

Individual studies were rated as “good,” “fair” or “poor” as defined below¹:

Studies rated “good” have the least risk of bias and results are considered valid. Good quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates, and clear reporting of dropouts; appropriate means for preventing bias; appropriate measurement of outcomes, and reporting results.

Studies rated “fair” are susceptible to some bias, but it is not sufficient to invalidate the results. These studies do not meet all the criteria for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The “fair” quality category is broad, and studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid.

Studies rated “poor” have significant flaws that imply biases of various types that may invalidate the results. They have a serious or “fatal” flaw in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting. The results of these studies are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Each criterion was give an assessment of yes, no, or unclear.

1. Was the assignment to the treatment groups really random?
2. Was the treatment allocation concealed?
 1. Adequate approaches to sequence generation:
 - Computer-generated random numbers
 - Random numbers tables
 - Inferior approaches to sequence generation:
 - Use of alternation, case record numbers, birth dates or week days
 - Randomization reported, but method not stated
 - Not clear or not reported
 - Not randomized
2. a) Was the treatment allocation concealed?
 - Adequate approaches to concealment of randomization:
 - Centralized or pharmacy-controlled randomization (randomization performed without knowledge of patient characteristics).
 - Serially-numbered identical containers
 - On-site computer based system with a randomization sequence that is not readable until allocation
 - Sealed opaque envelopes
 - Other approaches sequence to clinicians and patients
- b) Inferior approaches to concealment of randomization:
 - Use of alternation, case record numbers, birth dates or week days
 - Open random numbers lists

- Serially numbered non- opaque envelopes
 - Not clear or not reported
3. Were the groups similar at baseline in terms of prognostic factors?
 4. Were the eligibility criteria specified?
 5. Were outcome assessors and/or data analysts blinded to the treatment allocation?
 6. Was the care provider blinded?
 7. Was the patient kept unaware of the treatment received?
 8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?
 9. Did the study maintain comparable groups?
 10. Did the article report attrition, crossovers, adherence, and contamination?
 11. Is there important differential loss to followup or overall high loss to followup?

For Cohort Studies:

Each criterion was give an assessment of yes, no, or unclear.

1. Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?
2. Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?
3. Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?
4. Were outcome assessors and/or data analysts blinded to treatment?
5. Did the article report attrition?
6. Did the study perform appropriate statistical analyses on potential confounders?
7. Is there important differential loss to followup or overall high loss to followup?
8. Were outcomes pre-specified and defined, and ascertained using accurate methods?

For Case-control Studies

Each criterion was given an assessment of yes, no, or unclear.

1. Did the study attempt to enroll all (or a random sample of) cases using pre-defined criteria?
2. Were the controls derived from the same population as the cases, and would they have been selected as cases if the outcome was present?
3. Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?
4. Did the study report the proportion of cases and controls who met inclusion criteria that were analyzed?
5. Did the study use accurate methods for identifying outcomes?
6. Did the study use accurate methods for ascertaining exposures and potential confounders?
7. Did the study perform appropriate statistical analyses on potential confounders?

Systematic Reviews:

Each criterion was given an assessment of yes, no, unclear, or not applicable.

1. Was an ‘a priori’ design provided?

The research question and inclusion criteria should be established before the conduct of the review.

2. Was there duplicate study selection and data extraction?
There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.
3. Was a comprehensive literature search performed?
At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.
4. Was the status of publication (i.e. gray literature) used as an inclusion criterion?
The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language, etc.
5. Was a list of studies (included and excluded) provided?
A list of included and excluded studies should be provided.
6. Were the characteristics of the included studies provided?
In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.
7. Was the scientific quality of the included studies assessed and documented?
'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.
8. Was the scientific quality of the include studies used appropriately in formulating conclusions?
The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating the recommendations.
9. Were the methods used to combine the findings of studies appropriate?
Reviews should not combine or pool dissimilar studies. If studies are pooled using a fixed effects model, there should be a clear rationale for doing so. A test should be done to assess for statistical heterogeneity (i.e. Chi-squared test for homogeneity, I^2).
10. Was the likelihood of publication bias assessed?
An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test). If assessment of publication bias is not possible, the review should provide justification (e.g., small numbers of studies, too much heterogeneity, poor quality, etc.)
11. Was the conflict of interest stated?
Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

Appendix F References:

1. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001;20:21-35.

Appendix G. Quality Assessment of Trials, Systematic Reviews, and Observational Studies

Trials

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Chan, 2007	Yes	Yes	Yes	Yes	Yes	Unclear
Dahlberg, 2009	Yes	Unclear	Yes	Yes	Yes	Yes
Dequeker, 1998	Unclear	Unclear	Yes	No	Unclear	Unclear
Dickson, 1991	Unclear	Unclear	Yes	Yes	Unclear	Yes
Feng, 2008	Unclear	Unclear	Yes	Yes	Yes	Yes
Furst, 1987	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Goldstein, 2000	Yes	Unclear	Yes	Yes	Unclear	Unclear
Goldstein, 2007	Yes	Yes	No	Yes	Yes	Yes
Goldstein, 2010	Yes	Yes	Yes (slightly different % of those who have RA)	Yes	Yes	Yes
Hawkey, 1996	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Herrero-Beaumont, 2007	Yes	Yes	Yes	Yes	Unclear	Yes
Hochberg, 2008	Yes	Yes	Yes	Yes	Yes	Yes
Hosie, 1996	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Kahan, 2009	Yes	Unclear	Yes	Yes	Yes for radiographs, Unclear for other outcome assessment	Yes
Linden, 1996	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Mazieres, 2010	Yes	Unclear	Yes	Yes	Unclear	Yes
McKenna, 1998	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Messier, 2007	Unclear	Unclear	No	Yes	Unclear	Yes

Author, year	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to followup and attrition: Differential/high?	Intention-to-treat analysis?	Quality rating	Funding
Chan, 2007	Unclear	Yes; Unclear; Yes; Yes	Yes; No	Yes	Fair	Research grant
Dahlberg, 2009	Yes	No; No; Yes; No	No; Yes	Yes	Fair	Pfizer
Dequeker, 1998	Yes	No; No; No; No	No	No	Fair	Boehringer Ingelheim
Dickson, 1991	Yes	Yes; No; No; No	No; Yes	No	Fair	Pfizer Ltd.
Feng, 2008	Yes	No; No; Yes; No	Unclear; Unclear	No	Fair	Chinese Government
Furst, 1987	Unclear	No; No; No; No	No; No	No	Fair	Boehringer Ingelheim
Goldstein, 2000	Unclear	No; No; No; No	No; No	Yes	Fair	GD Searle; Pfizer
Goldstein, 2007	Yes	Yes, No, No, No	Yes, No	No	Fair	TAP pharmaceuticals
Goldstein, 2010	Yes	Yes; No; Yes; No	No, Yes	Yes	Fair	AstraZeneca
Hawkey, 1996	Unclear	No; No; No; No	No	Unclear	Fair	NR
Herrero-Beaumont, 2007	Yes	Yes; No; Yes; No	No; Yes	Yes	Fair	Rottapharm
Hochberg, 2008	Yes	Yes; No; Yes; No	No; No	Yes	Good	
Hosie, 1996	Unclear	No; No; No; No	No	Yes	Fair	NR
Kahan, 2009	Yes	Yes; No; Yes; No	No; Yes (32% at 2 years)	Yes	Fair	IBSA and Genevrier Laboratories
Linden, 1996	Unclear	No; No; No; No	No	No	Fair	NR
Mazieres, 2010	Yes	Yes; No; Yes; No	No; No	Yes	Fair	Pierre Fabre Company
McKenna, 1998	Unclear	No; No; No; No	No	Yes	Fair	NR (Pharmacia)
Messier, 2007	Yes	Yes; No; Yes; No	No; No	Yes	Fair	Rexall Sundown

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Michel, 2005	Yes	Unclear	Yes	Yes	Yes for reading radiographs, Unclear for other outcome assessment	Yes
Rother, 2007	Yes	Yes	Yes	Yes	Unclear	Yes
Rozendaal, 2008	Yes	Yes	Yes	Yes	Yes	Yes
Rozendaal, 2009	Yes	Yes	Yes	Yes	Yes	Yes
Sandelin, 1997	Unclear	Unclear	Yes	Yes	Unclear	Yes
Sawitzke, 2008 (See Hochberg, 2008)						
Scheiman, 2006	Yes	Yes	No	Yes	Yes	Yes
Silverstein, 2000	Yes	Yes	Yes	Yes	Yes	Unclear
Simon, 2009	Yes	Yes	Yes	Yes	Yes	Yes
Tiso, 2010	Yes	Yes	Yes	Yes	No	No
Tugwell, 2004	Yes	Yes	Yes	Yes	Yes	Yes
Underwood, 2007	Yes	Yes	Yes	Yes	No	No
Valat, 2001	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Wilkens, 2010	Yes	Yes	Yes	Yes	Unclear	Yes
Wojtulewski, 1996	Unclear	Unclear	Yes	Yes	Unclear	Unclear

Author, year	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?	Loss to followup and attrition: Differential/high?	Intention-to-treat analysis?	Quality rating	Funding
Michel, 2005	Yes	Yes; No; Yes; No	No; Yes (27.3% and 26.6% after 2 years)	Yes	Fair	
Rother, 2007	Yes	Yes; Yes; Yes; No	No; No	Yes	Good	IDEA AG and MnNeil Consumer and Specialty Pharmaceuticals
Rozendaal, 2008	Yes	Yes; No; Yes; No	No; No	Yes	Good	Erasmus Medical Center
Rozendaal, 2009	Yes	Yes; No; Yes; No	No; No	Yes	Good	Erasmus Medical Center
Sandelin, 1997	Yes	Unclear; No; No; No	Unclear; Unclear	Yes	Fair	
Sawitzke, 2008 (See Hochberg, 2008)						
Scheiman, 2006	Yes	Yes, No, No, No	Yes, No	Yes	Fair	AstraZeneca
Silverstein, 2000	Yes	No; No; No; No	No	No	Good	Pharmacia
Simon, 2009	Yes	Yes; No; No; No	No; No	Yes	Good	Nuvo Research Inc
Tiso, 2010	No	Yes; No; No; No	No; No	Yes	Fair	Helm Pharmaceuticals
Tugwell, 2004	Yes	Yes; No; Yes; No	No; No	Yes	Good	Dimethaid Healthcare Ltd.
Underwood, 2007	No	Yes; Yes; Yes; Yes	No; Yes	No	Fair	
Valat, 2001	Unclear	No; No; No; No	No	Yes	Fair	NR
Wilkins, 2010	Yes	Yes; No; Yes; No	No; No	Yes	Good	Norwegian Foundation for Health and Rehabilitation
Wojtulewski, 1996	Unclear	No; No; No; No	No	Yes	Fair	NR

Systematic reviews

Author, year	A priori' design provided?	Duplicate study selection and data extraction? a. Study selection b. Data extraction	Comprehensive literature search performed?	Status of publication used as an inclusion criteria?	List of studies (included and excluded) provided?	Characteristics of the included studies provided?
Ashcroft, 2001	Yes	Unclear; Unclear	Yes	Yes	Yes; No	Yes
Caldwell, 2006	Yes	Yes; Yes	Yes	Yes	Yes; No	Yes
Chen et al., 2008	Yes	Yes; Yes	Yes	Yes	Yes; Yes	Yes
Eisen, 2005	Yes	Unclear; Unclear	Unclear	No	Yes; No	Yes
Garner, 2004 (Celecoxib for RA)	Yes	Yes; Unclear	Yes	Yes	Yes; Yes	Yes
Juni, 2004	Yes	Unclear; Yes	Yes	Yes	Yes; No	Yes
Kearney et al., 2006	Yes	Unclear; Unclear	Yes	Yes	Yes; No	Yes
Lee, 2004	Yes	Unclear; Unclear	Yes	Yes	Yes; Yes	Yes
Masso Gonzalez 2010	Yes	Unclear; Yes	No	No	Yes; No	Yes
Matchaba et al., 2005	Yes	Unclear; Unclear	No	No	Yes; No	Yes
Moore, 2005	Yes	Unclear; Unclear	Yes	Yes	Yes; No	No
Ramey et al., 2005	Yes	Unclear; Unclear	Yes	No	Yes; No	Yes
Rostom, 2007	Yes	Yes; Yes	Yes	Yes	Yes; No	Yes
Rostom, 2005	Yes	Yes; Yes	Yes	Yes	Yes; No	No
Rubenstein, 2004	Yes	Yes; Yes	Yes	Yes	Yes; Yes	Yes
Solomon, 2008	Yes	Unclear; Yes (adjudicated)	Unclear	Yes	Yes; No	Yes
Soni, 2009	Unclear	No; Unclear	No (Pfizer database only)	No	Yes; No	Yes
Towheed, 2004	Yes	Yes; Yes	Yes	Yes	Yes; Yes	Yes
Towheed, 2005 Cochrane review: most recent substantive update	Yes	Yes; Yes	Yes	Yes	Yes; No	Yes
Watson, 2004	Yes	Unclear; Unclear	No (Merck database)	Yes	Yes; No	Yes
Wegman, 2004	Yes	Unclear; Unclear	Yes	Yes	Yes; Yes	Yes
White, 2003	Yes	Unclear; Unclear	No (Pfizer database only)	Yes	Yes; No	No
White, 2007	Yes	Unclear; Yes (adjudicated)	No (Pfizer database only)	Yes	Yes; No	No
Zhang, 2004	Yes	Unclear; Yes	Yes	Yes	Yes; Yes	No
Zhang, 2006	Unclear	Unclear; Yes	Yes	Unclear	Yes; No	Yes

Author, year	Scientific quality of included studies assessed and documented?	Scientific quality of the included studies used appropriately in formulating conclusions?	Methods used to combine the findings of studies appropriate?	Likelihood of publication bias assessed?	Conflict of interest stated? a. Systematic Review b. Individual Studies	Quality rating
Ashcroft, 2001	No	No	Unclear	No	No; No	Fair
Caldwell, 2006	No	No	Yes	Yes	Yes; No	Fair
Chen et al., 2008	Yes	Yes	Yes	No	Yes; No	Good
Eisen, 2005	No	No	Yes	Yes	Yes; No	Fair
Garner, 2004 (Celecoxib for RA)	Yes	Yes	NA	Yes	Yes; No	Good
Juni, 2004	Yes	Yes	Yes	Yes	Yes; Yes	Good
Kearney et al., 2006	No	No	Yes	Yes	Yes; No	Fair
Lee, 2004	Yes	Yes	Yes	Yes	Yes; Yes	Good
Masso Gonzalez 2010	No	No	Yes	No	Yes; No	Fair
Matchaba et al., 2005	No	No	Yes	No	Yes; No	Fair
Moore, 2005	Yes	No	No (test of heterogeneity not reported)	Yes	Yes; Yes	Fair
Ramey et al., 2005	No	No	No (test of heterogeneity not reported)	No	Yes; Yes (all Merck Trials)	Fair
Rostom, 2007	Yes	Yes	Yes	No	No; No	Fair
Rostom, 2005	Yes	Yes	No	Yes	Yes; No	Fair
Rubenstein, 2004	Yes	Yes	NA	No	Yes; No	Good
Solomon, 2008	No	No	No (test of heterogeneity not reported)	Yes	Yes; Yes	Fair
Soni, 2009	No	No	Yes	No	Yes; No	Fair
Towheed, 2004	Yes	Yes	Yes	Yes	Yes; Yes	Good
Towheed, 2005 Cochrane review: most recent substantive update	Yes	Yes	Yes	No	Yes; No	Fair
Watson, 2004	No	No	No	No	Yes; No	Poor
Wegman, 2004	Yes	Yes	Yes	No	Yes; No	Fair
White, 2003	No	No	No	No	Yes; Yes	Poor
White, 2007	No	No	No	No	No; No	Poor
Zhang, 2004	Yes	Yes	Yes	Yes	Yes; No	Good
Zhang, 2006	No	Unclear	Yes	Yes	Yes; No	Fair

Cohort studies

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?	Were outcome assessors and/or data analysts blinded to treatment?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to follow-up or overall high loss to followup?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality rating	Funding
Hudson, 2005	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Fair	
Ko, 2002	Yes	No	Yes	Yes	No	Yes	Unclear	Yes	Fair	
Kurth, 2003	No	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Fair	
Mamdani, 2002	Yes	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair	
Mamdani, 2003	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Fair	
Mamdani, 2004	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Fair	
Mann, 2004	No	N/A	Yes	Unclear	No	No	Unclear	Yes	Fair	
Mellemkjar, 2002	Yes	Unclear	Yes	Unclear	Yes	Unclear	Unclear	Yes	Fair	
Patel, 2004	No	No	Yes	Yes	No	Yes	Unclear	Yes	Fair	Funded by Canadian Institutes of Health Research (Previous funding by Merck, Pfizer, and Boehringer Ingelheim)
Rahme & Nedjar, 2007 <i>Rheumatology</i>	Yes	No	Yes	Unclear	No	Unclear	Unclear	Yes	Fair	

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?	Were outcome assessors and/or data analysts blinded to treatment?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to follow-up or overall high loss to followup?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality rating	Funding
Rahme, 2007 <i>Arthritis and Rheumatism</i>	Yes	No	Yes	Yes	No	Yes	Unclear	Yes	Fair	
Rahme, 2008	Yes	Yes	Yes	Yes	No	Yes	Unclear	Yes	Good	Merck
Rahme, Watson, et al, 2007 <i>Pharmacoepidemiology and Drug Safety</i>	Yes	No	Yes	Unclear	No	Unclear	Unclear	Yes	Fair	
Ray, 2007	Yes	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair	
Ray, 2002	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Fair	
Solomon, 2008	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Fair	
Velentgas, 2005	Yes	Yes	Yes	Yes	No	No	Unclear	Yes	Fair	

Case-control studies

Author, Year	Did the study attempt to enroll all or random sample of cases using pre-defined criteria?	Were the controls derived from the same population as the cases? Would they have been selected as cases if the outcome was present?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study report the proportion of cases and controls who met inclusion criteria that were analyzed?	Did the study use accurate methods for identifying outcomes?
Andersohn, 2005	Yes	Yes; Yes	Yes	No	Yes
Fischer, 2005	Yes	Yes; Yes	No	No	Yes
Garcia-Rodriguez, 2004	Yes	Yes; Unclear	Yes	Yes	Yes
Garcia-Rodriguez, 2000	Yes	Yes	No	No	Yes
Garcia-Rodriguez, 2001	Yes	Yes; Yes	Yes	No	Yes
Garcia-Rodriguez, 2007	Yes	Yes; Yes	Yes	Yes	Yes
Graham, 2005	Yes	Yes; Yes	Yes	No	Yes
Helin-Salmivaara, 2006	Yes	Yes	No	No	Yes
Hippisley-Cox, 2005	Yes	Yes; Yes	Yes	No	Yes
Johnsen, 2005	Yes	Yes; Yes	Yes	No	Yes
Kimmel, 2005	Yes	Yes; Yes	No	No	Yes
Lanas, 2006	Yes	Yes; Yes	No	Yes	Yes
Laporte, 2004	Yes	Yes; Yes	Yes	Unclear	Unclear
Layton, 2003	Yes	No	Yes	Unclear	No
Levesque, 2005	Yes	Yes; Yes	Yes	Yes	Yes
Mamdani, 2002	Yes	No	Yes	Unclear	No
Mann, 2004	No	N/A	Yes	Unclear	No
Mellemkjar, 2002	Yes	Unclear	Yes	Unclear	Yes
Norgard, 2004	Yes	Yes; Yes	No	No	Unclear
Patel, 2004	Yes	Yes	Yes	No	Yes
Rahme&Nedjar, 2007	Yes	No	Yes	Unclear	No
Rahme, 2002	Yes	Yes; Yes	Yes	Yes	Yes
Ray, 2007	Yes	No	Yes	Unclear	No
Schlienger, 2002	Yes	Yes; Yes	Yes	No	Yes
Solomon, 2002	Yes	Yes; Yes	Yes	No	Yes
Solomon, 2004a	Yes	Yes; Yes	Unclear	No	Yes
Solomon, 2004b	Yes	Yes; Yes	Yes	No	Yes
Weideman, 2004	No	No	Yes	Yes	No

Author, Year	Did the study use accurate methods for ascertaining exposures and potential confounders?	Did the study perform appropriate statistical analyses on potential confounders?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality rating	Funding
Andersohn, 2005	Yes	Yes		Fair	
Fischer, 2005	Yes	Yes		Fair	
Garcia-Rodriguez, 2004	Yes	Yes, but unclear reporting		Fair	Funded by Pharmacia
Garcia-Rodriguez, 2000	Yes	Yes		Fair	
Garcia-Rodriguez, 2001	No	Unclear		Fair	
Garcia-Rodriguez, 2007	Yes	Yes		Good	
Graham, 2005	Yes	Yes		Fair	
Helin-Salmivaara, 2006	Yes	Yes		Fair	
Hippisley-Cox, 2005	Yes	Yes		Fair	
Johnsen, 2005	Yes	Yes		Fair	
Kimmel, 2005	Yes	Yes		Fair	
Lanas, 2006	Yes	Yes		Good	
Laporte, 2004	Yes	Yes		Fair	
Layton, 2003	Yes	Unclear	Yes	Fair	
Levesque, 2005	Yes	Yes		Good	
Mamdani, 2002	Yes	Unclear	Yes	Fair	
Mann, 2004	No	Unclear	Yes	Fair	
Mellemkjar, 2002	Unclear	Unclear	Yes	Fair	
Norgard, 2004	Yes	Yes		Fair	
Patel, 2004	Yes-- matched by confounders	Yes		Fair	Funded by Canadian Institutes of Health Research (Previous funding by Merck, Pfizer, and Boehringer Ingelheim) Retrospective database analysis
Rahme&Nedjar, 2007	Unclear	Unclear	Yes	Fair	Funded by Merck
Rahme, 2002	Yes	Yes		Fair	
Ray, 2007	Yes	Unclear	Yes	Fair	
Schlienger, 2002	Yes	No (limited adjustment for cardiovascular risk factors)		Fair	
Solomon, 2002	Yes	Yes		Fair	
Solomon, 2004a	Yes	Yes		Fair	
Solomon, 2004b	Yes	Yes		Fair	
Weideman, 2004	Yes	Unclear	Yes	Fair	

Appendix H. Evidence Tables: Oral NSAIDs

Trials

Author year	Subjects	Demographics (age, gender, race)	Comparison		Number of subjects	Duration (weeks)	Aspirin permitted?
Chan 2007 (Fair)	Arthritis (OA, RA and others)	Mean age: 71 years 52% female	Celecoxib 200	Esomeprazole 20	273	52	No
Dahlberg 2009 (Fair)	Knee or hip osteoarthritis	Mean age: 71 years Female: 69% Race: NR	Celecoxib 200	Diclofenac 50	925	52	Unclear
Goei The 1997	OA knee	Mean age: 71 years Female: 81.9% Race: NR	Meloxicam 7.5	Diclofenac 100	258	6	Yes
Goldstein 2006 (Fair)	OA and RA with no ulcer on EGD	Mean age: 57 years Female: 57% White: 84% Black: 13% Hispanic: 4%	Celecoxib 200	Naproxen 500	537	12	Yes (included in study)
Goldstein 2007 (Fair)	OA without history of ulcer taking low-dose ASA	Mean age: 56.7 years Female: 66% White: 72% Black: 13% Hispanic: 11% Asian: 2% Other: 2%	Celecoxib 200	Naproxen 500 + Lansoprazole 30	1045	12	Yes (included in study)
Goldstein 2010 (Fair) , included two Phase III studies	H pylori negative patients with OA, RA, ankylosing spondylitis or other condition requiring daily NSAID therapy	Mean age: 60 years Female: 67% White: 86% Black: 12% Other: 2%	enteric-coated(EC) naproxen 500 mg and immediate-release esomeprazole 20 mg	Enteric-coated naproxen 500	438; 423	26	Yes

Author year	Efficacy measures	Withdrawals due to adverse events		Other outcomes	Run-in/washout	Class naïve patients only
Chan 2007 (Fair)	PGA, pain	NR	NR	Combination therapy with PPI was more effective in preventing ulcers	NR/NR	No
Dahlberg 2009 (Fair)	Pain, Physician and patient PGA and adverse events	27%	31%	No difference	Unclear/NR	No
Goei The 1997	pain during active movement, PGA, acetaminophen use	3.9%	2.3%	No difference, trend favored meloxicam	NR/7 day minimum	No
Goldstein 2006 (Fair)	PGA, withdrawals	7.0%	9.0%	No difference in adverse event severity.	NR/NR	No
Goldstein 2007 (Fair)	Joint pain, GI complications and GDU incidence at final visit	6.30%	6.60%	No difference	Unclear/NR	No
Goldstein 2010 (Fair) , included two Phase III studies	Ulcer incidence, other harm related outcomes	9.3%; 9.4%	15.7%14.2%	Enterica coded with PPI protective	Unclear/14 days	No

Author year	Subjects	Demographics (age, gender, race)	Comparison		Number of subjects	Duration (weeks)	Aspirin permitted?
Hawkey (MELISSA) 1998 (Fair)	OA hip, knee, hand, or spine	Mean age: 61 years Female: 67% Race: NR	Meloxicam 7.5	Diclofenac 100	9323	4	Unclear
Hosie 1996 (Fair)	OA hip or knee	Mean age: 64 years Female: 68% Race: NR	Meloxicam 7.5	Diclofenac 100	336	24	Unclear
Hosie 1997	OA hip or knee	Mean age: 65 years Female: 55% Race: NR	Meloxicam 15	Piroxicam 20	455	24	Unclear
Linden 1996 (Fair)	OA hip	Mean age: 67 years Female: 63% Race: NR	Meloxicam 15	Piroxicam 20	255	6	Unclear
McKenna 1998 (Fair)	OA of the knee with flare		100			26	

Author year	Efficacy measures	Withdrawals due to adverse events		Other outcomes	Run-in/ washout	Class naïve patients only
Hawkey (MELISSA) 1998 (Fair)	Pain, PGA, withdrawals	1.7%	1.0%	No difference, trend slightly favored meloxicam	NR/washout 3 days	No
Hosie 1996 (Fair)	Pain, quality of life	4.0%	4.2%	No difference	NR/washout 3 days	No
Hosie 1997	Overall pain, pain on movement, joint stiffness, global efficacy and quality of life	57.0%	15.0%	No difference	NR/ 7 day minimum	No
Linden 1996 (Fair)	Pain, pain on active movement, global efficacy, withdrawals	9.3%	7.9%	No difference	NR/washout 3-7 days	No
McKenna 1998 (Fair)	Index joint pain, WOMAC	7.00%	11.00%	No difference	NR/NR	No

Author year	Subjects	Demographics (age, gender, race)	Comparison		Number of subjects	Duration (weeks)	Aspirin permitted?
Scheiman 2006 (Fair); Includes two similar RCT	At risk of ulcer (age 60 or greater or history of ulcer within past 5 yr) and taking NSAID for OA or RA	Mean age: 64 years Female: 72% Race: NR	COX-2 + esomeprazole 20 or 40	COX-2 + placebo	844; 585	26	Yes
Silverstein 2000 (CLASS) (Good)	OA and RA	Mean age: 60 years Female: 69% White: 88.2% Black: 7.7% Hispanic: 2.8% Asian: 0.8%	Celecoxib 400	Ibuprofen 800 or Diclofenac 75	7968	24	Yes
Valat 2001 (Fair)	OA lumbar spine	Mean age: 58 years Female: 82% Race: NR	Meloxicam 7.5	Diclofenac 100	229	2	Unclear
Wojtulweski 1996 (Fair)	RA	Aged 18-75 years Gender and race: NR	Meloxicam 7.5	Naproxen 750	379	24	No

Author year	Efficacy measures	Withdrawals due to adverse events		Other outcomes	Run-in/ washout	Class naïve patients only
Scheiman 2006 (Fair); Includes two similar RCT	Related to ulcer development including pain and other symptoms	4.2% 20 mg 8.3% 40 mg	11% 20 mg 18% 40 mg	PPI reduced risk compared to placebo. COX-2 users: 16.5% placebo vs 0.9% 20 mg esomeprazole (P < 0.001) non-selective NSAID: 17.1% placebo vs 6.8% 20 mg esomeprazole (P <0.001).	NR/NR	No
Silverstein 2000 (CLASS) (Good)	No efficacy measures reported except withdrawals	18.4%	20.6%	No difference	NR/NR	No
Valat 2001 (Fair)	Pain on motion	0.0%	0.0%	No difference	NR/washout 3-7 days	No
Wojtulweski 1996 (Fair)	PGA, several others	23.6%	14.4%	No difference, trend favored naproxen	NR/washout 3-11 days	No

Oral NSAID Systematic Reviews

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
Ashcroft, 2001 (Fair)	To evaluate incidence of gastroduodenal ulcers in patients with RA or OA treated with celecoxib	1988-2000 MEDLINE, EMBASE and CCTR	RCTs of OA or RA patients treated with celecoxib who had scheduled endoscopies.	4632	5 RCTs: All parallel group double-blinded 12wks (4 studies) or 24 wks (one study) in duration. 2 published and 3 unpublished studies.	One unpublished study assessed OA patients only, 2 studies (both published) assessed RA patients only and two studies (both unpublished) assessed OA and RA patients. All patients had at least one endoscopic evaluation at 4, 8, 12 or 24 weeks. In all but one study patients also had baseline evaluation.

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
Caldwell, 2006 (Fair)	To examine whether the increased risk of cardiovascular events with rofecoxib represents a class effect of COX-2 specific inhibitors (celecoxib).	Searches through April 2005 MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, ACP Journal Club, Database of Abstracts of Review of Effects, EMBASE, FDA website, requested additional data from Pfizer (none provided)	RCTs of celecoxib of at least 6 weeks duration and reported serious cardiovascular thromboembolic events	12,780 (6,859 randomized to celecoxib)	6 RCTs: 3 celecoxib vs. placebo, 1 celecoxib vs. another NSAID, 1 celecoxib vs. another NSAID vs. placebo, 1 celecoxib vs. paracetamol	Osteoarthritis (2 trials) Mixed osteoarthritis or rheumatoid arthritis (1 trial) Prevention of colorectal carcinoma recurrence (2 trials) Prevention of Alzheimer's disease (1 trial)

Author Year	Characteristics of identified articles: interventions	Main results	Subgroups	Adverse events	Comments
Ashcroft, 2001 (Fair)	Various doses of celecoxib ranging from 50mg - 400 mg/day vs. naproxen (500mg), diclofenac (75mg) or ibuprofen (800 mg)	<p>Celecoxib vs. diclofenac (200 mg vs. 75mg 2x/day) One study found no difference b/t celecoxib vs. diclofenac at 12 wks (RR 0.73 (95% CI: 0.11-0.52)). However, another trial comparing ulcers at 24 wks found lower rates with celecoxib (RR 0.24 (95% CI 0.11-0.52)) Sensitivity analysis revealed that there were significantly fewer endoscopic ulcers w/celecoxib 200mg 2x/day vs. modified-release diclofenac 75mg 2x/day. RR 0.24 (95% CI: 0.16-0.40) Celecoxib vs. ibuprofen (200mg vs. 800mg 3x/day) Fewer ulcers were found at 12wks w/celecoxib RR 0.30 (95% CI: 0.20-0.46) Celecoxib vs. naproxen (doses 100mg - 800mg vs. 1000 mg) For all doses, fewer ulcers w/celecoxib at 12 wks. Pooled data for dose of celecoxib 100mg resulted in RR 0.22 (95% CI: 0.13-0.37) At 200mg, pooled RR was 0.24 (95% CI: 0.17-0.33) Celecoxib vs. placebo Doses from 100-800mg/day. Pooled analysis - celecoxib 100mg 2x/day RR 1.96 (95% CI: 0.85-4.55) 200mg 2x.day RR 2.35 (95% CI: 1.02-5.38)</p>	Not reported	<p>Celecoxib vs. diclofenac Risk of endoscopically detected ulcer - pooled analysis: RR 0.24 (95% CI: 0.16-0.40) Celecoxib vs. ibuprofen Risk of endoscopically detected ulcer - RR 0.30 (95% CI: 0.20-0.46) Celecoxib vs. naproxen Pooled analysis - celecoxib 100mg 2x/day RR 0.22 (95% CI: 0.13-0.37) 200mg 2x/day RR 0.24 (95% CI: 0.17-0.33) Celecoxib vs. placebo Pooled analysis - celecoxib 100mg 2x/day RR 1.96 (95% CI: 0.85-4.55) 200mg 2x.day RR 2.35 (95% CI: 1.02-5.38)</p>	
Caldwell, 2006 (Fair)	2 trials 6 weeks in duration, 2 trials 52 weeks in duration, 1 trial 156 weeks in duration, 1 trial 145-161 weeks in duration			<p>Celecoxib vs. placebo Myocardial infarction (n=2574 vs. n=1247): RR 2.3 (1.0, 5.1) Cerebrovascular event (n=2775 vs. n=1447): RR 1.0 (0.51, 1.8) Cardiovascular death (n=2574 vs. n=1247): RR 1.06 (0.38, 3.0) Composite cardiovascular events (n=2775 vs. n=1447): RR 1.4 (0.91, 2.1) Celecoxib vs. placebo, diclofenac, ibuprofen, or paracetamol Myocardial infarction (n=6658 vs. n=5522): RR 1.9 (1.2, 3.1) Cerebrovascular event (n=6859 vs. n=5921): RR 0.73 (0.42, 1.3) Cardiovascular death (n=6561 vs. n=5428): RR 1.0 (0.52, 2.0) Composite cardiovascular events (n=6859 vs. n=5921): RR 1.2 (0.92, 1.6)</p>	

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
Chen, et al 2008 (Good)	To review the clinical and cost effectiveness of COX-2s for osteoarthritis (OA) and rheumatoid arthritis (RA)	Cochrane Library through Issue 4, 2003; Ovid MEDLINE 1966-October 2003; Ovid MEDLINE In-Process and Other Non-Indexed Citations November 4 and 11, 2003; EMBASE 1980-October 2003; EMEA and FDA websites	RCTs with duration of treatment ≥ 2 weeks; OA or RA population; COX-2 vs placebo, nonselective NSAID or other COX-2	Etodolac n=5,775 Meloxicam n=22,886 Celecoxib n=not reported	Etodolac: 29 RCTs; etodolac vs naproxen, piroxicam, diclofenac, indomethacin, tenoxicam, ibuprofen, nabumetone, nimesulide, placebo Meloxicam: 16 RCTs; meloxicam vs diclofenac, piroxicam, nabumetone, naproxen nabumetone, placebo; 11 abstracts reporting adverse event outcomes also included in meta-analysis but not quality-rated Celecoxib: 40 RCT; celecoxib vs naproxen, diclofenac, dexibuprofen, acetaminophen, ibuprofen, rofecoxib, lumiracoxib, placebo	OA (63 trials), RA (15 trials) or both (7 trials)

Author Year	Characteristics of identified articles: interventions	Main results	Subgroups	Adverse events	Comments
Chen, et al 2008 (Good)	Etodolac 300-1000 mg/day vs naproxen 750-1000 mg/day (10 studies), piroxicam 20 mg/day (7 studies), diclofenac 100-150 mg/day (4 studies), indomethacin 100-150 mg/day (2 studies); tenoxicam 20 mg/day (2 studies), nimesulide 200 mg/day (1 study), nabumetone 1500 mg/day (1 study), ibuprofen 2400 mg/day (1 study) Meloxicam 3.75-15 mg/day vs diclofenac 100-150 mg/day (6 studies), piroxicam 20 mg/day (5 studies), nabumetone 1000 mg/day (2 studies), naproxen 750 mg/day (1 study) Celecoxib 80-800 mg/day vs naproxen 1000 mg/day, diclofenac 100-150 mg/day, acetaminophen 4000 mg/day, ibuprofen 1000 mg/day (not all interventions and doses could be listed and number of studies for each intervention could not be accurately determined; information from some studies not reported)	<u>Etodolac vs NSAIDs</u> Mean difference, pain score: 2.06 (CI -2.09 to 6.22) Mean difference, global efficacy: -0.08 (CI -0.25 to 0.09) Withdrawals due to lack of efficacy RR 1.00 (CI 0.85 to 1.19) <u>Meloxicam vs NSAIDs</u> Mean difference, pain score: 1.7 (CI 0.8 to 2.7) Mean difference, global efficacy: -0.05 (CI -0.25 to 0.15) Withdrawals due to lack of efficacy RR 1.47 (CI 1.24 to 1.73) <u>Celecoxib vs NSAIDs</u> Mean difference, pain score: -0.42 (CI -2.4 to 1.6) Mean difference, global efficacy: 0 (-0.05 to 0.03) ACR-20 RR 1.00 (CI 0.89 to 1.14) Withdrawals due to lack of efficacy RR 0.94 (CI 0.77 to 1.14)	<u>Etodolac vs NSAIDs</u> No analysis; 1 trial reported higher AE incidence in patients >65 yrs in etodolac and placebo groups <u>Meloxicam vs NSAIDs</u> No analysis; two studies reported lower AE rates in patients >65 yrs in meloxicam arms relative to piroxicam and diclofenac <u>Celecoxib vs NSAIDs</u> Risk of POBs, concomitant low-dose aspirin use: comparative RR 2.82; p=0.138 Risk of PUBs, concomitant low-dose aspirin use: comparative RR 0.67; p=0.04 Risk of MI, concomitant low-dose aspirin use: comparative RR 2.24; p=0.121	<u>Etodolac vs NSAIDs</u> All-cause withdrawals RR 0.97 (CI 0.90 to 1.05) Withdrawals due to AEs RR 0.93 (CI 0.77 to 1.12) Withdrawals due to GI AEs RR 0.95 (CI 0.54 to 1.65) Any AE incidence RR 0.83 (CI 0.70 to 0.99) GI AE incidence RR 0.77 (CI 0.55 to 1.08) PUBs RR 0.32 (CI 0.15 to 0.71) POBs RR 0.39 (CI 0.12 to 1.24) <u>Meloxicam vs NSAIDs</u> All-cause withdrawals RR 0.86 (CI 0.77 to 0.96) Withdrawals due to AEs RR 0.92 (CI 0.66 to 1.28) Withdrawals due to GI AEs RR 0.61 (CI 0.54 to 0.69) Any AE incidence RR 0.91 (CI 0.84 to 0.99) GI AE incidence RR 0.31 (CI 0.24 to 0.39) PUBs RR 0.53 (CI 0.29 to 0.97) POBs RR 0.56 (CI 0.27 to 1.15) MI RR 0.33 (CI 0.01 to 8.03) Serious CV events 0.99 (CI 0.06 to 15.9) <u>Celecoxib vs NSAIDs</u> All-cause withdrawals RR 0.93 (CI 0.84 to 1.05) Withdrawals due to AEs RR 0.86 (CI 0.73 to 1.00) Withdrawals due to GI AEs RR 0.45 (CI 0.35 to 0.56) Any AE incidence RR 0.96 (CI 0.91 to 1.01) GI AE incidence RR 0.90 (CI 0.78 to 1.04) PUBs RR 0.55 (CI 0.40 to 0.76) POBs RR 0.57 (CI 0.35 to 0.95) MI RR 1.77 (CI 1.00 to 3.11) Serious CV events RR 0.99 (CI 0.54 to 1.79)	

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
Garner, 2004 (Celecoxib for RA) (Good)	To establish the efficacy and safety of celecoxib in the management of RA.	1966- July, 2002 MEDLINE 1980 - July, 2002 EMBASE CCTR through Issue 3: 2002	RCTs that used any accepted method to assess disease severity or progression, particularly ACR core set of disease activity measures for RA clinical trials endorsed by EULAR and/or OMERACT.	4465	5 RCTs: 2 placebo-controlled double-blinded studies; 3 active-comparator double-blinded studies	Patients with RA with no restrictions regarding age or sex. Studies that include both RA and OA patients were also eligible for inclusion.

Author Year	Characteristics of identified articles: interventions	Main results	Subgroups	Adverse events	Comments
Garner, 2004 (Celecoxib for RA) (Good)	<p>1 study celecoxib (200mg 2x/day) vs. diclofenac (75mg 2x/day)</p> <p>1 study celecoxib (400mg 2x/day) vs. diclofenac (75 mg 2x/day) or ibuprofen (800mg 3x/day)</p> <p>1 study celecoxib (200mg 2x/day) vs. naproxen (500mg 2x/day)</p> <p>1 study celecoxib at varied doses (40mg, 200mg or 400mg 2x/day each) vs. placebo</p> <p>1 study celecoxib at varied doses (100mg, 200mg or 400mg 2x/day each) vs. naproxen (500 mg 2x/day) or placebo</p>	<p>Efficacy Celecoxib vs. naproxen: Differences in withdrawal rates according to intervention or dosage were not statistically significant (29% for naproxen, 28%, 21% and 27% respectively for 100mg, 200mg and 400mg). % of patients showing improvement were also similar regardless of intervention or dosage. When compared to naproxen, RR of improvement were 1.1 (95% CI:0.8, 1.4) at 100mg 1.2 (95% CI: 1.0, 1.5) at 200mg and 1.1 (95% CI: 0.9, 1.4) at 400mg. Celecoxib vs. diclofenac: Withdrawals due to lack of efficacy were nearly the same for both interventions (8% for celecoxib and 7% for diclofenac). % of patients showing improvement according to ACR 20 responder index was also essentially the same (25% for celecoxib, 22% for diclofenac. RR 1.1 (95% CI: 0.8, 1.5)) Celecoxib vs. placebo: Withdrawal rates due to lack of efficacy varied widely between the two placebo-controlled studies: Placebo - 18% and 45%; 40mg -17%; 100mg -28%; 200mg - 4% and 21%; and 400mg - 6% and 27%. % of patients showing improvement: 100 mg - 40%; 200mg - 44% and 51%; 400mg - 39% and 52%; placebo - 29% for both studies.</p> <p>Safety Celecoxib vs. naproxen: Two studies reported data on endoscoped ulcers at 12 wks at 200mg dose. Pooled RR was 0.2 (95% CI: 0.1, 0.4) For other doses of celecoxib when compared to naproxen the RR of developing an ulcer 3mm or greater was 0.2 at 100mg (95% CI: 0.2, 0.5) and 0.2 at 400mg (95% CI: 0.1, 0.5) Only at 100mg was celecoxib statistically favored over naproxen for GI events (RR 0.3 (95% CI: 0.07, 0.9). Celecoxib vs. diclofenac: At 24 wks, 15% of diclofenac and 3% of celecoxib patients had endoscopically detected ulcers of 3mm or greater (RR 0.3 (95% CI: 0.6, 0.9)) Total number of AEs was similar for both interventions (68% of patients taking celecoxib and 73% of patients taking diclofenac) but more diclofenac patients withdrew due to AEs (10% of celecoxib patients vs. 19% of diclofenac patients (RR 0.5 (95% CI: 0.4, 0.8)). Celecoxib vs. placebo: For one study, only number of patients withdrawn due to AEs was reported. There was no significant difference amongst doses or vs. placebo (40mg - 4%; 200mg - 5%; 400mg - 5%; placebo - 6%.) For the other study, GI AEs were also similar (100mg - 28%, 200mg - 25%, 400mg - 26%, placebo - 19%).</p>	<p>Celecoxib vs. placebo No effect for H. pylori status, concurrent aspirin or corticosteroid use, history of GI tract bleeding and ulcers.</p> <p>No other subgroup analysis reported</p>	<p>Celecoxib vs. diclofenac Total AEs: 68% vs. 73% RR 0.9 (95% CI: 0.9, 1.0) GI: 36% vs. 48% RR 0.8 (95% CI: 0.6, 0.9) Peripheral edema: 3% vs. 2% Hypertension: 1% vs. 2%</p> <p>Celecoxib vs. naproxen No difference between total AE rate and withdrawal rate due to AEs GI: RR of ulcer 3mm or greater at 200mg of celecoxib 0.2 (95% CI: 0.1, 0.4) Celecoxib vs. placebo GI: In celecoxib patients, RR of ulcer development 3mm or greater at 12 wks was 1.5 at 100mg (95% CI: 0.5, 4.8); 1.0 at 200mg (95% CI: 0.3, 3.5); and 1.5 at 400mg (95% CI: 0.5, 5.0)</p>	<p>Study design problems with both CLASS and VIGOR studies</p>

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
Kearney, et al 2006 (Fair)	To assess the effects of selective COX-2 inhibitors and traditional NSAIDs on the risk of vascular events	January 1966-April 2005 (MEDLINE and Embase)	RCTs at least 4 wks "scheduled treatment" of COX-2 vs placebo or NSAID that reported serious CV events	145,373	only described as RCTs (n=138); either placebo (n=121) or active	Numerous indications, including: RA, OA, low back pain, ankylosing spondylitis, polyps and Alzheimer's Disease.

Author Year	Characteristics of identified articles: interventions	Main results	Subgroups	Adverse events	Comments
Kearney, et al 2006 (Fair)	Randomized trials that included a comparison of a selective COX 2 inhibitor versus placebo or a selective COX 2 inhibitor versus a traditional NSAID, of at least four weeks' duration, with information on serious vascular events. 41 Celecoxib trials, 17 Etoricoxib trials, 12 Lumiracoxib trials, 14 Valdecoxib trials.	NA	No subgroup analysis	COX-2 vs placebo short- and long-term studies: COX-2s associated with increase in rate of MI - 0.6%/yr vs 0.3%/yr (RR 1.86 CI 95% 1.33-2.59 p=0.0003) RR or all vascular events increases to 1.45 (95% CI 1.12-1.80, p=0.0003) when only long-term (>1 yr) were analyzed. COX-2 vs NSAID: Overall RR of any vascular event among heterogeneous studies 1.0%/yr vs 0.9%/yr was 1.16 (CI 95% 0.97-1.38, p=0.1)	Quality of included studies not considered Of 121 placebo trials, nine were long-term. 2/3 of CV events occurred in long-term trials.

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
Lee, 2004 (Good)	To compare efficacy and safety of recommended doses of NSAIDs, including Cox 2 inhibitors, vs acetaminophen in the treatment of symptomatic hip and knee osteoarthritis	1966 through February 2003 MEDLINE 1991 to 1st quarter 2003 EMBASE Drugs and Pharmacy database	Original clinical trials with direct comparisons of an NSAID with acetaminophen or paracetamol without combination with a nonnarcotic analgesic or narcotic agent. Duration of NSAID exposure \geq 7 days. Sufficient analyzable data	1252	7 clinical trials: 2 randomized active comparator trials without placebo arms, 2 randomized parallel-group double-blinded trials, 2 randomized crossover trials, and 1 randomized placebo-controlled double-blinded trial.	All trials included patients with knee OA, and 2 also included patients with hip OA. 71% were women.

Author Year	Characteristics of identified articles: interventions	Main results	Subgroups	Adverse events	Comments
Lee, 2004 (Good)	<p>1 study compared acetaminophen to placebo, and 5 compared acetaminophen to NSAIDs. Acetaminophen dose ranged from 2600 mg/d (1 study) to 4000 mg/d (5 studies).</p> <p>Mean duration of trials was 22 weeks, with a range from 6 days to 2 years. If outlier study (104 weeks) removed, mean duration was 5.8 weeks.</p>	<p>Acetaminophen vs Placebo Based on 1 cross-over, double-blind RCT Improvement in rest pain: 16/22 (73%) vs 2/22 (9%) Improvement in pain on motion: 15/22 (68%) vs 4/22 (18%) Physician global assessment: 20/21 (95%) vs 1/21 (5%) Patient global assessment: 10/10 (100%) vs 1/10 (10%)</p> <p>Acetaminophen vs NSAIDs : absolute values not available except for global assessment Rest pain and HAQ pain: NSAIDs superior to acetaminophen. Rest pain effect sizes measured by standard mean difference (SMD): 0.32(95% CI, 0.08 - 0.56) and 0.34 (95% CI, 0.10 - 0.58). HAQ pain: 0.27 (95% CI, 0.05 - 0.48) and 0.24 (95% CI, 0.03 - 0.45). Pain on motion: SMDs not significant. Physical function: Neither 50 foot walk time nor HAQ showed significant differences between NSAIDs and acetaminophen. Group 1 (ibuprofen 2400 mg, Arthrotec, celecoxib, naproxen) Physician global assessment: 23/61 (38%) vs 23/61 (38%) Patient global assessment: 37/94(39%) vs 45/97(46%) Group 2 (ibuprofen 1200 mg, Arthrotec, rofecoxib 25 mg, naproxen) Physician global assessment: 23/61(38%) vs 27/62 (44%) Patient global assessment: 37/94 (39%) vs 57/95 (60%) Group 3 (ibuprofen 1200 mg, Arthrotec, rofecoxib 12.5 mg, naproxen) Physician global assessment: not reported Patient global assessment: 37/94 (39%) vs 54/96 (56%)</p>	Not reported	<p>Acetaminophen vs Placebo No participant removed from study due to side effects. Withdrawals/total number of AEs: 10/25 (40%) acetaminophen vs 8/25 (32%) placebo.</p> <p>Acetaminophen vs NSAIDS Group 1: Total # of AEs: 164/360 (46%) vs 179/353 (51%). Withdrawals due to toxicity: 35/448 (8%) vs 38/443 (8%). Group 2: Total # of AEs: 164/360 (46%) vs 170/352 (48%). Withdrawals due to toxicity: 35/448 (8%) vs 38/442 (9%). Group 3: Total # of AEs: 164/360 (46%) vs 180/353 (51%). Withdrawals due to toxicity: 35/448 (8%) vs 39/443 (9%).</p> <p>GI events, acetaminophen vs traditional NSAIDs 10/148 (7%) vs 38/212 (18%) GI events, acetaminophen vs Coxib NSAIDs 16/94 (17%) vs 47/288 (16%) GI withdrawals, acetaminophen vs traditional NSAIDs 9/151 (6%) vs 24/213 (11%)</p>	<p>Results do not account for differences in baseline pain</p> <p>Most trials had short follow-up periods.</p> <p>1 included trial was an abstract only (Altman 1999)</p>

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Moore, 2005 (Fair)	The objective was to improve understanding of adverse events occurring with celecoxib in the treatment of osteoarthritis and rheumatoid arthritis.	Trials completed by December 2003 Pfizer supplied company clinical trial reports	RCTs, 2 weeks or longer in duration, any dose of celecoxib and any comparator, in osteoarthritis or rheumatoid arthritis	38,746 (22,192 randomized to celecoxib)	31 RCTs: 12 celecoxib vs. another NSAID, 5 celecoxib vs. placebo, 14 celecoxib vs. another NSAID vs. placebo	Osteoarthritis (21 trials) Rheumatoid arthritis (4 trials) Mixed osteoarthritis or rheumatoid arthritis (6 trials)	All trials 2-12 weeks in duration, with the exception of 1 trial 24 weeks (n=655), 1 trial 52 weeks (n=7968)
Rostom, 2005 (Fair)	To determine the frequency of lab and clinical hepatic side effects associated with NSAID use.	MEDLINE, EMBASE and Cochrane through January 2004.	RCTs (>4 wks, >40 pts) in duration of adults with OA or RA including one of the following drugs: celecoxib, rofecoxib, valdecoxib, meloxicam, diclofenac, naproxen or ibuprofen.	Total NR	64 RCTs: designs not specified	Patients age >18 with a diagnosis of OA or RA	18 NSAID vs. placebo; 33 diclofenac studies; 12 ibuprofen studies; 14 naproxen studies; 5 meloxicam studies; 8 rofecoxib studies; 5 celecoxib studies; 1 valdecoxib study.
Rostom, 2007 (Fair)	To assess upper GI harms of long-term COX-2 use	CCRCT through 2005; Cochrane Collaboration library through 2005; MEDLINE 1966-2006; EMBASE 1980-2005	RCTs of COX-2s reporting upper GI toxicity relative to nonselective NSAID or placebo; study participants age ≥18 yrs with osteoarthritis, rheumatoid arthritis or other arthritic condition; NSAID exposure ≥4 wks	31,106 celecoxib vs nonselective NSAID; other interventions not abstracted (outside scope of report)	4 RCTs celecoxib vs nonselective NSAID (clinical outcomes)	Not described; all had OA, RA or other arthritic condition per inclusion criteria	Celecoxib doses not specified

Author Year	Main results	Subgroups	Adverse events	Comments
Moore, 2005 (Fair)			<p>Myocardial infarction</p> <p>Celecoxib vs. placebo: 0.12% vs. 0.07%, RR not reported (10 events, n=9315)</p> <p>Celecoxib vs. paracetamol: RR not reported (0 events, n=1056)</p> <p>Celecoxib 200-400 mg vs. NSAID to maximum daily dose: 0.15% vs. 0.04%, RR 1.9 (95% CI, 0.87, 4.1) (23 events, n=21,818)</p> <p>Celecoxib any dose vs. NSAID to maximum daily dose: 0.22% vs. 0.14%, RR 1.6 (0.93, 2.6) (56 events, n=30,220)</p> <p>Celecoxib any dose vs. any active comparator: 0.19% vs. 0.13%, RR 1.4 (0.88, 2.2) (57 events, n=34,174)</p> <p>Celecoxib any dose vs. any comparator: 0.18% vs. 0.12%, RR 1.4 (0.88, 2.2) (59 events, n=38,499)</p> <p>Celecoxib any dose vs. any noncoxib: 0.19% vs. 0.12%, RR 1.4 (0.88, 2.2) (57 events, n=36,316)</p>	
Rostom, 2005 (Fair)	See Adverse Events	Use of high dose of diclofenac (>100mg/day) was associated with a higher proportion of patients having aminotransferase elevation >3x ULN. No SS differences for other subgroups (high dose rofecoxib; longer duration for all comparators including placebo)	Among all comparisons, no NSAID had higher rates of renal serious adverse events, hospitalizations or death. Diclofenac and rofecoxib both showed higher rates of aminotransferase elevations (>3x ULN) when compared to all other NSAIDs (3.55% [95% CI, 3.12-4.03%] and 1.80%[95% CI, 1.52-2.13%] respectively, vs <0.43%)	Assessed adverse events only

Author Year	Main results	Subgroups	Adverse events	Comments
Rostom, 2007 (Fair)	Clinical GI events - celecoxib vs NSAIDs: PODs (perforation, obstruction or bleeding) RR 0.23 (CI 0.07 to 0.76) PUDs (perforation, obstruction, bleeding or symptomatic ulcer) RR 0.39 (CI 0.21 to 0.73) Sensitivity analysis removing combined analysis study eliminated heterogeneity and results still favored celecoxib	Not reported	Not stratified according to intervention; for all COX-2s vs NSAIDs: Withdrawals due to GI tolerability RR 0.65 (CI 0.57 to 0.73) Withdrawals due to dyspepsia RR 0.37 (CI 0.18 to 0.74) Withdrawals due to abdominal pain RR 0.25 (CI 0.13 to 0.49) GI symptoms (low-dose COX-2s) RR 0.78 (CI 0.74 to 0.82) Dyspepsia RR 0.83 (CI 0.75 to 0.90) Nausea RR 0.72 (CI 0.64 to 0.82) Abdominal pain RR 0.25 (CI 0.58 to 0.70)	

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
Rubenstein, 2005 (Good)	To systematically review the published literature of population-based epidemiological studies reporting the incidence or comparative risk of NSAIDs for liver injury resulting in clinically significant events (defined as hospitalization or death)	MEDLINE, Pre-MEDLINE and EMBASE through 2004.	Case-control, controlled cohort, single cohort population-based studies.	Total NR; 396,392 patient years included in analysis	1 case-control; 1 nested case-control; 2 retrospective single-cohort w/ nested case-control studies; 3 retrospective single-cohort w/out nested case-control.	Patients taking NSAIDs for any indication
Solomon, 2008 (Fair)	inhibitor celecoxib affects CV risk,	Time period covered not specified (publication date 2008) Electronic databases not specified, "asked" NIH and Pfizer for unpublished trials	RCTs that were double-blind and placebo-controlled, planned follow-up at least 3 years	7950 (3664 randomized to celecoxib)	6 RCTs of celecoxib vs. placebo	Prevention of colorectal adenoma recurrence (3 trials) Prevention of recurrent breast cancer in postmenopausal women receiving aromatase inhibitors (1 trial) Prevention of Alzheimer's disease and age-related cognitive decline (1 trial) Treatment of diabetic retinopathy with photocoagulation (1 trial)
Towheed, 2004 (Good)	To determine which NSAID is most effective and which is most toxic in the treatment of hip OA	1966 - August, 1994 MEDLINE Cochrane Musculoskeletal Group trials register and CCTR through August 1994	RCTs published in English; placebo-controlled comparative treatment w/analgesics or NSAIDs; single and double-blinded trials	Total number of patients not specified, however mean number of randomized patients per trial was 95, with a range from 9 to 455. Mean number of patients completing trial was 81, range of 9 to 397.	43 RCTs: 21 crossover study design and 22 parallel group design.	Eligible participants were any adult (>18) with a diagnosis of primary or secondary OA. 53% of trial participants were women, mean age 63.

Author Year	Characteristics of identified articles: interventions	Main results	Subgroups	Adverse events	Comments
Rubenstein, 2005 (Good)	6 studies: unspecified NSAIDs (including any of the following: diclofenac, diflunisal, fenbufen, fenoprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, naproxen, nimesulide, sulindac, tenoxicam); 2 of these 6 included aspirin. 1 study: diclofenac, naproxen and piroxicam only.	See Adverse events	Not reported	No SS difference between current NSAID user and past NSAID users in hospitalization rates for liver injury (range 1.2-1.7) Incidence of liver injury resulting in hospitalization ranged from 3.1-23.4/100,000 patient years for current NSAID users, compared to 4.8-8.6/100,000 patient years for past NSAID users.	Assessed adverse events only
Solomon, 2008 (Fair)	Planned follow-up >=3 years in all trials			Cardiovascular death, MI, stroke, heart failure, or thromboembolism Celecoxib any dose (101/4286) vs. placebo (52/3664): HR 1.6 (1.1, 2.3) Celecoxib 400 mg QD (30/1347) vs. placebo (20/1038): HR 1.1 (0.6, 2.0) Celecoxib 200 mg bid (38/1450) vs. placebo (29/1809): HR 1.8 (1.1, 3.1) Celecoxib 400 mg bid (33/1489) vs. placebo (11/1496): HR 3.1 (1.5, 6.1)	Risk increased from low- to moderate-CV risk groups (HR 2.0 [1.5, 2.6]) and from low-risk to high-risk groups (HR 3.9 [2.3, 6.7]). Celecoxib associated with increased risk regardless of baseline aspirin use
Towheed, 2004 (Good)	Placebo v: etodolac, tenoxicam, ketoprofen, diacerhein Head to head: flurbiprofen vs. sulindac diclofenac vs. naproxen proquazone vs. naproxen piroxicam vs. naproxen diclofenac vs. ibuprofen sulindac vs. ibuprofen carprofen vs. diclofenac piroxicam vs. indomethacin naproxen vs. indomethacin tenoxicam vs. diacerhein	Efficacy When compared to placebo, all NSAIDs except diacerhein resulted in pain decrease and improvement of global assessment (no RR provided) In head to head trials, no SS difference amongst any of the compared interventions (no RR provided) Low-dose ibuprofen (<1600 mg/day) and low-dose naproxen (<750 mg/day) less efficacious than other NSAIDs An alternative, more sensitive technique of results analysis (Heller, et al) found that indomethacin was more effective than its comparators in 5 of 7 cases.	Not reported	Out of 29 NSAID combinations, 9 revealed clinically relevant differences in toxicity. Indomethacin was found to be more toxic in 7 of these 9 combinations. However, only 6 of the 29 comparisons were tested for SS differences.	SR limited by lack of standardization of OA diagnosis and OA outcomes Results suggest that best NSAID varies widely depending on a particular patient

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
Towheed, 2005 Cochrane review: most recent substantive update 9/16/02 (Fair)	1) To assess the efficacy and safety of acetaminophen (or paracetamol) vs placebo and 2) vs NSAIDS (ibuprofen, Arthrotec, celecoxib, naproxen and rofecoxib) for treating osteoarthritis (OA)	1966 - July 2002 MEDLINE Through March 2002 Current contents To August 2002 Cochrane Controlled Trials Registry	Published RCTs evaluating efficacy and safety of acetaminophen alone in OA for adults with a diagnosis of primary or secondary OA at any site.	1689	6 RCTs, including 2 with crossover and 4 with parallel-group designs	All trials were of patients with OA of the knee, with one also including OA of the hip

Author Year	Characteristics of identified articles: interventions	Main results	Subgroups	Adverse events	Comments
Towheed, 2005 Cochrane review: most recent substantive update 9/16/02 (Fair)	2 trials of paracetamol vs placebo, 4000 mg/d and 3000 mg/d. 2 trials of NSAIDs vs paracetamol vs placebo, 150 - 200 mg, and 4000 mg, respectively. 6 trials of NSAIDs vs paracetamol, 12.5 mg/d - 2400 mg/d and 2000 mg/d - 4000 mg/d respectively. Duration of trials 1 week to 2 years.	<p>Pain reduction</p> <p>2 placebo controlled trials provided pain intensity at baseline and end point. Pooled ES 0.21 (95% CI 0.02-0.41, p=0.02), favoring paracetamol. 8 trials of NSAIDs vs paracetamol. Pooled ES 0.20 (95% CI 0.10-0.30, p=0.000) indicating NSAIDs better than paracetamol for OA pain relief.</p> <p>Overall Western Ontario and McMaster Universities OA Index (WOMAC)</p> <p>In the 2 placebo controlled trials, no significant difference between paracetamol and placebo (pooled ES 0.14, 95% CI -0.06-0.34).</p> <p>In the 8 other trials, NSAIDs significantly better than placebo (pooled ES 0.34, 95% CI 0.14-0.54) or paracetamol (pooled ES 0.3, 95% CI 0.17-0.44).</p> <p>Clinical response rate</p> <p>The 2 placebo controlled trials showed paracetamol better than placebo, but results were heterogeneous (Q=4.93; p=0.03). Clinical response RRs were 16 (95% CI 2.32-110.45; p=0.02) and 1.67 (95% CI 1.00-2.76; p=0.05).</p> <p>Trials comparing NSAIDs and paracetamol were homogeneous and showed NSAIDs superior to paracetamol. Pooled response RR 1.24 (95% CI 1.08-1.41, p=0.001). NNT was 8 (95% CI 5-19, p<0.001), indicating 8 persons needed to be treated before NSAID showed benefit over paracetamol for moderate to excellent pain relief.</p> <p>Patient preference for NSAIDs or paracetamol</p> <p>Examined in 3 trials in crossover or n of 1 design. More patients preferred NSAIDs (61% vs 20%). Pooled RR 2.46 (95% CI 1.51-4.12, p<0.001) and NNT was 3 (95% CI 2-7, p<0.001). Percentage of patients preferring paracetamol similar to that preferring neither treatment (18%). Pooled RR 0.96 (95% CI 0.79-1.32).</p>	Not reported	<p>Paracetamol vs placebo</p> <p>GI discomfort: 5/55 (9.1%) vs 6/55 (10.9%)</p> <p>Nausea: 1/25 (4.0%) vs 0/25 (0)</p> <p>Headache: 2/55 (3.6%) vs 2/55 (3.6%)</p> <p>Dizziness: 1/55 (1.8%) vs 7/55 (12.7%)</p> <p>NSAIDs overall vs paracetamol</p> <p>GI discomfort: 108/704 (15.3%) vs 82/702 (11.7%)</p> <p>RR 1.35 (95%CI 1.05-1.75)</p> <p>Nausea: 29/491(5.9%) vs 23/492 (4.7%)</p> <p>Headache: 27/581(4.6%) vs 32/580 (5.5%)</p> <p>Dizziness: 5/288 (1.7%) vs 3/282 (1.1%)</p> <p>Conventional NSAIDs vs paracetamol</p> <p>GI discomfort: 105/416 (25.2%) vs 76/420 (18.1%)</p> <p>RR 1.39, 95% CI 1.07-1.80</p> <p>Nausea: 15/203 (7.4%) vs 8/210 (3.8%)</p> <p>Headache: 5/293 (1.7%) vs 8/298 (2.7%)</p> <p>Dizziness: -</p> <p>Coxibs vs paracetamol</p> <p>GI discomfort: 3/288 (1.0%) vs 6/282 (2.1%)</p> <p>RR 0.65, 95% CI 0.17-2.52</p> <p>Nausea: 14/288 (4.9%) vs 15/282 (5.3%)</p> <p>Headache: 22/288 (7.6%) vs 24/282 (8.5%)</p> <p>Dizziness: 5/288 (1.7%) vs 3/282 (1.1%)</p>	<p>Only the 2 placebo controlled studies considered baseline pain levels</p> <p>Most trials had short follow-up periods of approximately 6 weeks</p> <p>1 included trial was an abstract only (Shen 2003)</p> <p>One RCT was an "n of 1" design</p>

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
Watson, 2004 (Poor)	To determine difference in efficacy of NSAIDs in treatment of knee OA.	1966 - November, 1996 MEDLINE 1980-December, 1995 EMBASE	Double-blind RCTs published in English evaluating two NSAIDs	not stated	16 RCTs: All double-blind although most failed to report method used to achieve double-blind conditions	Patients age >16 with a confirmed diagnosis of OA of the knee.
Wegman, 2004 (Fair)	To systematically evaluate RCT evidence on short and long term efficacy of NSAID compared to acetaminophen for OA of the hip or knee. To critically appraise the quality of guidelines for management of OA, and compare content of recommendations in these guidelines on treatment of OA with NSAID or acetaminophen.	To December 2001	For evidence review: RCTs published as full reports comparing NSAIDs with acetaminophen for patients with pain and/or disability related to OA of the hip or knee. At least one of the following outcomes included: overall change, pain or disability. Random allocation of interventions. For guidelines: Guidelines developed by a professional working group of experts. Recommendations on pharmacological management of hip or knee OA.	655	7 publications describing 5 RCTs, two of which were of cross-over design 9 guidelines	All trials included patients with knee OA, and two included those with hip or knee OA.

Author Year	Characteristics of identified articles: interventions	Main results	Subgroups	Adverse events	Comments
Watson, 2004 (Poor)	Etodolac (600 mg and 800 mg) vs. diclofenac (100-150 mg), naproxen (1000 mg), piroxicam (20 mg), indomethacin (150 mg), nabumetone (1500 mg) Nabumetone (1000 mg) vs. diclofenac (100 mg) Tenoxicam (20 mg) vs. piroxicam (20 mg) Tenoxicam (20 mg) vs. diclofenac (150 mg) Flurbiprofen (150 mg) vs. diclofenac (150 mg) Naproxen (750 mg) vs. diclofenac (150 mg)	Efficacy Withdrawal due to lack of efficacy: Meta-analysis of nine trials showed no SS differences between etodolac, diclofenac or naproxen. Patient Global Assessment: Favored etodolac in two trials however results are questionable due to nonequivalent dose comparisons. Pain: Only 2 of 14 trials assessed pain measurement with adequate power (70%) to detect minimum clinical difference between treatments. Both trials favored etodolac over the comparator drug. Again, nonequivalent dose comparisons resulted in questionable validity of results. Physical function: Only one trial showed a SS difference in favor of tenoxicam vs. diclofenac (OR 3.93 CI: 95% 1.07-14.44)	not reported		Poor methodology resulted in little SS evidence favoring one NSAID over another Only 5 of 16 trials compared equivalent dosing of trial and comparators
Wegman, 2004 (Fair)	7 different types of NSAIDs, including 3 coxibs within recommended dose ranges were compared to acetaminophen with daily doses ranging from 2600 mg to 4000 mg. Mean duration of trial period from which data were drawn was 49 ± 25 days, with a range of 24 - 84 days.	Rest pain (Based on 5 trials with 1208 subjects) Overall improvement using pooled data: inverse-variance-weighted mean difference (WMD) = -6.33 (95%CI -9.24, -3.41) and an average ES of 0.23 favoring NSAID-treated groups. In 3/6 studies, there was a reduction in rest pain favoring NSAIDs (p<0.05) Walking pain (Based on 6 trials with 1051 subjects) Pooled data demonstrated a WMD of -5.76 (95% CI -8.99, -2.52) and an average ES of 0.23 favoring NSAID-treated groups.	Not reported	Dropouts due to adverse events All NSAID groups: 63/752 (8.4%) High dose NSAID groups only: 48/497 (9.7%) Acetaminophen: 32/500 (6.4%) The overall safety measure derived from pooled data for dropouts due to AEs showed no statistically significant difference between NSAID vs acetaminophen (OR 1.45; 95% CI 0.93, 2.27). Specific types of AEs resulting in withdrawal were not discernable due to lack of data in primary studies.	No data on specific AEs

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
White, 2003 (Poor)	To determine whether the celecoxib affects cardiovascular thrombotic risk.	Time period covered not specified (publication date 2003) Databases not described, possibly Pfizer database of trials.	Completed RCTs of celecoxib for arthritis with planned duration of ≥ 4 weeks	31,879 (18,942 randomized to celecoxib)	15 RCTs: 9 celecoxib vs. another NSAID, 4 celecoxib vs. placebo, 2 celecoxib vs. another NSAID vs. placebo	Osteoarthritis (8 trials) Rheumatoid arthritis (4 trials) Mixed osteoarthritis or rheumatoid arthritis (3 trials)
White, 2007 (Poor)	To determine whether the celecoxib affects CV risk.	Trials completed through October 31, 2004 Pfizer's celecoxib drug safety database	RCTs with a parallel group design; 1 treatment arm given celecoxib at doses of ≥ 200 mg/day; 1 treatment arm given a placebo comparator or a NSAID comparator; planned double-blind treatment period ≥ 2 weeks; final study report completed by October 31, 2004	41,077 (23,030 randomized to celecoxib)	41 RCTs: 12 celecoxib vs. another NSAID, 16 celecoxib vs. placebo, 13 celecoxib vs. another NSAID vs. placebo	Osteoarthritis (21 trials) Rheumatoid arthritis (4 trials) Mixed osteoarthritis or rheumatoid arthritis (6 trials) Ankylosing spondylitis (2 trials) Low back pain (4 trials) Alzheimer's disease (2 trials)

Author Year	Characteristics of identified articles: interventions	Main results	Subgroups	Adverse events	Comments
White, 2003 (Poor)	All trials 4-12 weeks in duration with the exception of 1 trial 24 weeks (n=655), 1 trial 26 weeks (n=7968)			<p>Antiplatelet Trialists' Collaboration composite CV events All patients Celecoxib (n=4849) vs. placebo (n=1794): 9/700 vs. 3/200 patient-years, RR 0.85 (95% CI 0.23, 3.15) Celecoxib (n=17,473) vs. NSAIDs (n=11,143): 54/4969 vs. 38/3613 patient-years, RR 1.06 (95% CI 0.70, 1.61) Celecoxib (n=12,449) vs. naproxen (2,271): 4/606 vs. 2/171 patient-years, RR 0.85 (95% CI 0.29, 2.46)</p> <p>Aspirin nonusers Celecoxib (n=4192) vs. placebo (n=1,553): 4/606 vs. 2/171 person-years, RR 0.60 (95% CI 0.11, 3.29) Celecoxib (n=15,353) vs. NSAIDs (n=9649): 24/4224 vs. 20/3012 person-years, RR 0.86 (95% CI 0.48, 1.56) Celecoxib (n=11,289) vs. naproxen (n=1975): 11/2204 vs. 3/343 person-years, RR 0.82 (95% CI 0.18, 2.46)</p>	Pooled CV across all trials (instead of pooling RR's from individual trials)

Author Year	Characteristics of identified articles: interventions	Main results	Subgroups	Adverse events	Comments
White, 2007 (Poor)	All trials 4-12 weeks in duration, with the exception of 1 trial 24 weeks (n=655), 2 trials 52 weeks (n=1341), 1 trial 52-65 weeks (n=7968), 1 trial 104 weeks (n=36)			<p>Celecoxib 200-800 mg (n=7462) vs. placebo (n=4057) (adjudicated events, nonadjudicated events) Antiplatelet Trialists' Collaboration composite CV events (18 vs. 7, 23 vs. 8): RR 1.1 (0.47, 2.7), RR 1.3 (0.57, 2.8) CV deaths (8 vs. 3, 11 vs. 3): RR 1.3 (0.33, 4.8), RR 1.7 (0.49, 6.2) Nonfatal MI (5 vs. 1, 7 vs. 2): RR 1.6 (0.21, 12), RR 1.2 (0.27, 5.8) Nonfatal stroke (5 vs. 3, 5 vs. 3): RR 0.80 (0.19, 3.3), RR 0.80 (0.19, 3.3)</p> <p>Celecoxib 200-800 mg (n=19,773) vs. nonselective NSAIDs (n=13,990): (adjudicated events, nonadjudicated events) Antiplatelet Trialists' Collaboration composite CV events (54 vs. 49, 57 vs. 54): RR 0.90 (0.60, 1.3), RR 0.86 (0.59, 1.3) CV deaths (12 vs. 19, 15 vs. 19): RR 0.57 (0.28, 1.1), RR 0.72 (0.37, 1.4) Nonfatal MI (32 vs. 15, 35 vs. 19): RR 1.8 (0.93, 3.4), RR 1.5 (0.82, 2.7) Nonfatal stroke (10 vs. 15, 7 vs. 16): RR 0.51 (0.23, 1.1), RR 0.33 (0.14, 0.78)</p>	Appeared to simply pool CV events across all trials (instead of pooling RR's from individual trials), did not include Pre SAP, ADAPT, or APC trials

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
Zhang, 2004 (Good)	To assess the best available evidence for efficacy of paracetamol (acetaminophen) in the treatment of osteoarthritis (OA).	1966 through July, 2003	RCTs comparing paracetamol with placebo or NSAIDs for treatment of OA (radiographic evidence or ACR clinical criteria) or OA pain.	1712	10 RCTs: 5 double blind parallel, 3 double blind crossover, one "n of 1" and one undefined RCT (abstract only) design	Patients with either symptomatic OA of the knee (6 trials) or hip/knee (3 trials) or multiple joints (1 trial).

Author Year	Characteristics of identified articles: interventions	Main results	Subgroups	Adverse events	Comments
Zhang, 2004 (Poor)	5 types of NSAIDs were compared to acetaminophen with daily doses ranging from 2600 mg/d to 6000 mg/d. Trial periods ranged from 7 days to 2 years.	<p>General pain/rest pain (Based on 3 trials, OA of hip or knee, 4 - 6 weeks follow-up) Pooled standardized mean difference of 0.33 (95% CI 0.15 - 0.51), indicating a small effect in favor of NSAIDs. Pain on motion, comparison with high dose ibuprofen: 0.24 (0.00, 0.48); with low dose: 0.18 (-0.06, 0.42) Functional disability, comparison with high dose ibuprofen: 0.19 (0.01, 0.37); with low dose: 0.18 (0.00, 0.35) Overall change (physician assessment): 0.22 (0.02, 0.43)</p> <p>3/9 guidelines satisfied more AGREE criteria than others, especially rigor of development. Most guidelines had poor descriptions of stakeholder involvement, applicability and editorial independence were poorly described in most guidelines. The recommendations on use of NSAIDs or acetaminophen was fairly consistent.</p>	Not reported	Not reported	<p>Main results based on 3 trials with a total n of 589</p> <p>Baseline pain levels not accounted for in analysis</p>

Cardiovascular safety in observational studies

Author, year Data source Sample size (Quality rating)	Population	Categorization of exposure	Demographics (Age, gender, race)	Study Design/Type	Adjusted variables, selection of controls (for case-control studies)
Andersohn 2006 UK General Practice Research Database (GPRD) (6/1/00-10/31/04) Cases=3,643 (Fair)	Age ≥ 40 years; ≥ 1 NSAID prescription between June 1, 2000 and October 31, 2004; from a practice with ensured quality standards of data recording for ≥ 1 year	Recent use: within 15 to 183 days before index date Past use: 184 days to 1 year Nonuse: no use during 1 year before index date	Age: Mean 69 years Female: 41% Race: Not reported	Nested case-control study	CHD, hypertension, diabetes mellitus, cerebrovascular disease, hyperlipidemia, rheumatoid arthritis, body mass index, smoking status. Controls matched on age, sex, practice, year of cohort entry.
Cunnington 2008 Medical and pharmacy claims from Life-link database (1/1/94-12/31/98) N=71, 026 (Fair)	Patients diagnosed with osteoarthritis before 1999	Chronic user: At least 90 days continuous use with at least two prescriptions Non-user: No recorded exposure to NSAIDs	Chronic user vs. non-user Age: 52% vs. 46% >=65 years Female: 64% vs. 54% Race: Not reported	Retrospective cohort study	Diabetes, smoking-related illness, anticoagulant use, use of lipid lowering drugs, antihypertensive medication, estrogen hormone replacement therapy, intermittent COX-2 inhibitor use or chronic non-selective NSAID use, prior acute myocardial infarction, ischemic stroke, revascularizations, time since osteoarthritis diagnosis
Farkouh, 2007 TARGET Trial post hoc analysis N=18,224	Patients > 50 years with osteoarthritis who participated in TARGET trial stratified by CV risk and ASA use	CV risk and ASA use	Age: Mean 66 years Female: 74%% Race: NR	Post-hoc analysis trial	Not applicable: stratified by CV risk and aspirin use
Fischer, 2005UK GPRD database January 1995 - April 2001 Cases= 8688 (Fair)	Residents of the England and Wales who see a GP registered with the General Practice Research Database (GPRD)	Current users: supply of the last prescription for an NSAID before the index date ended or after the index date Non-users: without exposure before index date	Age: ≤89 years Female: 37.1% Race: NR	Case-control	Age, sex, smoking status, aspirin use, body mass index, and diagnosed CV or metabolic diseases (hypertension, hyperlipidemia, diabetes mellitus, ischemic heart disease, arrhythmias of heart failure, arterial thrombosis, kidney disease, rheumatoid arthritis, lupus), acute chest infections and NSAID drug use

Author, year Data source Sample size (Quality rating)	NSAIDs evaluated	Aspirin use (%)	Outcome: incidence	Results	Effects of confounders, dose, duration
Andersohn 2006 UK General Practice Research Database (GPRD) (6/1/00- 10/31/04) Cases=3,643 (Fair)	(A) Celecoxib (B) Diclofenac (C) Ibuprofen (D) Naproxen (E) Other nonselective NSAIDs	NR	AMI, death from AMI, or sudden death from coronary heart disease (CHD): 3.7 per 1000 person-years	Current use vs. nonuse: adjusted RR (95% CI) (A) 1.56 (1.23, 1.98) (B) 1.36 (1.17, 1.58) (C) 1.00 (0.83, 1.21) (D) 1.16 (0.86, 1.58) (E) 1.19 (1.02, 1.39)	Risk increased with dose for celecoxib. No significant interaction with age, gender, or presence of risk factors
Cunnington 2008 Medical and pharmacy claims from Life-link database (1/1/94- 12/31/98) N=71, 026 (Fair)	(A) Celecoxib (B) Naproxen	NR	Hospitalization for acute myocardial infarction or ischemic stroke: 8.6/1000 person-years for acute myocardial infarction and 4.2 per 1000 person-year for ischemic stroke	Chronic use vs. non-use: adjusted HR (95% CI) (A) 1.05 (0.91, 1.22) (B) 0.99 (0.64, 1.54)	No effect on estimates in stratified analysis by age or history of ischemic stroke
Farkouh, 2007 TARGET Trial post hoc analysis N=18,224	(A) Ibuprofen (B) Naproxen	Stratified by aspirin use	Incidence of CV outcome by baseline risk	Use of Lumiracoxib vs. NSAID HR (95% CI): Low CV risk: (A) 1.13 (0.48, 2.66) (B) 0.88 (0.43, 1.78) High CV risk: (A) 0.91 (0.15, 5.47)	Stratification by aspirin use showed no difference
Fischer, 2005UK GPRD databaseJanuary 1995 - April 2001Cases= 8688 (Fair)	(A) Current use (B) Diclofenac (C) Ibuprofen (D) Naproxen (E) Indomethacin (F) Piroxicam (G) Ketoprofen (H) Fenbufen (I) Nabumetone (J) Etodolac (K)Flurbiprofen	4.4% of cases (and never NSAIDs use)	First-time acute myocardial infarction	Current use vs. no use: adjusted OR (95% CI)(1)1.07 (0.96-1.19)(A) 1.23 (1.00-1.51)(B) 1.16 (0.92- 1.46)(C) 0.96 (0.66-1.38)(D) 1.36 (0.82 - 2.25)(E) 0.95 (0.53-1.69)(F) 0.86 (1.44-1.70)(G) 3.08 (1.18- 8.06)(H) 0.62 (0.25-1.53)(I) 1.13 (0.40-3.22)(J) 0.68 (0.22-2.12)	Concomitant use of aspirin with NSAIDs was associated with a decreased risk of MI 0.74 (0.57-0.97)

Author, year Data source Sample size (Quality rating)	Population	Categorization of exposure	Demographics (Age, gender, race)	Study Design/Type	Adjusted variables, selection of controls (for case-control studies)
Garcia-Rodriguez, 2000 (1/1/1991-12/31/1995) N=164,769 Cases= 1,013 (Fair)	Residents of the England and Wales who see a GP registered with the General Practice Research Database (GPRD)	Current user: prescribed aspirin/NSAIDs during the month before the index date Past user: No prescribed NSAID before index date	Age: 50-74 years (60% < 65 years) Female only Race: NR	Case-control (authors state within a cohort)	Age, HRT use, smoking, hypertension, diabetes, obesity, surgical menopause, family history of CHD, and aspirin use (if applies)
Garcia-Rodriguez, 2004 UK GPRD (1/1997- 12/2000) Controls= 20,000 Cases= 4975 (Fair)	Residents of the UK who see a GP registered with the General Practice Research Database (GPRD)	Current user: supply of the most recent prescription lasted until index date or ended in the 30 days before the index date Recent user: ended between 31 and 180 days before the index date Past user: ended between 6 months and 2 years before the index date Nonusers: no recorded use in the 2 years before the index date	Age: 50-84 years Men and women Race: NR	Case-control (authors state within a cohort)	Age, sex, calendar year, cancer diagnosis, smoking, diabetes, hypertension, hyperlipidemia, BMI, RA, osteoarthritis, anemia, CHD, cerebrovascular disease, alcohol intake, use of steroids, aspirin, anticoagulants, paracetamol, and NSAIDS

Author, year Data source Sample size (Quality rating)	Population	Categorization of exposure	Demographics (Age, gender, race)	Study Design/Type	Adjusted variables, selection of controls (for case-control studies)
Graham 2005 State of California Kaiser Permanente health care database (1/1/99-12/31/09) Cases=8,143 (Fair)	Age 18-84 years, filled ≥ 1 prescription for celecoxib, rofecoxib or any other non- selective NSAID; ≥ 12 months of health plan coverage before index prescription date	Current use: overlap with index date Remote use: ended >60 days before index date Recent use: ended 1-60 days before index date	Age: Mean 67 years Female: 38% Race: Not reported	Nested case- control study	Age, sex, health plan region, cardiovascular risk score, admission for non-cardiac- related disorders and same-day procedures, emergency room visits for non-cardiac reasons, hormone replacement therapy, and high-dose prednisone. Controls matched on index date, age, sex, health plan region.

Author, year Data source Sample size (Quality rating)	NSAIDs evaluated	Aspirin use (%)	Outcome: incidence	Results	Effects of confounders, dose, duration
Garcia-Rodriguez, 2000 (1/1/1991- 12/31/1995) N=164,769 Cases= 1,013 (Fair)	(A) Aspirin (B) NSAIDs	N/A Aspirin evaluated as drug	First recorded date of MI	Current user vs. non user: adjusted OR (95% CI) (A) 0.80 (0.41-1.53) (B) 1.45 (1.18-1.79) Past user vs. non user: adjusted OR (95% CI) (A) 0.86 (0.46 - 1.58) (B) 0.89 (0.76-1.05)	Beneficial effects of aspirin use seen in women using ≤ 150 mg
Garcia-Rodriguez, 2004 UK GPRD (1/1997- 12/2000) Controls= 20,000 Cases= 4975 (Fair)	(A) Naproxen (B) Ibuprofen (C) Diclofenac (D) Ketoprofen (E) Meloxicam (F) Piroxicam (G) Indomethacin	27% of cases 14% of controls	MI association with current use of individual NSAIDS	NSAID use vs. non-use of NSAIDs OR (95% CI) (A) 0.89 (0.64-1.2) (B) 1.1 (0.87-1.3) (C) 1.2 (0.99-1.4) (D) 1.1 (0.59-2.0) (E) 0.97 (0.60-1.6) (F) 1.2 (0.69-2.2) (G) 0.86 (0.56-1.3)	Duration or daily dose did not change the results

Author, year Data source Sample size (Quality rating)	NSAIDs evaluated	Aspirin use (%)	Outcome: incidence	Results	Effects of confounders, dose, duration
Graham 2005 State of California Kaiser Permanente health care database (1/1/99-12/31/09) Cases=8,143 (Fair)	(A) Celecoxib (B) Ibuprofen (C) Naproxen (D) Other NSAIDs	Random sample of n=817 cases participated in phone interview and 23% reported using aspirin	Acute MI requiring admission or sudden cardiac death: 3.5/1000 person- years	Current use vs. remote use: adjusted OR (95% CI) (A) 0.84 (0.67, 1.04) (B) 1.06 (0.96, 1.17) (C) 1.14 (1.00, 1.30) (D) 1.13 (1.01, 1.27) Current use vs. celecoxib use (A) 1 (reference) (B): 1.26 (1.00, 1.60) (C): 1.36 (1.06, 1.75) (D): 1.35 (1.06, 1.72)	3.8% taking anticoagulants

Author, year Data source Sample size (Quality rating)	Population	Categorization of exposure	Demographics (Age, gender, race)	Study Design/Type	Adjusted variables, selection of controls (for case-control studies)
Hippisley-Cox 2005b Case-control QRESEARCH database (8/1/00- 7/31/04) Cases=9218 (Fair)	Age 25 to 100 years, registered for at least 1 year prior to index date	No use in past 3 years Use >3 months before index date Use within 3 months of index date	Age: 20% 55-64 years, 28% 65-74 Male: 63% Race: Not reported	Nested case- control study	Other NSAIDs, use of aspirin, statin, tricyclic antidepressant, SSRI, ischemic heart disease, diabetes, hypertension, osteoarthritis, rheumatoid arthritis, smoking obesity, deprivation. Controls matched on age, calendar time, sex, and practice.
Hudson 2005 Database of hospital discharge summaries (4/1/00-3/31/02) N=997 (Fair)	Aged > 66 with admission for congestive heart failure from 4/00-3/02	Prescription following hospitalization for congestive heart failure	Celecoxib vs. NSAIDs Age: Median 79 vs. 76 years Female: 60% vs. 44% Race: Not reported	Retrospective cohort study	Age, sex, comorbidities, other drugs prescribed, characteristics of the treating doctor or hospital, length of stay, year of exposure, acute myocardial infarction in the previous 3 years, time to first prescription, episodes of congestive heart failure after the index admission but before the first prescription
Johnsen 2005 Denmark National Health Service registries (1/100-12/31- 03) Cases=10,280 (Fair)	Persons living in 3 counties in Denmark, using a hospital registry	Nonuser: No recorded prescription Current user: Filled prescription within 0-30 days New users: Current users who filled first prescription within 0-30 days Recent users: Filled prescription within 31-90 days Former users: Filled prescription >90 days before index date	Age: Mean 70 years Female: 40% Race: Not reported	Case-control study	Discharge diagnosis of cardiovascular disease, various comorbid conditions, various prescription drugs. Controls matched on age and sex.

Author, year Data source Sample size (Quality rating)	NSAIDs evaluated	Aspirin use (%)	Outcome: incidence	Results	Effects of confounders, dose, duration
Hippisley-Cox 2005b Case-control QRESEARCH database (8/1/00- 7/31/04) Cases=9218 (Fair)	(A) Celecoxib (B) Ibuprofen (C) Diclofenac (D) Naproxen (E) Other non- selective NSAIDs	Yes, but proportion NR	First ever MI: 1.7/1000 person-years	Use within 3 months vs. no use in past three years: adjusted OR (95% CI) (A) 1.21 (0.96, 1.54) (B) 1.24 (1.11, 1.39) (C) 1.55 (1.39, 1.72) (D) 1.27 (1.01, 1.60) (E) 1.21 (1.02, 1.44)	No interactions between any NSAID and aspirin use or coronary heart disease; smoking and BMI interacted only with naproxen; age 65 and over only interacted with other non-selective NSAIDs
Hudson 2005 Database of hospital discharge summaries (4/1/00-3/31/02) N=997 (Fair)	(A) Celecoxib (B) Any nonselective NSAID	Yes, in 1006 (53.9%)	Celecoxib vs. nonselective NSAIDs Recurrent CHF: 28 vs. 34/100 person-years Death: 19 vs. 29/100 person- years Death OR recurrent HF: 42 vs. 53/100 person-years (Primary outcome)	Nonselective NSAID use vs celecoxib use: adjusted hazard ratio, (95% CI) Recurrent CHF: 1.21 (0.92, 1.60) Death: 1.54 (1.17, 2.04) Death or recurrent CHF: 1.26 (1.00, 1.57)	NR
Johnsen 2005 Denmark National Health Service registries (1/100- 12/31-03) Cases=10,280 (Fair)	(A) Celecoxib (B) Naproxen (C) Other nonselective NSAID	6.9% high dose	Acute MI: Incidence not reported	Current user vs. non-user: adjusted HR (95% CI) (A) 1.25 (0.97, 1.62); (B) 1.50 (0.99, 2.29) (C) 1.68 (1.52, 1.85) New user vs. non-user: (A) 2.13 (1.45, 3.13) (B) 1.65 (0.57, 4.83) (C) 2.65 (2.00, 3.50)	13.7% CV disease; 2.2% cc anticoagulant use; rofecoxib was associated with increased risk regardless of baseline risk status

Author, year Data source Sample size (Quality rating)	Population	Categorization of exposure	Demographics (Age, gender, race)	Study design/type	Adjusted variables, selection of controls (for case-control studies)
Kimmel 2005 Hospitals in 5- county region (5/98-12/02) Cases: 1718 (Fair)	Persons aged 40 to 75 years in a 5-country region	Use within 1 week before the index date	Cases vs. controls Age: Mean 58 vs. 53 years Female: 37% vs. 59% Non-white: 28% vs. 19%	Case-control study	Age, sex, race, smoking, insurance, number of physician visits in the previous year, family history of coronary disease, body mass index, activity score, year, previous angina or coronary disease, history of diabetes, hypertension, heart failure, and hypercholesterolemia, use of statins, beta-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, and diuretics. Controls randomly selected from study population.
Levesque 2005 Computerized health insurance and vital statistics databases of Quebec, Canada (1/1/99-6/30/02) Cases=2844 (Good)	≥ 66 years of age prescribed an NSAID or COX-2 who've never had an MI	Current user: Duration of the last prescription dispensed overlapped with the index date Past user: Filled at least 1 NSAID prescription in the year prior to the index date but not currently exposed Ever user: Current or past user Nonuser: No NSAIDs in the last year	Age: Mean 78 years Female: 54% (cases) vs. 68% (controls) Race: Not reported	Nested case-control study	Age, sex, hypertension, coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure, diabetes, use of lipid-lowering drugs, anticoagulant, and aspirin; co-morbid conditions or use of oral corticosteroids; measures of health utilization, measures of comorbidity. Controls matched on month and year of cohort entry and age.
Mamdani 2003 Ontario healthcare administrative database (4/1/98- 3/31/01) N=154,808 (Fair)	NSAID-naïve patients aged ≥ 66 years of age prescribed an NSAID or COX- 2	New user: Received prescription for a drug of interest, no prior prescription within the last year Control: Not prescribed a drug of interest in the 1 year prior to the index date, or during the observation period	Age: Mean 75 years Female: 64% Race: Not reported	Retrospectiv e cohort study	Age, sex, long-term care, low-income status, hospitalizations, cancer, cardiovascular hospitalizations, cardiovascular procedures, concomitant drugs
Mamdani 2004 Ontario healthcare administrative database (4/17/00- 3/31/01) N=130,514 (Fair)	NSAID-naïve patients aged ≥ 66 years of age prescribed an NSAID or COX- 2	New user: Prescribed drug of interest (at least two successive prescriptions), no drug of interest in the year prior to the index prescription	Age: Mean 76 years Female: 58% Race: Not reported	Retrospectiv e cohort study	Age, sex, long-term care, low-income status, hospitalizations, cancer, cardiovascular hospitalizations, cardiovascular procedures, concomitant drugs

Author, year Data source Sample size (Quality rating)	NSAIDs evaluated	Aspirin use (%)	Outcome: incidence	Results	Effects of confounders, dose, duration
Kimmel 2005 Hospitals in 5- county region (5/98-12/02) Cases: 1718 (Fair)	(A) Celecoxib (B) Any nonselective NSAID (C) Ibuprofen or diclofenac (D) Naproxen	33.60%	Nonfatal MI: Incidence not reported	NSAID use within 1 week vs. no use within 1 week: adjusted OR (95% CI) overall, among aspirin nonusers, and among aspirin users (A) 0.43 (0.23, 0.79), 0.35 (0.16, 0.76), 0.67 (0.25, 1.80) (B) 0.61 (0.52, 0.71), 0.55 (0.46, 0.66), 0.77 (0.59, 1.00) (C) 0.53 (0.43, 0.66) overall (D) 0.48 (0.32, 0.73) Celecoxib vs. ibuprofen or diclofenac use within 1 week: 0.77 (0.40, 1.48) overall Celecoxib vs. naproxen use within 1 week: 0.81 (0.37, 1.77)	Some results stratified by aspirin use
Levesque 2005 Computerized health insurance and vital statistics databases of Quebec, Canada (1/1/99-6/30/02) Cases=2844 (Good)	(A) Celecoxib (B) Naproxen (C) Meloxicam (D) Non-naproxen nonselective NSAIDs	22.50%	Acute MI, fatal or nonfatal: 10.4/1000 person-years	Current use vs. no use: adjusted RR (95% CI) (A) 0.99 (0.85, 1.16) overall, 0.98 (0.83, 1.17) low-dose, 1.00 (0.78, 1.29) high dose, 1.07 (0.89, 1.30) no aspirin, 0.88 (0.70, 1.10) taking aspirin (B) 1.17 (0.75, 1.84) overall, 1.59 (0.95, 2.65 no aspirin), 0.60 (0.24-1.50) taking aspirin (C) 1.06 (0.49, 2.30) overall, 0.59 (0.14, 2.41) no aspirin, 1.59 (0.61, 4.14) on aspirin (D) 1.00 (0.73, 1.37) overall, 1.04 (0.71, 1.54) no aspirin, 0.94 (0.57, 1.54) taking aspirin	
Mamdani 2003 Ontario healthcare administrative database (4/1/98- 3/31/01) N=154,808 (Fair)	(A) Celecoxib (B) Naproxen (C) Non-naproxen nonselective NSAIDs	14.70%	Hospitalization for acute MI: 9/1000 person- years	New user vs. nonuser: adjusted RR (95% CI) (A) 0.9 (0.7-1.2) (B) 1.0 (0.6-1.7) (C) 1.2 (0.9, 1.4)	
Mamdani 2004 Ontario healthcare administrative database (4/17/00- 3/31/01) N=130,514 (Fair)	(A) Celecoxib (B) Nonselective NSAIDs	NR	Admission for CHF: 10/1000 person-years	New user vs. nonuser: adjusted RR (95% CI) (A) 1.0 (0.8, 1.3) (B) 1.4 (1.0, 1.9) Non-selective NSAIDs vs. celecoxib: 1.4 (1.0, 1.9)	History of heart failure admission within past 3 years increased risk

Author, year Data source Sample size (Quality rating)	Population	Categorization of exposure	Demographics (Age, gender, race)	Study design/type	Adjusted variables, selection of controls (for case-control studies)
Patel, 2004 Durham VA 1/1/1990-12/31/2000 Cases=3850 aspirin + ibuprofen; 10239 aspirin only (Controls matched by patient month, not patient) (Fair)	Patients in clinical database of the Durham VA Medical Center	Outpatient prescription of aspirin or ibuprofen; aspirin alone, aspirin + ibuprofen and combined	Average birth year, 1933 97% Male Race: 29% black	Case control	Controls matched to cases by sex, race, age and LDL cholesterol level
Rahme 2002 Quebec, Canada RAMQ and Med-Echo databases (1/1/1988- 12/31/1994) Controls= 14,160 Cases= 4163 (Fair)	Residents of Quebec (all persons ≥ 65 years are eligible) registered for health coverage, maintained by RAMQ and Med-Echo databases	Current user: prescriptions with a duration that covered or overlapped with the index date Chronic user: filled at least twice and with 60+ consecutive days of prescription duration Current-chronic user: subject of primary analysis Interrupted-chronic user: chronic user without use at the index date	Age: ≥ 65 years Men: 52.8% cases; 52.8% controls	Case-control (population- based)	Age, sex, use of anticoagulants, nitrates, lipid- lowering agents, antidiabetic agents, or antihypertensive agents, prior AMI, cardiovascular diseases, presence of comorbidity factors
Rahme 2007 Health care records and hospital records of patients in Quebec Canada including those with OA (1997 to 12/2002)(Fair)	Patients of 65 years of age or older who filled a prescription for acetaminophen or a NSAIDs.	The number of days of supply for each NSAID or acetaminophen prescription with a grace period of 25%.	Age ≥ 65 years Male: 45%	Retrospective cohort	Age, gender, alcohol/drug use, co-morbidities (e.g., COPD) and other drugs
Rahme 2007 Quebec government health insurance database and hospital discharge summary database (RAMQ and Med-Echo) (1/1998 to 12/2004) N=644,183 (Fair)	Patients of 65-80 years of age or older who filled a prescription for NSAIDs	The number of days of supply for each NSAID or acetaminophen prescription. Exposure was designated to be 1.25 x number of days supplied).	Age 65-80 years of age Male: 40%	Retrospective cohort	Concomitant drugs and baseline characteristics

Author, year Data source Sample size (Quality rating)	Population	Categorization of exposure	Demographics (Age, gender, race)	Study design/type	Adjusted variables, selection of controls (for case-control studies)
Ray 2002a Tennessee Medicaid program database (1/1/99-6/30/01) N=354,644 (Fair)	Aged 50-84 (mean=61.5); eligible for TennCare benefits for past 365 days; not in a nursing home; no history of non-CV life- threatening illness; new users	User: Taking an NSAID at enrollment, or during the time they were eligible for the study New user: Began an NSAID during follow-up Non-users: No NSAID within 1 year	Age: Mean 61 years Female: 66% Non-white: 27%	Retrospective cohort study	Age, sex, summary cardiovascular disease risk score, ethnic origin, calendar year, basis for inclusion in TennCare, use of estrogen, hospital admission for non- cardiovascular illness, visits to emergency department, rheumatoid arthritis, visits to family doctor, current aspirin use
Schlienger 2002 UK General Practice Research Database (GPRD) (1/1/92- 10/31/97) Cases=3,315 (Fair)	≤ 75 years of age; free of metabolic or cardiovascular diseases predisposing to AMI; registered on the database for at least 3 years before the index date	Current user: Last prescription for an NSAID ended on or after the index date Recent user: Supply ended between 1 and 29 days prior to index date Past user: Supply ended 30 or more days prior to index date Nonuser: No NSAID prescription prior to index date	Age: 25% 50-59 years, 37% 60- 69 Female: 26% Race: Not reported	Case-control study	Smoking status, body mass index, hormone replacement therapy, aspirin use. Controls matched on age, sex, index date, practice attended.
Shaya 2005 Medicaid database (1/1/00-6/30/02) N=6,250 (Fair)	Enrollees who received at least a 60-day supply of a drug of interest over the 2- year study period and did not use the drug for at least 6 months prior; 70% female; 50% African American; 70% were aged 50 years or younger	New user: First NSAID prescription at least 6 months after data collection began and prescribed at least a 60-day supply over the study period	COX-2 vs. other NSAID, excluding naproxen Age: 28% vs. 20% 50-59 years, 19% vs. 7% 60-69 years Female: 70% Non-white: 41%	Retrospective cohort study	Age, sex, race, gastrointestinal bleeding, rheumatoid arthritis, osteoarthritis, acute pain, back pain, hypertension, diabetes, tobacco/alcohol/drug abuse, hyperlipidemia, obesity, renal problems, prior cardiovascular event
Solomon 2002 New Jersey Medicaid or Medicare and Pharmaceutical Assistance for the Aged and Disabled programs (1/1/91- 12/31/95) Cases=4425 (Fair)	Participants in a state Medicaid program or a program for older adults with moderate incomes, who were continuous participants in the program	Cumulative duration in the prior 6 months 1 to 30 days, 31 to 90 days, or 91 to 180 days	Age: 15% ≤64 years, 30% 65- 74 years Female: 69% (cases) vs. 79% (controls) Non-white: 28% (cases) vs. 31% (controls)	Case-control study	Age, sex, ethnicity, Medicaid enrollment, nursing home use, diabetes mellitus, hypertension, congestive heart failure, Charlson Comorbidity Index, number of different drug prescriptions, number of hospitalizations. Controls matched on age.

Author, year Data source Sample size (Quality rating)	NSAIDs evaluated	Aspirin use (%)	Outcome: incidence	Results	Effects of confounders, dose, duration
Ray 2002a Tennessee Medicaid program database (1/1/99-6/30/01) N=354,644 (Fair)	(A) Celecoxib (B) Ibuprofen (C) Naproxen	NR	Serious CHD (hospital admission for AMI or death from CHD): 12/1000 person- years	Current user vs. nonuser (A) 0.96 (0.76, 1.21) (B) 0.91 (0.78, 1.06) (C) 0.93 (0.82, 1.06) New user vs. nonuser (A) 0.88 (0.67, 1.16) (B) 1.01 (0.77, 1.33) (C) 0.92 (0.73, 1.16)	NR
Schlienger 2002 UK General Practice Research Database (GPRD) (1/1/92- 10/31/97) Cases=3,315 (Fair)	(A) Ibuprofen (B) Diclofenac (C) Piroxicam (D) Ketoprofen (E) Indomethacin (G) Naproxen	Yes	First-time acute MI: Proportion not reported	Current use vs. nonuse: adjusted OR (95% CI) (A) 1.17 (0.87, 1.58) (B) 1.38 (1.08, 1.77) (C) 1.65 (0.78, 3.49) (D) 2.06 (0.80, 5.30) (E) 1.39 (0.77, 2.51) (F) 1.03 (0.58, 1.85) (G) 2.26 (0.93, 5.46) (H) 0.68 (0.42, 1.13)	Current use of aspirin at the index date and longer-term use of HRT in women interacted with AMI risk; exposure duration, age, and gender did not.
Shaya 2005 Medicaid database (1/1/00-6/30/02) N=6,250 (Fair)	(A) Celecoxib (B) Non-naproxen, nonselective NSAIDs	NR	Cardiovascular thrombotic events (Antiplatelet Trialists' Collaboration criteria: cardiovascular, hemorrhagic, and unknown deaths; nonfatal MIs; nonfatal strokes): 12%	New celecoxib user vs. non- naproxen, nonselective NSAID user: adjusted RR (95% CI) 1.19 (0.93, 1.51)	
Solomon 2002 New Jersey Medicaid or Medicare and Pharmaceutical Assistance for the Aged and Disabled programs (1/1/91- 12/31/95) Cases=4425 (Fair)	(A) Any nonselective NSAID (B) Naproxen (C) Ibuprofen (D) Etodolac (E) Fenoprofen	Excluded	Acute MI: Incidence not reported	NSAID user vs. non-user: adjusted OR (95% CI) (A) 1.00 (0.92, 1.08) (B) 0.84 (0.72-0.98) (C) 1.02 (0.88, 1.18) (D) 1.28 (1.00, 1.64) (E) 1.95 (1.16, 3.30) Naproxen user vs. ibuprofen user: 0.82 (0.67-1.01)	No dose- or duration- response relationship

Author, year Data source Sample size (Quality rating)	Population	Categorization of exposure	Demographics (Age, gender, race)	Study design/type	Adjusted variables, selection of controls (for case-control studies)
Solomon 2004a Chart review of prescription drug benefit program participants (1998- 2000) Cases=10,895 (Fair)	Low-income, elderly, Medicare beneficiaries who had at least 1 healthcare visit in each 6-month period	Cumulative duration of exposure during the 1- 30 days 31-90 days > 90 days	Mean age: 82 years Female: 78% Non-white: 9%	Case-control study	Race, number of physician visits, hospitalized in previous year, comorbid conditions, diabetes, hypertension, number of prescription drugs, history of cardiovascular conditions, use of statin, hormone replacement therapy, an anticoagulant, rheumatoid arthritis, osteoarthritis, prior nonselective NSAID use. Controls matched on age, sex, and month of index date.
Solomon 2004b Medicare Prescription Drug Benefit Program databases through Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE) or the New Jersey Pharmaceutical Assistance Program for the Aged and Disabled (PAAD) (1998-2000) Cases=3,915 (Fair)	Active users of prescription drug benefit program for 2 consecutive years out of the 3- year period with no prior diagnosis of hypertension and no use of antihypertensive medications	NSAID use: Active prescription on the day before the index date Short duration of use: 1-30 days Long duration of use: 31-90 days	Mean age: 79 years Female: 81% Non-white: 5%	Case-control study	Age >=75 years, sex, race, hospitalization in prior year, nursing home resident in prior year, diabetes, coronary artery disease, osteoarthritis, physician visits in prior year, number of different medications, and comorbid illnesses. Controls randomly selected from eligible pool of patients

Author, year Data source Sample size (Quality rating)	NSAIDs evaluated	Aspirin use (%)	Outcome: incidence	Results	Effects of confounders, dose, duration
Solomon 2004a Chart review of prescription drug benefit program participants (1998- 2000) Cases=10,895 (Fair)	(A) Celecoxib (B) Naproxen (C) Ibuprofen (D) Other nonselective NSAID	NR	Acute MI: Incidence not reported	Adjusted OR (95% CI) Celecoxib use vs. no current NSAID use: 0.93 (0.84, 1.02) Celecoxib use vs. naproxen use: 0.95 (0.74, 1.21) Celecoxib use vs. ibuprofen use: 0.98 (0.76, 1.26) Celecoxib use vs. other nonselective NSAID use: 0.95 (0.82, 1.10)	Dose had an effect for rofecoxib but not celecoxib; couldn't adjust for aspirin use
Solomon 2004b Medicare Prescription Drug Benefit Program databases through Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE) or the New Jersey Pharmaceutical Assistance Program for the Aged and Disabled (PAAD) (1998-2000) Cases=3,915 (Fair)	(A) Celecoxib (B) Nonspecific NSAID	NR	New onset hypertension and the filling of at least 1 antihypertensive medication prescription: Incidence not reported	Adjusted OR (95% CI) Celecoxib use vs. no NSAID use: 1.0 (0.9, 1.2) Celecoxib use vs. nonspecific NSAID use: 0.9 (0.7, 1.1) Celecoxib use <=200 mg vs. no NSAID use: 1.0 (0.8, 1.2) Celecoxib use >200 mg vs. no NSAID use: 1.2 (0.8, 1.7) Celecoxib use <=200 mg vs. nonspecific NSAID use: 0.9 (0.6, 1.1) Celecoxib use >200 mg vs. nonspecific NSAID use: 1.1 (0.6, 1.7) Celecoxib use 1-30 days vs. no NSAID use: 1.4 (1.0, 1.9) Celecoxib use >30 days vs. no NSAID use: 0.9 (0.7, 1.1) Celecoxib use 1-30 days vs. nonspecific NSAID use: 0.8 (0.5, 1.3) Celecoxib use >30 days vs. nonspecific NSAID use: 0.9 (0.7, 1.2)	Dose, duration had no effect; but presence of renal disease, liver disease, or congestive heart failure appeared in increase risk for rofecoxib users

Author, year Data source Sample size (Quality rating)	Population	Categorization of exposure	Demographics (Age, gender, race)	Study design/type	Adjusted variables, selection of controls (for case-control studies)
Solomon, 2008 Medicare database (1999-2004) N=140, 437 (Fair)	Medicare beneficiaries also eligible for a drug benefits program for older adults and enrolled for at least 12 continuous months during 1999 to 2003	New user: No use in 180 days prior to the study, initiated drug during study Continuous user: No gap longer than 15 days between successive prescription periods	Age: Mean 80 years Female: 86% Non-white race: 7%	Retrospective cohort study	Age, sex, race, hospitalized, nursing home resident, physician visits, number of different medications, myocardial infarction, CHF, coronary revascularization, angina, diabetes, hypertension, hyperlipidemia, statin use, clopidogrel use, peripheral vascular disease, stroke, carotid revascularization, chronic renal disease, rheumatoid arthritis, osteoarthritis, malignancy, number of comorbid conditions
Velentgas 2005 Insurance claims/administrative records of United Healthcare (1/1/99 to 6/30/01) N=424,584 (Fair)	Patients aged 40-64 who received at least one dispensing of rofecoxib, celecoxib, naproxen, ibuprofen, or diclofenac in oral tablet or capsule from 1/1/99 to 6/30/01	Current use: Use began on day of new medication dispensing and continued through the number of days supplied Recent use: Began the day following the last day of current use and continued for 60 days	Age: range 21% to 24% for 50-54 years, 14% to 21% for 55-59 years Female: 57% Race: Not reported	Retrospective cohort study	Age, sex, and prior history of vascular event

Author, year Data source Sample size (Quality rating)	NSAIDs evaluated	Aspirin use (%)	Outcome: incidence	Results	Effects of confounders, dose, duration
Solomon, 2008 Medicare database (1999-2004) N=140, 437 (Fair)	(A) Celecoxib (B) Diclofenac (C) Ibuprofen (D) Naproxen (E) Other nonspecific NSAID	NR	Hospitalization for myocardial infarction, stroke, or congestive heart failure; or out-of-hospital death attributable to cardiovascular disease: 8.5 to 15/1000 person-years	New user vs. nonuser: adjusted HR (95% CI) (A) 0.89 (0.83, 0.94) (B) 0.91 (0.74, 1.13) (C) 0.96 (0.83, 1.10) (D) 0.79 (0.67, 0.93) (E) 0.87 (0.79, 0.96)	Ibuprofen associated with additional 3.4 CVD events/1000 person-years in patients >80 years old, and additional 11.4 CVD events/1000 person-years in persons with prior myocardial infarction
Velentgas 2005 Insurance claims/administrative records of United Healthcare (1/1/99 to 6/30/01) N=424,584 (Fair)	(A) Celecoxib (B) Naproxen (C) Ibuprofen or diclofenac	NR	Acute coronary syndrome or myocardial infarction: 8.0 to 10/1000 person-years	Current NSAID use vs. current ibuprofen or diclofenac use: adjusted RR (95% CI) (A) 1.03 (0.83, 1.27) (B) 1.14 (0.93, 1.39) Recent NSAID use vs. current ibuprofen or diclofenac use: adjusted RR (95% CI) (A) 0.91 (0.70, 1.17) (B) 0.86 (0.70, 1.04) (C) 1.00 (0.83, 1.20)	No dose-relationship; increased risk for males and for individuals with a cardiac history, peripheral arterial disease, diabetes, beta blocker use, nitrate use

Gastrointestinal safety in observational studies

Author, year Data source Sample size (Quality rating)	Population	Categorization of exposure	Demographics (age, gender, race)	Study design/type	Adjusted variables, selection of controls (for case-control studies)	NSAIDs evaluated
Garcia-Rodriguez, 2001 UK General Practice Research Database (4/2003-10/2008); Cases=2,105 Controls=11,500 (Fair)	Age 40-79 years; enrolled with the General Practitioner free of cancer, esophageal varices, Mallory-Weiss disease, liver disease, coagulopathies, and alcohol-related disorders at start date	<p>Current use: prescription lasted until the index date or ended in the 30 days before the index date Recent use: prescription ended 31-90 days before index date Past use: 91-180 days before the index date Non-use: no recorded use in the 6 months before index date</p> <p>Duration evaluated by adding periods of an interval of < 2 months between 2 prescriptions ("consecutive" prescriptions)</p> <p>Dose-response for Acetaminophen: 1) ≤1,000g 2) 1,001-1,999 3) 2,000 4) 2,001-3,999 5) ≥ 4,000g</p>	Age= 40-79 years Male and Female Race not reported	Nested, case-control	Age, sex, calendar year, smoking, antecedents to of upper GI disorders and use of possible meds with interactions Controls frequency matched by age and sex (randomly selected index-date)	A) Etodolac B) Ibuprofen C) Ketoprofen D) Nabumetone E) Tenoxicam F) Meloxicam G) Naproxen H) Diclofenac I) Flurbiprofen J) Indomethacin K) Piroxicam

Author, year Data source Sample size (Quality rating)	Outcome: incidence	Results	Effects of confounders, dose, duration	Notes
<p>Garcia-Rodriguez, 2001 UK General Practice Research Database (4/2003-10/2008); Cases=2,105 Controls=11,500 (Fair)</p>	<p>Codes for upper GI complications (UGIC): 1) Bleed/perforation in stomach or duodenum 2) Clinical diagnosis of peptic ulcer with referral to consultant or admitted to a hospital a) Uncomplicated ulcer NSAID use: 16.0/1,000 person-years b) Complicated ulcer NSAID use: 24.6/1000 person-years</p> <p>*Case status validated by a random sample of 100 patients; 99% had confirmed UGIC)</p>	<p>Adjusted RR (95% CI) Acetaminophen vs. nonuse: 1.3 (1.1-1.5)</p> <p>NSAIDs vs. nonuse A) Etodolac: 2.2 (0.4-11.3) B) Ibuprofen: 2.5 (1.9, 3.4) C) Ketoprofen: 3.3 (1.9, 5.9) D) Nabumetone: 3.4 (1.1, 10.6) E) Tenoxicam: 3.4 (0.9, 13.1) F) Meloxicam: 3.8 (0.8, 17.2) G) Naproxen: 4.0 (2.8, 5.8) H) Diclofenac: 4.6 (3.6, 5.8) I) Flurbiprofen: 4.6 (2.0, 10.9) J) Indomethacin: 5.2 (3.2, 8.3) K) Piroxicam: 6.2 (3.7, 10.1)</p>	<p>Dose: Acetaminophen $\geq 2g$ had greater risk of UGIC compared to lower doses and risk of dose-response increase was independent of duration</p> <p>Dose NSAIDs: Medium or lower daily dose, 2.5 (CI: 1.9-3.1) High daily dose, 4.9 (CI: 4.1-5.8)</p> <p>Substantial interaction when taking NSAIDs and ≥ 2 g or more of acetaminophen</p>	<p>Etodolac, nabumetone, meloxicam: risk estimates compatible with average NSAID; small sample size per NSAID resulted in wide CI's</p>

Author, year Data source Sample size (Quality rating)	Population	Categorization of exposure	Demographics (age, gender, race)	Study design/type	Adjusted variables, selection of controls (for case-control studies)	NSAIDs evaluated
Garcia-Rodriguez, 2007UK Health Improvement Network database (1/2000-2005)Cases=1,561 Controls=10,000 (Good)	Age 40-85 years enrolled at least 2 years with GP and 1 year since first recorded prescription without cancer, esophageal varices, Mallory-Weiss syndrome, coagulopathies, alcohol-related disorders and liver disease	Prescription records; duration determined by consecutive prescriptions (less than 2 months between prescriptions)	Mean age, gender, race not reported	Nested, case-control	Age, sex, calendar year, GP visits, smoking, alcohol consumption, history of peptic ulcer disease, use of aspirin, anticoagulants and steroidsControls random date matched (based on case length follow-up)	A) Aceclofenac B) Acemetacin C) Apazone D) Azapropazone, Celecoxib E) Diclofenac F) Diflunisal G) Etodolac, Etoricoxib H) Fenbufen I) Fenoprofen J) Flurbiprofen K) Ibuprofen L) Indomethacin M) Ketoprofen N) Ketorolac O) Mefenamic acid P) Meloxicam Q) Nabumetone R) Naproxen S) PiroxicamRofecoxib T) Sulindac U) Tenoxicam V) Tiaprofenic acid W) Valdecoxib
Hippisley-Cox, 2005 367 general practices in the UK contributing to the QRESEARCH database (8/1/00-7/31/04)Cases: 9407Controls: 88,867 (Fair)	Aged ≥ 25 with first ever upper GI event and ≥ 3 yrs of recorded medical data	Grouped by usage and type (COX-2 inhibitor), other NSAIDs, and aspirin Non-use: no prescription in past 3 yearsPast use: prescribed > 90 days of index date Current use: prescribed ≤ 90 days of index date	Age at index date, Median (IQR): Cases: 68 years, (53-79)Controls: 67 years, (52-78)Gender (% Female): Cases: 47.2Controls: 52.8Race not reported	Nested, case-control	Smoking, obesity, Townsend score (comparable to SES), ulcer healing drugs, antidepressants, statins, and comorbidities (i.e., diabetes)Controls matched up to 10 per case by age, calendar time, sex and general practice	A) Celecoxib B) Other selective NSAIDs C) Ibuprofen D) Diclofenac E) Naproxen F) Other non-selective NSAIDs

Author, year Data source Sample size (Quality rating)	Outcome: incidence	Results	Effects of confounders, dose, duration	Notes
Garcia-Rodriguez, 2007 UK Health Improvement Network database (1/2000-2005) Cases=1,561 Controls=10,000 (Good)	Upper GI complications, bleeding or perforations	Adjusted RR of upper GI complications – Celecoxib 2.7 (CI 1.5 to 4.1*) Ibuprofen 2.0 (CI 1.4 to 2.9) Meloxicam 2.7 (CI 1.4 to 4.3*) Diclofenac 3.7 (CI 2.4 to 4.2*) Ketoprofen 5.4 (CI 1.5 to 16.1*) Indomethacin 7.2 (CI 3.8 to 13.8*) Naproxen 8.1 (CI 4.9 to 12.2*) *CIs estimated based on graph	Non-use vs current steroid use RR 1.4 (CI 1.0 to 1.9) Non-use vs past steroid use RR 1.1 (CI 0.8 to 1.5) Non-use vs current aspirin use RR 1.1 (CI 1.5 to 2.0) Non-use vs recent aspirin use RR 1.7 (CI 1.3 to 2.2) Non-use vs current warfarin use RR 2.0 (CI 1.5 to 2.6) Non-use vs past warfarin use RR 1.6 (CI 0.9 to 2.8)	
Hippisley-Cox, 2005 367 general practices in the UK contributing to the QRESEARCH database (8/1/00-7/31/04) Cases: 9407 Controls: 88,867 (Fair)	Complicated GI event (those involving hemorrhage, perforation, or surgery) Overall incidence: 1.36 per 1000 p-years (95% CI: 1.34 to 1.39)	Adjusted Odds Ratio (95% CI): Past use vs. non-use A) 1.00 (0.77 to 1.29) B) 0.87 (0.69 to 1.10) C) 1.05 (0.96 to 1.15) D) 1.09 (0.99 to 1.19) E) 1.06 (0.89 to 1.26) F) 1.08 (0.94 to 1.24) Current Use vs. non-use A) 1.25 (0.91 to 1.72) B) 1.72 (1.29-2.29) C) 1.58 (1.37-1.83) D) 2.07 (1.82-2.35) E) 1.97 (1.48-2.61) F) 1.59 (1.29 to 1.96) Aspirin: Past use vs. non-use 1.64 (1.49, 1.81) Current Use vs. non-use 1.60 (1.49, 1.72)	Increase incidence of peptic ulcer or gastrointestinal hemorrhage Reduction in GI adverse events in NSAIDs with concurrent use of ulcer healing drugs	# pts taking celecoxib was low

Author, year Data source Sample size (Quality rating)	Population	Categorization of exposure	Demographics (age, gender, race)	Study design/type	Adjusted variables, selection of controls (for case-control studies)	NSAIDs evaluated
Lanas 2006 Hospitals in the Spanish Association of Gastroenterology (2001-2005) Cases=2,777 Controls=5,532 (Good)	Age 20-85 years free of liver disease, coagulation disorders or malignancies, excluding GI varices, vascular lesions, tumors, Mallory-Weiss syndrome, coagulopathy and esophagitis	Current use: drug taken up to 7 days prior to index date Past use: drug taken more than 7 days prior to index date	Mean age 61 years Gender, race not reported	Case-control	Age, sex, calendar semester, ulcer history, nitrate use, oral anticoagulants, antiplatelets, acid- suppressing drugs, NSAIDs, coxibs and aspirin Controls age-matched based on hospital admission of outpatient visit for reasons considered to be unrelated to NSAIDs	A) Aceclofenac B) Diclofenac C) Ibuprofen D) Indomethacin E) Ketoprofen F) Ketorolac G) Lornoxicam H) Meloxicam I) Naproxen J) Piroxicam
Laporte 2004 18 hospitals in Spain and Italy (9/1998-12/2001) Cases=2,813 Controls=7193 (Fair)	Patients aged > 18 years admitted with primary diagnosis of acute upper GI bleeding, acute lesions of gastric mucosa, erosive duodenitis, or mixed lesions	Any use in the 7 days before the index day	> 18 years of age Male and female Race not reported	Case-control	History of peptic ulcer, diabetes, heart failure, smoking, alcohol consumption, SSRI's and other medications with possible interactions Controls: randomly selected and matched according to center, date of admission (within 2 months), sex and age (+/- 5 years)	(A) Diclofenac (B) Ibuprofen (C) Indomethacin (D) Ketoprofen (E) Ketorolac (F) Meloxicam (G) Naproxen (H) Nimesulide (I) Piroxicam (J) Other NSAIDs
Layton 2003b National Health Service prescription data N=36,545 Celecoxib, n=17,458 (May - Dec 2000) Meloxicam, n=19,087 (Dec 1996- Mar 1997) (Fair)	Patients dispensed celecoxib or meloxicam by general practitioner	Dispensed celecoxib or meloxicam	Celecoxib Cohort: Age: \geq 60 years, 59.5% Female: 68.3% Meloxicam Cohort: Age: > 60 years, 55.0% Female: 67.1%	Two Retrospectiv e Cohorts: Celecoxib and Meloxicam	History of upper GI problems, previous prescription of a NSAIDs within 3 months, age, age2 sex and indication of osteoarthritis	A) Celecoxib B) Meloxicam

Author, year Data source Sample size (Quality rating)	Outcome: incidence	Results	Effects of confounders, dose, duration	Notes
Lanas 2006 Hospitals in the Spanish Association of Gastroenterology (2001- 2005) Cases=2,777 Controls=5,532 (Good)	Clinically confirmed hospitalization due to GI bleeding	Adjusted RR, upper GI bleeding - Non-use vs current use RR 5.3 (CI 4.5 to 6.2) Non-use vs past use RR 0.9 (CI 0.7 to 1.2) Non-use vs low/medium dose RR 4.0 (CI 3.2 to 5.0) Non-use vs high dose RR 6.8 (CI 5.3 to 8.8) Non-use vs use 1-30 days RR 7.6 (CI 6.0 to 9.5) Non-use vs use 90 days RR 7.3 (CI 4.0 to 13.2) Non-use vs use 91-365 days RR 2.6 (CI 1.6 to 4.1) Non-use vs use >365 days RR 2.5 (CI 1.8 to 3.4)		
Laporte 2004 18 hospitals in Spain and Italy (9/1998-12/2001) Cases=2,813 Controls=7193 (Fair)	Upper GI bleeding	Adjusted Odds Ratio (95%): Exposed vs. non-exposed Acetaminophen: 1.2 (1.0, 1.5) NSAIDs (A) 3.7 (2.6, 5.4) (B) 3.1 (2.0, 4.9) (C) 10.0 (4.4, 22.6) (D) 10.0 (3.9, 25.8) (E) 24.7 (8.0, 77.0) (F) 5.7 (2.2, 15.0) (G) 10.0 (5.7, 17.6) (H) 3.2 (1.9, 5.6) (I) 15.5 (10.0, 24.2) (J) 3.6 (2.0, 6.8)	Risk increased with dose, history of peptic ulcer and/or upper GI bleeding, and use of antiplatelet drugs	Excluded patients on anticoagulants Small sample size= wide CI's
Layton 2003b National Health Service prescription data N=36,545 Celecoxib, n=17,458 (May - Dec 2000) Meloxicam, n=19,087 (Dec 1996- Mar 1997) (Fair)	Complicated upper GI conditions: perforations/bleeding	Adjusted rate ratios (95% CI) Meloxicam vs. Celecoxib 0.56 (0.32, 0.96)	Reduction of risk in meloxicam is more significant for those with OA and female	2 cohorts and baseline differences are significant; objective of study was to compare safety of meloxicam vs. celecoxib

Author, year Data source Sample size (Quality rating)	Population	Categorization of exposure	Demographics (age, gender, race)	Study design/type	Adjusted variables, selection of controls (for case-control studies)	NSAIDs evaluated
Mellemkjaer 2002 Pharmaco- Epidemiologic Database of North Jutland (1991-1995) n=156,138 (Fair)	Age range not reported, but <16 year or >105 years excluded; other exclusions due to alcoholism, esophageal varices, Mallory-Weiss syndrome, liver cirrhosis; cancer	Dispensed prescriptions based on database information	Mean age not reported; 70% (110,062/156,138) <60 years; 12% (19,307/156,138) 60-69 years; 17% (26,768/156,138) >70 years 55% female Race not reported	Retrospective cohort	Sex, five-year age group, 1 -year calendar period	A) Diclofenac B) Ibuprofen C) Indomethacin D) Ketoprofen E) Naproxen F) Piroxicam
Norgard 2004 County Hospital Discharge Registry of Denmark, North Jutland County Denmark and Pharmaco- Epidemiological Prescription Database of North Jutland (1/1/2000 to 12/31/2002) Cases= 780 Controls=2906 (1/1/2000 to 12/31/2002) (Fair)	First upper GI bleed (UGIB) in patients living within the county defined as high risk because of previous GI disease	Prescription of celecoxib and other non-selective NSAIDs	Age Mean: Cases= 66.8 Controls=72.5 Ranges=18-89 years Female: Cases= 42.9% Controls= 46.9% Race: not reported	Case-control	Gender, age, history of alcoholism, esophagitis, non-bleeding gastritis or duodenitis; Mallory-Weiss lesions; non-bleeding ulcer diagnosis, co-morbidity index, prescriptions for meds with possible interactions Controls selected from Civil Registration System	A) Celecoxib B) Other NSAIDs
Rahme 2007 Health care records and hospital records of patients in Quebec Canada including those with OA (1997 to 12/2002) (Fair)	Patients of 65 years of age or older who filled a prescription for acetaminophen or a NSAIDs.	The number of days of supply for each NSAID or acetaminophen prescription with a grace period of 25%.	Age ≥65 years Male: 45%	Retrospective cohort	Age, gender, alcohol/drug use, co-morbidities (e.g., COPD) and other drugs	A) Celecoxib B) Ibuprofen C) Diclofenac D) Naproxen

Author, year Data source Sample size (Quality rating)	Outcome: incidence	Results	Effects of confounders, dose, duration	Notes
Mellemkjaer 2002 Pharmaco-Epidemiologic Database of North Jutland (1991-1995) n=156,138 (Fair)	Hospitalization for upper GI bleeding	Relative risk, hospitalization due to UGIB, non-use vs: Diclofenac RR 4.9 (3.5-6.6) Ibuprofen RR 2.4 (2.0-2.9) Indomethacin RR 4.3 (2.9-6.0) Ketoprofen RR 6.3 (4.5-8.5) Naproxen RR 3.0 (2.1-4.2) Piroxicam RR 5.0 (3.3-7.2)	Women 4.2 (CI 3.7 to 4.8) Men 2.9 (CI 2.4 to 3.4)	
Norgard 2004 County Hospital Discharge Registry of Denmark, North Jutland County Denmark and Pharmaco-Epidemiological Prescription Database of North Jutland (1/1/2000 to 12/31/2002) Cases= 780 Controls=2906 (1/1/2000 to 12/31/2002) (Fair)	First incident of upper gastrointestinal bleeding	Adjusted OR (95% CI) Exposed vs. not exposed A) 1.3 (0.7-2.5) B) 3.3 (2.4-4.4)	Celecoxib was associated with a lower risk of upper GI than non-selective NSAIDs in both men and women and those ≥ 65	
Rahme 2007 Health care records and hospital records of patients in Quebec Canada including those with OA (1997 to 12/2002) (Fair)	First hospitalization for AMI or GI bleed	Adjusted HR (95% CI) for GI bleed with acetaminophen as a reference A) 0.82 (0.66-1.01) B) 1.11 (0.56-2.16) C) 1.18 (0.86-1.62) D) 2.75 (2.05-3.69) Adjusted HR (95% CI) in patients with OA of AMI or GI bleed A) 1.13 (0.92-1.40) B) 0.61 (0.19-1.91) C) 1.54 (1.12-2.11) D) 1.86 (1.23-2.80)	Aspirin use with a NSAID increased risk of GI bleed	

Author, year Data source Sample size (Quality rating)	Population	Categorization of exposure	Demographics (age, gender, race)	Study design/type	Adjusted variables, selection of controls (for case-control studies)	NSAIDs evaluated
Rahme 2007 Quebec government health insurance database and hospital discharge summary database (RAMQ and Med-Echo) (1/1998 to 12/2004) N=644,183 (Fair)	Patients of 65 years of age or older who filled a prescription for acetaminophen or a NSAIDs with or w/o PPI versus those taking acetaminophen alone.	The number of days of supply for each NSAID or acetaminophen prescription. Exposure was designated to be 1.25 x number of days supplied). Doses of ≤ 3 g/day of acetaminophen and/or NSAIDs.	Age ≥ 65 years Male: 39%	Retrospective cohort	Aspirin, anticoagulants, clopidogrel and other baseline characteristics	(A) Acetaminophen ≤ 3 g/day (B) Acetaminophen > 3 g/day (C) Acetaminophen and NSAIDs (D) NSAIDs
Rahme 2007 Quebec government health insurance database and hospital discharge summary database (RAMQ and Med-Echo) (1/1998 to 12/2004) N=644,183 (Fair)	Patients of 65 years of age or older who filled a prescription for acetaminophen or a NSAIDs with or w/o PPI versus those taking acetaminophen alone.	The number of days of supply for each NSAID or acetaminophen prescription. Exposure was designated to be 1.25 x number of days supplied). Doses of ≤ 3 g/day of acetaminophen and/or NSAIDs.	Age ≥ 65 years Male: 39%	Retrospective cohort	Aspirin, anticoagulants, clopidogrel and other baseline characteristics	A) Celecoxib B) Ibuprofen C) Diclofenac D) Naproxen
Weideman 2004 Dallas Veterans Affairs Medical Center (1/1/1999 to 12/31/2001) N=16,286 (Fair)	Patients of the Dallas VA who received outpatient prescription of Etodolac or Naproxen	Prescription of Etodolac \geq 800 mg/day or Naproxen ≥ 1000 mg/day NSAID naïve patients: those with no exposure to other NSAIDs in the 120 days before starting treatment with etodolac or naproxen	Age mean: 56.4 years Male: 89.5%	Cohort	Congestive heart failure, concomitant use of aspirin	A) Etodolac B) Naproxen

Author, year Data source Sample size (Quality rating)	Outcome: incidence	Results	Effects of confounders, dose, duration	Notes
Rahme 2007 Quebec government health insurance database and hospital discharge summary database (RAMQ and Med-Echo) (1/1998 to 12/2004) N=644,183 (Fair)	Number of GI hospitalizations (crude rate/1,000 patient-years) A) 640 (4.3) B) 234 (4.9) C) 68 (8.6)	Adjusted HR (95% CI): with acetaminophen \leq 3g/day (Upper and Lower GI hospitalizations) A) Reference B) 1.20 (1.03-1.40) C) 2.55 (1.98-3.28) D) 1.63 (1.44-1.85) Users of PPI: A) 0.95 (0.81-1.11) B) 1.16 (0.94-1.43) C) 2.15 (1.35-3.40) D) 1.07 (0.82-1.39)	NSAIDs and acetaminophen increase GI ris, PPIs were not protective	
Rahme 2007 Quebec government health insurance database and hospital discharge summary database (RAMQ and Med-Echo) (1/1998 to 12/2004) N=644,183 (Fair)	Hospitalization for GI bleeding or acute MI	Celecoxib: HR 0.82 (CI 0.66 to 1.0) Ibuprofen: HR 1.1 (CI 0.56 to 2.2) Diclofenac: HR 1.2 (CI 0.86 to 1.6) Naproxen: HR 2.8 (CI 2.0 to 3.7)	Celecoxib + aspirin: HR 1.85 (CI 1.48 to 2.31) Ibuprofen + aspirin: HR 1.81 (CI 0.75 to 4.40) Diclofenac + aspirin: HR 3.06 (CI 2.16 to 4.35) Naproxen + aspirin: HR 2.37 (CI 1.40 to 3.99)	
Weideman 2004 Dallas Veterans Affairs Medical Center (1/1/1999 to 12/31/2001) N=16,286 (Fair)	Clinically significant upper GI event, (perforation, obstruction, bleeding, symptomatic ulcer); all events validated blindly by a gastroenterologist, radiologist and general surgeon Incidence (person years): <u>Not taking aspirin</u> All (Etodolac): 2.36/1000 All (Naproxen): 7.8/1000 NSAID-naïve (Etodolac): 2.4/1000 NSAID-naïve (Naproxen): 9.9/1000 <u>Taking aspirin</u> All (Etodolac): 16.5/1000 All (Naproxen): 16.5/1000 NSAID-naïve (Etodolac): 21.2/1000 NSAID-naïve (Naproxen): 14.3/1000	Adjusted odds ratio (95% CI) Etodolac vs Naproxen: <u>Not taking aspirin</u> All: 0.24 (0.09-0.63) NSAID-naïve: 0.18 (0.05-0.61) <u>Taking aspirin</u> All: 0.75 (0.28-1.99) NSAID-naïve: 1.24 (0.35-4.42)	See previous cell	Concurrent use of aspirin increases risk of upper GI event Etodolac shows a protective effect over naproxen

Glucosamine chondroitin trials

Author Year (Quality rating)	Eligibility criteria	Demographics (age, gender, race)	Study design/type	Interventions (drug, dose, duration)	Run-in/ washout period	Allowed other medications/ interventions	Other population characteristics (diagnosis, etc)
Herrero-Beaumont, 2007 GUIDE trial (Fair)	Male and female outpatients, diagnosed with primary symptomatic knee OA in 1 or both knees according to the American College of Rheumatology criteria. Grade II or III on the Kellgren/Lawrence radiographic system. Discouraged enrollment of obese patients. Excluded patients with inflammatory joint disease.	Age: Mean age NR overall Placebo: 64.5 +/- 7.2 Acetaminophen: 63.8 +/- 6.9 Glucosamine sulfate: 63.4 +/- 6.9 Female: 278/318 (87.4%) Placebo: 89/104 (86%) Acetaminophen: 93/108 (86%) Glucosamine: 96/106 (91%) Race/Ethnicity NR	RCT	A: Glucosamine: 1500 mg glucosamine sulfate, oral solution, once daily. Rottapharm. B: Acetaminophen side comparator: 1 gram tablets 3 times per day C: Placebo 6 month treatment duration	Narcotic, non-narcotic analgesics or anti-inflammatory symptomatic medications including topical agents were discontinued for the duration of at least 5 half-lives or 72 hours, whichever was longer. Recommended washout for corticosteroids was 3 months and was 6 months for glucosamine or other drugs considered specific for OA.	Ibuprofen 400mg tablets as rescue medication. Physical and/or occupational therapy were allowed if the regimen had been stable for at least 3 months prior to randomization.	Duration of knee OA: 7.4+/-6.0 vs. 6.5 +/-5.3 vs. 7.2+/-5.8 Baseline Lequesne index: 11.0+/-3.1 vs. 11.1+/-2.7 vs. 10.8+/-2.6 Baseline Kellgren/Lawrence grade: Grade 2: 50% vs. 56% vs. 52% Grade 3: 41% vs. 31% vs. 36% Grade 2/3 unspecified: 9% vs. 12% vs. 11% Baseline WOMAC: Total: 38.3+/-15.2 vs. 40.4+/-14.8 vs. 37.9+/-14.3 Pain: 7.8+/-3.0 vs. 8.0+/-2.9 vs. 7.9+/-3.0 Function: 27.8+/-11.4 vs. 29.4+/-11.0 vs. 27.2+/-10.9

Author Year (Quality rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to FU/ analyzed	Results	Adverse effects assessment: pre-specified, active or passive ascertainment, measured the severity of adverse effect?	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Herrero-Beaumont, 2007 GUIDE trial (Fair)	334 screened 325 randomized 7 excluded with no efficacy data 318 ITT population	A: 4 Adverse Events 7 Lack of efficacy 5 Loss to fu 12 Protocol violations Analyzed 78 protocol completers. 106 ITT population. C: 9 Adverse Events 8 Lack of efficacy 5 Loss to fu 12 Protocol violations Analyzed 70 protocol completers 104 ITT population B: 12 Adverse Events 5 Lack of efficacy 3 loss to fu 8 protocol violations Analyzed 80 protocol completers. 108 ITT population	Comparisons to placebo. No head-to-head. 6 month change in Lequesne Index from baseline A: -3.1 (-3.8, -2.3); p=0.032 B: NS: -2.7 (-3.3,-2.1); p=0.18 C: -1.9 (-2.6, -1.2) 6 month change in WOMAC from baseline Total: A: -12.9 (-15.6, -10.1); p=0.039 B: NS: -12.3 (-14.9, -9.7); p=0.08 C: -8.2 (-11.3,-5.1) Pain: A: NS: -2.7 (-3.3, -2.1); p=0.12 B: NS: -2.4 (-3.0, -1.8); p=0.41 C: -1.8 (-2.6, -1.1) Function: A: -9.2 (-11.2, -7.2); p=0.022 B: -8.7 (-10.6, -6.8); p=0.049 C: -5.5 (-7.7, -3.3) OARSI-A responders: A: 39.6 (p=0.004) B: 33.3 (P=0.047) C: 21.2 OARSI-B, Pain MCII, Function MCII, Pain PASS, Function PASS also reported as secondary outcomes Per-protocol Completers- For all 3 treatments, the degree of improvement in per-protocol completers was higher than that in the ITT population.	Pre-specified: For non- lab AEs: No (general question): For lab AEs: Yes, laboratory tests including measurement of serum glucose and liver function tests were perfumed at enrollment, 3 months and 6 months of treatment. Active or passive ascertainment: Active-asked a non leading question during clinic visits and drew labs Assessment of severity: Yes, MedDRA	A vs. B vs. C Total AEs: 95 vs. 96 vs. 89 Symptoms occurring in at least 3 patients during treatment: Dyspepsia: 5 vs. 2 vs. 4 Abdominal pain: 3 vs. 4 vs. 4 Diarrhea: 3 vs. 4 vs. 4 Respiratory tract infections: 8 vs. 4 vs. 9 Gastroenteritis: 4 vs. 0 vs. 2 Coughing and associated symptoms: 1 vs. 4 vs. 0 Headache: 2 vs. 6 vs. 4 Dizziness: 1 vs. 4 vs. 1 Back pain: 7 vs. 4 vs. 5 Neck pain: 3 vs. 2 vs. 0 Fall: 5 vs. 3 vs. 2 Injury: 2 vs. 4 vs. 0 Laboratory: Liver function (transaminases and/or GGT) : 2 vs. 21 vs. 6 Glucose: no change	Withdrawal due to AEs: 4 vs. 12 vs. 9

Author Year (Quality rating)	Eligibility criteria	Demographics (age, gender, race)	Study design/ type	Interventions (drug, dose, duration)	Run-in/ Washout period	Allowed other medications/ interventions	Other population characteristics (diagnosis, etc)
Kahan, 2009 (Fair)	Male and female outpatients 45-80 years, primary knee OA of the medial tibiofemoral compartment diagnosed according to ACR.	Chondroitin Sulfate: Age: 62.9 ± 0.5 Female: 70% Race: NR Placebo: Age: 61.8 ± 0.5 Female: 67% Race: NR	RCT	A: Chondroitin Sulfates 4&6 800mg sachet daily, every evening with glass of water B: Placebo sachet daily, every evening with glass of water 2 years	24 hours for acetaminophen, 5 days for NSAIDs prior to symptom assessments	Acetaminophen in 500-mg tablets (max dosage 4 gm/day) NSAIDs in cases of acute pain	Duration of knee OA: Left knee: 6.1 ± 0.3 vs. 6.5 ± 0.4 Right knee: 6.6 ± 0.4 vs. 6.3 ± 0.4 KL grade 1: 17.4% vs. 19.7% KL grade 2: 26.2% vs. 21.6% KL grade 3: 56.4 vs. 58.7% Minimum JSW, mm: 3.73 ± 0.08 vs. 3.81 ± 0.07 Pain score, 100 mm VAS: 57.2 ± 0.9 vs. 57.3 ± 1.0 WOMAC score, normalized 100mm scales: Total: 40.5 ± 1.2 vs. 41.6 ± 1.2 Pain: 40.0 ± 1.2 vs. 40.5 ± 1.2 Function: 39.2 ± 1.3 vs. 39.0 ± 1.2 Stiffness: 42.3 ± 1.5 vs. 43.5 ± 1.5

Author Year (Quality rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to FU/ analyzed	Results	Adverse effects assessment: pre-specified, active or passive ascertainment, measured the severity of adverse effect?	Adverse effects reported	Total withdrawals; Withdrawals due to adverse events
Kahan, 2009 (Fair)	1052/NR/622	103 vs. 96 withdrawals/18 vs. 18 lost to fu/ ITT analysis 622	<p>Interaction between time and treatment effect, indicating that the effect of treatment significantly increased over time ($P < 0.01$) Decrease in minimum JSW loss: -0.07 ± 0.03 vs. -0.31 ± 0.04, median effect of treatment 0.14mm (0.06-0.21mm), $P < 0.0001$.</p> <p>Percentage of patients with radiographic progression: 28% vs. 41%, $p < 0.0005$. Relative risk reduction: 33% (16%, 46%) Reduction in minimum JSW loss at 2 years: -0.11 ± 0.04mm vs. -0.39 ± 0.04mm. treatment effect= 0.20mm (0.11, 0.30 mm), $p < 0.0001$ Percentage of responder patients at 6 months: reduction in VAS pain score of at least 40%: 53% vs. 45%, $p = 0.04$ reduction in VAS pain score of at least 60%: 41% vs. 32%, $p = 0.03$ reduction in VAS pain score of at least 40mm: 28% vs. 19%, $p = 0.01$ reduction in VAS pain score of at least 60mm: 9% vs. 4%, $p < 0.01$ decreased WOMAC of at least 40%: 41% vs. 34%, $p = 0.05$ patient assessed VAS at 6 months: 42.2 ± 1.8mm vs. 36.6 ± 1.7mm, $p < 0.02$ doctor assessed VAS at 6 months: 39.6 ± 1.6mm vs. 34.8 ± 1.7mm, $p < 0.04$</p>	Pre-specified: NR Active or passive ascertainment: NR Severity: NR	Gastrointestinal side effects were the most frequently reported, 6% vs. 5.9% No significant laboratory abnormalities	103 vs. 96 withdrawals. 16 vs. 17 withdrawals due to AE

Author Year (Quality rating)	Eligibility criteria	Demographics (age, gender, race)	Study Design/ Type	Interventions (drug, dose, duration)	Run-in/ washout period	Allowed other medications/ interventions	Other population characteristics (diagnosis, etc)
Mazieres, 2007 (Fair)	Male and female outpatients 50-80 years with medial OA, defined according to ACR criteria. Patients with symptomatic knee OA that had lasted for >6 months, with pain during daily activity \geq 40 mm on a 0-100 mm visual analogue scale, a Lequesne's Index Score of between 6 and 12, and Kellgren/Lawrence grade 2 or 3 on an anterior-posterior view in an extended standing position taken within the previous 6 months.	CS: Age: 66 (8.8) Female 71% Race: NR Placebo: Age: 66 (7.7) Female: 69% Race: NR	RCT	A: Chondroitin Sulfate 500mg, twice daily by oral route B: Placebo, twice daily by oral route 24 weeks	NR	Start with paracetamol (up to 4 gm/day). NSAIDs allowed if paracetamol was not effective. NSAIDs not allowed 2 days and paracetamol not allowed 12 hours prior to evaluation visits.	Duration of disease: 6.2 (6.8) vs. 6.6 (7.6) VAS pain during activity: 62 (13) vs. 61 (12) VAS pain at rest: 40 (20) vs. 40 (22) Lequesne's Index: 9.5 (2) vs. 9.4 (2) KL stages 2-3: 69% vs. 59%

Author Year (Quality Rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Results	Adverse effects assessment: pre-specified, active or passive ascertainment, measured the severity of adverse effect?	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Mazieres, 2007 (Fair)	322/NR/307 (153 CS, 154 Placebo)	14 vs. 14 withdrawals during treatment period, 12 vs. 11 withdrawals during washout period. 307 ITT population	<p>Pain During Activity: VAS, mm; Mean (SD) Week 0: 61 (13) vs. 61 (13) Week 4: 48 (21) vs. 51 (20) Week 12: 40 (23) vs. 42 (21) Week 24: 36 (24) vs. 41 (23) Week 32: 33 (23) vs. 40 (24) Change from baseline to week 24: -26.2 (24.9) mm vs. -19.9 (23.5) mm, p= 0.029</p> <p>Lequesne's Index: Mean (SD): Week 0: 9.5 (2.1) vs. 9.4 (1.8) Week 4: 8.3 (2.8) vs. 8.4 (2.4) Week 12: 7.8 (3.6) vs. 7.9 (3.1) Week 24: 7.2 (3.7) vs. 7.7 (3.3) Week 32: 6.8 (3.9) vs. 7.5 (3.6) Change from baseline to week 24: -2.4 (3.4) vs. -1.7 (3.3), p=0.109.</p> <p>OMERACT-OARSI responders: 68% vs. 56% (p=0.03) Change in pain at rest (VAS; mm): -18.8 (23.8) vs. -16.6 (24.2), NS Patient's global assessment: 3.1 (3.0) vs. 2.5 (3.1), NS Investigator's global assessment: 3.1 (2.7) vs. 2.5 (3.0), p=0.044 Consumption of analgesics (days): 28 (29) vs. 28 (32), NS Consumption of NSAIDs (days): 6.9 (20.2) vs. 9.2 (24.6), NS QOL, mental: 1.2 (10.4) vs. 0.3 (11.3), NS QOL, physical: 5.8 (9.0) vs. 3.8 (10.2), p=0.021</p> <p>Carry over effect: changes at the end of the follow-up (week 32) compared to the end of the treatment period (week 24): Change in pain on activity -1.9 (20.9) vs. -0.4 (18.7), NS Change in Lequesne's index: -0.4 (2.3) vs. -0.2(2.6), NS</p>	Pre-specified: No Active ascertainment: requested at visits Severity: NR	Total Number of AEs: 141 vs. 155, majority were gastro-intestinal troubles including dyspepsia, nausea, vomiting, abdominal pain and diarrhea. Patients with at least one AE: 49% vs. 49% Patients with at least on SAE: 6.5% vs. 5.2%, one in each group was considered related to treatment, eczema and urticaria	total withdrawals: 26 vs 25 due to AE: 13 vs. 8

Author Year (Quality rating)	Eligibility criteria	Demographics (age, gender, race)	Study design/type	Interventions (drug, dose, duration)	Run-in/ washout period	Allowed other medications/ interventions	Other population characteristics (diagnosis, etc)
Messier, 2007 (Poor)	Males and females ≥ 50 years with radiographic evidence of mild to moderate knee OA, Kellgren-Lawrence grade II-III; radiographic classification criteria or confirmation of mild to moderate radiographic evidence of knee OA from a personal physician; not participating in any other intervention study.	<p>Mean Age Overall NR GH/CS: 70.0 ± 1.28 Placebo: 74.1 ± 1.32, p0.03</p> <p>Female: GH/CS: 75.6% Placebo: 65.9%</p> <p>Race, GH/CS vs. Placebo: Caucasian: 68.9% vs. 77.3% African American: 20% vs. 11.4% Asian/Pacific Islander: 6.7% vs. 2.3% Native American: 4.4% vs. 6.8%</p>	RCT with run-in/washout period, Phase 1 treatment. Phase 2 treatment plus exercise.	<p>A: Glucosamine hydrochloride 1500mg/ day and Chondroitin sulfate 1200mg/day taken either once or three times per day</p> <p>B: Placebo taken either once or three times per day</p> <p>1 year treatment period</p>	2-week discontinuation of all over-the-counter or prescription medications. Rescue medication with acetaminophen up to 4g per day and any other necessary medications unrelated to OA were permitted.	Rescue medication of acetaminophen up to 4g/day	

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Messier, 2007 (Poor)	865 screened/435 not interested/341 ineligible 89 randomized	17 withdrawn/ 89 analyzed using ITT last observation carried forward	<p>(A) Function (WOMAC physical function 0-68) Mean(SE): Baseline: 25.9 (1.7) vs. 21.1 (1.5), p=0.04 6 months: 21.9 (1.1) vs. 22.9 (1.1), NS 12 months: 19.4 (1.2) vs. 20.6 (1.2), NS</p> <p>(B) Pain (WOMAC pain 0-20): Baseline: 7.1 (0.5) vs. 5.9 (0.5), NS 6 months: 6.2 (0.4) vs. 6.2 (0.4), NS 12 months: 6.0 (0.5) vs. 5.18 (0.5), NS</p> <p>6 minute walk (meters): Baseline: 384.7 (17.6) vs. 398.7 (17.3), NS 6 months: 393.6 (8.0) vs. 396.5 (7.9), NS 12 months: 409.2 (8.7) vs. 410.5(8.6), NS</p> <p>Knee concentric extension strength (N): Baseline: 209.4 (31.2) vs. 163.9 (20.6), NS 6 months: 176.9 (16.3) vs. 202.7 (17.5), NS 12 months: 207.6 (14.1) vs. 209.7 (15.0), NS</p> <p>Knee concentric flexion strength (N): Baseline: 106.0 (16.1) vs. 83.0 (10.9), NS 6 months: 106.1 (7.3) vs. 106.7 (7.8), NS 12 months: 102.9 (7.7) vs. 124.8 (8.3), P=0.05</p> <p>Balance (foot length): Baseline: 0.52 (0.04) vs. 0.53 (0.03) 6 months: 0.523 (0.014) vs. 0.583 (0.017), P=0.01 12 months: 0.538 (0.017) vs. 0.591 (0.020), P=0.05</p> <p>During Phase II: Pill compliant GH/CS group had less pain than the non-compliant group (p=0.02) and a non-significant trend in function (p=0.06).</p>	Pre-specified: NR Active or passive: NR Severity: NR	17 withdrawals, 0 due to adverse events 1 AE reported: Hair loss	Groups differ at baseline on age, BMI, gender, annual household income and WOMAC function

Author Year (Quality rating)	Eligibility criteria	Demographics (age, gender, race)	Study design/type	Interventions (drug, dose, duration)	Run-in/ washout period	Allowed other medications/ interventions	Other population characteristics (diagnosis, etc)
Michel, 2005 (Fair)	Male and female patients 40-85 years with clinically symptomatic knee OA (knee pain while standing, walking, and/or on motion for at least 25 of the 30 days prior to study entry) diagnosed according to the ACR clinical and radiographic criteria for OA of the knee. Exclusion criteria: Kellgren/Lawrence grade 4, any causes of secondary OA, traumatic knee lesions, severe comorbidity (severe renal, heart, lung, or neurologic disease), previous joint surgery, intraarticular medications, including corticosteroids in the last month, and the foreseeable prospect of major surgery during the 2- year study period.	Chondroitin Group: Mean age: 62.5 ± 9.1 Female: 51% Race: NR Placebo Group: Mean age: 63.1 ± 10.7 Female: 52% Race: NR	RCT	A: Chondroitin Sulfates 4 & 6, 800mg tablet daily B: Placebo 2 years	3 month washout required for potentially longer acting substances such as Chondroitin Sulfate and Glucosamine	Acetaminophen in 500-mg tablets at a maximum dose of 3 gm/day. Secondary rescue with NSAIDs were allowed up to a maximum 5 consecutive days if the primary rescue analgesia with acetaminophen was insufficient. Physical therapy was limited to application of warmth and strengthening exercises No other interventions allowed	ITT Group: Minimum JSW, mm: 2.41 ± 0.14 vs. 2.35 ± 0.14 Mean JSW, mm: 3.04 ± 0.14 vs. 3.00 ± 0.15 WOMAC score, range 0-10: Total: 2.3 ± 1.6 vs. 2.6 ± 1.7 Pain: 2.5 ± 1.6 vs. 2.7 ± 1.8 Function: 2.1 ± 1.6 vs. 2.5 ± 1.8 Stiffness: 3.0 ± 2.3 vs. 3.5 ± 2.5

Author Year (quality rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to FU/ analyzed	Results	Adverse effects assessment: pre-specified, active or passive ascertainment, measured the severity of adverse effect?	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Michel, 2005 (Fair)	341/300/300	40 vs. 41 withdrawals during treatment 300 ITT analysis	<p>A vs. B, at 2 years JSN Minimum: 0.045 ± 0.48 vs. -0.07 ± 0.56, difference: 0.12 (95% CI 0.00 to 0.24), p=0.05 JSN Mean: 0.00 ± 0.53 vs. -0.14 ± 0.61, difference 0.14 (95% CI 0.01 to 0.27), p =0.04</p> <p>NS changes in WOMAC: Total: -3.9% vs. 2.1% Pain: -11.0% vs -6.2% Stiffness: -7.8% vs. -4.6% Function: -0.8% vs. 5.9%</p>	Pre-specified: No Active ascertainment Assessment of severity: No	<p>AEs with frequencies of at least 5% in one of the two study groups: Upper respiratory tract infection: 29% vs. 31% Headache: 7% vs. 9% Abdominal pain: 4% vs. 11% Allergic episode: 6% vs. 6% Cardiac problem: 6% vs. 5% Urinary tract infection: 5% vs. 5%</p>	9 vs. 9 withdrawals due to AE 2 events judged to be related to Chondroitin: abdominal pain and nausea in 1 patient each.

Author Year (Quality rating)	Eligibility criteria	Demographics (age, gender, race)	Study design/type	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/interventions	Other population characteristics (diagnosis, etc)
Rozendall, 2008 (Good)	Patients met the American College of Rheumatology clinical criteria for hip osteoarthritis and were able to complete questionnaires in Dutch. Excluded patients who had undergone or were awaiting hip replacement surgery, Kellgren and Lawrence score of 4, renal disease, liver disease, diabetes mellitus, or a disabling comorbid condition that would make visits to the research center impossible, patients receiving glucosamine.	Age: Mean age NR overall Placebo: 63.7 (8.5) Glucosamine sulfate: 63.1 (9.5) Female: Placebo: 70.3% Glucosamine: 68.5% Race/Ethnicity NR	RCT	1500mg oral glucosamine sulfate, administered once daily or as two 750 mg tablets Placebo 24 months treatment duration	NR	Baseline Pain Med use: Placebo overall: Daily 18.9% Sometimes: 27.9% None: 53.2% Glucosamine overall: Daily: 28.8% Sometimes: 25.2% None: 46.0% Interventions NR, except Total Hip Arthroplasty was collected and used in analyses.	Kellgren and Lawrence Score (%): 1: 49.5 vs. 53.2 ≥2: 50.5 vs. 46.8 Mean minimum JSW (SD), mm: 2.13 (1.00) vs 2.33 (0.90) Mean WOMAC score (SD): Pain: 35.9 (23.0) vs. 32.4 (23.2) Function: 36.0 (24.1) vs. 34.1 (21.7) Stiffness: 44.2 (27.2) Mean pain in past week (SD), mm: 34.3 (26.5) vs. 30.5 (25.2)

Author Year (quality rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to FU/ analyzed	Results	Adverse effects assessment: pre-specified, active or passive ascertainment, measured the severity of adverse effect?	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Rozendall, 2008 (Good)	Screened: 387 Eligible & Randomized: 222	Withdrawals during treatment period: NR Lost to follow-up: 7 vs 8 ITT analysis: 111 vs. 111	<p>Primary Outcomes: WOMAC (negative difference favors glucosamine): Pain overall (SE): -1.90 ± 1.6 vs. -0.30 ± 1.6; Unadjusted difference: -1.60 (-5.60, 2.40); Adjusted difference: -1.54 (-5.43, 2.36) Function overall (SE): -1.69 ± 1.3 vs. 0.38 ± 1.3; Unadjusted difference: -2.07 (-5.53, 1.39); Adjusted difference: -2.01 (-5.38, 1.36)</p> <p>JSN, <i>mm</i> (positive difference favors glucosamine sulfate): Minimal: -0.094 (0.32) vs. -0.057 (0.32); Unadjusted difference: -0.038 (-0.130, 0.055); Adjusted difference: -0.029 (-0.122, 0.064) Lateral: -0.180 (0.34) vs. -0.159 (0.36); Unadjusted difference: -0.020 (-0.124, 0.083); Adjusted difference: -0.017 (-0.121, 0.088) Superior: -0.123 (0.36) vs. -0.129 (0.30); Unadjusted difference: 0.006 (-0.090, 0.101); Adjusted difference: 0.016 (-0.079, 0.111) Axial: -0.070 (0.48) vs. -0.079 (0.30); Unadjusted difference: 0.009 (-0.108, 0.124); Adjusted difference: -0.005 (-0.118, 0.108)</p> <p>Secondary Outcomes: WOMAC (Negative difference favors glucosamine): <i>Pain, 3mos.</i> -2.50 (19.2) vs. -1.79 (16.2); Unadjusted difference: -0.71 (-5.47, 4.05); Adjusted difference: 0.06 (-4.11, 4.22). <i>12 mos.</i> -0.54 (19.9) vs. -0.89 (23.3); Unadjusted difference: 0.35 (-5.66, 6.36); Adjusted difference: 1.42 (-3.82, 6.67). <i>24 mos.</i> -1.47 (20.7) vs. 0.88 (26.4); Unadjusted difference: -2.34 (-9.16, 4.48); Adjusted difference: -0.77 (-6.53, 4.98) <i>Function, 3 mos.</i> -3.29 (14.9) vs. -1.08 (12.7); Unadjusted difference: -2.22 (-5.97, 4.05); Adjusted difference: -2.04 (-5.48, 1.40). <i>12 mos.</i> -0.98 (14.9) vs. -0.88 (17.6); Unadjusted difference: -0.11 (-4.63, 4.42); Adjusted difference: 0.11 (-4.14, 4.35). <i>24 mos.</i> -0.84 (19.1) vs. 1.92 (19.7); Unadjusted difference: -2.76 (-8.35, 2.84); Adjusted difference: -1.63 (-6.73, 3.47). <i>Stiffness, 3 mos.</i> -4.59 (22.6) vs. -3.39 (17.7). Unadjusted difference: -1.20 (-6.66, 4.26); Adjusted difference: -0.12 (-4.94, 4.71). <i>12 mos.</i> -1.38 (22.1) vs. -3.43 (21.6); Unadjusted difference: 2.06 (-4.00, 8.12); Adjusted difference: 3.11 (-2.07, 8.28). <i>24 mos.</i> -3.43 (26.2) vs. -2.19 (24.1); Adjusted difference: -1.24 (-8.47, 5.98); Unadjusted difference: 0.66 (-5.27, 6.59).</p>	<p>Pre-specified: yes, used a checklist</p> <p>Active ascertainment; used a checklist at baseline and every 3 months</p> <p>Severity measured: NR</p>	<p>Serious Adverse Events: 4 vs. 2</p> <p>AE resulting in treatment termination: 4 vs. 6</p> <p>Abdominal pain: 14 vs. 10 Stomach symptoms: 25 vs. 19 Intestinal symptoms: 19 vs. 17 Increased blood pressure: 11 vs. 19 Decreased blood pressure: 4 vs. 3 Fatigue: 24 vs. 18 Headache: 16 vs. 26 Vertigo: 16 vs. 18 Cardiac problems: 6 vs. 9 Depressive mood: 10 vs. 6 Allergic episode: 7 vs. 5</p>	<p>Lost to follow up: 7 vs. 8, withdrawal during treatment NR.</p> <p>Withdrawal of treatment due to AE: 4 vs. 6</p>

Author Year (Quality rating)	Eligibility criteria	Demographics (age, gender, race)	Study design/type	Interventions (drug, dose, duration)	Run-in/ washout period	Allowed other medications/ interventions	Other population characteristics (diagnosis, etc)
Rozendall, 2009 (See Rozendall, 2008)	Same study as Rozendall, 2008		RCT, subgroup analysis of Rozendall, 2008 data Predefined subgroups: KL=1, KL ≥ 2, localized OA, generalized OA Exploratory subgroups: VAS ≤ 30, VAS > 30, No pain medication, pain medication, no knee OA, knee OA, JSN ≥ 2.5mm, <2.5 mm				
Sawitzke, 2008 GAIT [Hochberg] (Good)	Males and females ≥ 40 years of age, had knee pain for at least 6 months occurring on the majority of days in the month preceding their enrollment in GAIT, and had Kellgren/Lawrence grade 2 or 3 knee OA determined on a screening AP radiograph of the knee in a weight bearing position. Exclusion: Minimum baseline medial tibiofemoral JSW of <2mm, predominant lateral compartment OA on any film of the MTP joints, history of significant trauma or surgery to the knee	Age (mean ± SD years): Glucosamine: 56.7± 10.4 CS: 56.4± 9.2 Glucosamine + CS: 56.5± 9.9 Celecoxib: 58.3± 10.7 Placebo: 56.6± 8.4 Female (%): Glucosamine: 61.0 CS: 71.8 Glucosamine + CS: 55.9 Celecoxib: 63.8 Placebo: 64.3 Race: NR	Prospective observational study of GAIT enrollees; ancillary study to assess structural changes in knee OA	A: Glucosamine 500mg 3 times daily B: Chondroitin sulfate (400mg 3 times daily) C: Combination of Glucosamine and Chondroitin D: Celecoxib 200mg daily E: Placebo 24 months	NR-check other GAIT pubs	NR- check other GAIT pubs	Kellgren/Lawrence Grade 2, %: 80.5 vs. 81.0 vs. 69.2 vs. 72.6 vs. 80.5 Kellgren/Lawrence Grade 3, %: 19.5 vs. 19.0 vs. 30.9 vs. 27.4 vs. 19.5

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Rozendall, 2009 (See Rozendall, 2008)			<p>The predefined subgroup analyses based on radiographic severity of OA and type of OA did not yield differences between GS and placebo in WOMAC pain, function and JSN.</p> <p>The exploratory analyses showed no difference in WOMAC pain, function and JSN.</p> <p>WOMAC Pain (Negative value favors glucosamine): No Knee OA: 0.3 (21.5) vs. 0.1 (26.2); Unadjusted difference: 0.3 (-7.9, 8.5); Adjusted difference: -0.1 (-4.9, 4.7). WOMAC pain: Concomitant Knee OA: -5.8 (18.1) vs. 2.9 (27.1); Unadjusted difference: -8.7 (-21.2, 3.8); Adjusted difference: -5.68 (-12.62, 1.26).</p>			
Sawitzke, 2008 GAIT [Hochberg] (Good)	662 GAIT participants consented to this study	A(177 initial): 33/NR/77 B (123 initial): 30/NR/71 C (128 initial): 40/NR/59 D (143 initial): 32/NR/80 E (134 initial): 36/NR/70	<p>Mean loss in JSW over 2 years: All NS 0.013 vs. 0.107 vs. 0.194 vs. 0.111 vs. 1.166</p> <p>Difference from placebo (negative value = less JSW loss): -0.153 (-0.379, 0.074) vs. -0.059 (-0.287, 0.169) vs. 0.028 (-0.214,0.271) vs. -0.055 (-0.279, 0.170)</p> <p>Disease progression over 2 years, % of patients: All NS 18.6 vs. 21.4 vs. 24.4 vs. 20.2 vs. 22.4</p> <p>OR versus placebo for disease progression: 0.79 (0.48,1.3) vs. 0.94(0.57,1.55) vs. 1.12(0.67,1.88) vs. 0.87(0.53,1.43)</p>	NR- check earlier GAIT pub	<p>Withdrawals: 33 vs 30 vs 40 vs 32 vs 36</p> <p>Technical Loss: 9 vs 6 vs 11 vs 10 vs 8</p> <p>Withdrawals due to AE: see earlier GAIT report</p>	

Author Year (Quality rating)	Eligibility criteria	Demographics (age, gender, race)	Study design/type	Interventions (drug, dose, duration)	Run-in/ washout period	Allowed other medications/ interventions	Other population characteristics (diagnosis, etc)
Wilkens, 2010 (Good)	<p>INCLUSION: Nonspecific chronic LBP (defined as the area below the 12th rib and above the gluteal folds); LBP for at least 6 months with summed score of at least 3 out of 24 points on the Roland Morris Disability Questionnaire, older than 25 years of age. Patients with concomitant leg pain were included as long as the LBP pain rating was higher than the leg pain rating. MRI scans no older than 1 year prior to inclusion consisting of at least 1 axial view and 2 sagittal views were required. MRI confirmed degenerative process. At least one of the following MRI criteria: disk signal intensity changes, reduced disk height compared with adjacent superior disk, facet joint changes, modic changes, or high-intensity zone.</p> <p>EXCLUSION: symptomatic intervertebral disk herniation or spinal stenosis, previous lumbar fracture or surgery, pregnancy or breastfeeding, seafood allergy, ongoing psychiatric or somatic disease potentially influencing a patient's pain and use of any type of glucosamine 1 year prior to enrollment.</p>	<p>Age; mean (SD): Total: 48.5 (11.24) Glucosamine: 47.5 (11.5) Placebo: 49.4 (11.0)</p> <p>Female: Total: 121/250 (48.4%) Glucosamine: 54/125 (43.2%) Placebo: 67/125 (53.6%)</p> <p>Race: NR</p>	RCT	<p>A: Glucosamine sulfate 1500mg or placebo administered as three 500-mg capsules per day. Could be taken as one pill 3 times per day or all at once.</p> <p>B: Placebo</p> <p>6 month treatment period</p>	NR	Rescue medication: Pain killers or NSAIDs, existing analgesics, or usual LBP therapy (e.g., manipulation, physiotherapy, massage)	<p>Mean (SD)</p> <p>Roland Morris Disability Questionnaire (RMDQ) (0-24): 9.2 (3.9) vs. 9.7 (4.5)</p> <p>Numeric Rating Scale (NRS) (0-10): LBP at rest: 3.7 (2.6) vs. 3.9 (2.4) Leg pain at rest: 1.8 (2.2) vs. 2.0 (2.3) LBP when active: 4.9 (2.5) vs. 5.1 (2.3) Leg pain when active: 2.4 (2.6) vs. 2.7 (2.6)</p> <p>EuroQol-5 Dimensions (EQ-5D) (-0.59 - 1.0): 0.57 (0.3) vs. 0.63 (0.2)</p> <p>EuroQol- Visual analog scale (EQ-VAS) (0-100): 5.8 (2.2) vs. 6.4 (2.0)</p>

Author Year (quality rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to FU/ analyzed	Results	Adverse effects assessment: pre-specified, active or passive ascertainment, measured the severity of adverse effect?	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Wilkens, 2010 (Good)	473 screened/ 250 randomized and enrolled	Withdrawals during treatment period: 7 vs. 10 Loss to fu: 4 vs. 4 Primary analysis is ITT and includes all 250 randomized patients	<p>Mean SD (95% CI)</p> <p>RMDQ (0-24): 6 weeks: 7.0 (6.1, 7.8) vs. 7.1 (6.3, 7.9); 3 months: 5.8 (5.0, 6.6) vs. 6.5 (5.7, 7.3); 6 months: 5.0 (4.2, 5.8) vs. 5.0 (4.2, 5.8); 1 year: 4.8 (3.9, 5.6) vs. 5.5 (4.7, 6.4)</p> <p>NRS LBP at rest (0-10): 6 weeks: 2.9 (2.5, 3.3) vs. 2.9 (2.5, 3.3); 3 months: 2.7 (2.4, 3.1) vs. 2.9 (2.5, 3.3); 6 months: 2.5 (2.1, 2.9) vs. 2.4 (2.0, 2.8); 1 year: 2.5 (2.1, 2.9) vs. 2.8 (2.4, 3.1)</p> <p>NRS Leg pain at rest (0-10): 6 weeks: 1.3 (1.0, 1.7) vs. 1.5 (1.2, 1.9); 3 months: 1.4 (1.0, 1.8) vs. 1.7 (1.4, 2.1); 6 months: 1.4 (1.0, 1.7) vs. 1.5 (1.1, 1.8); 1 year: 1.5 (1.1, 1.8) vs. 1.6 (1.3, 2.0)</p> <p>NRS LBP when active (0-10): 6 weeks: 3.7 (3.2, 4.1) vs. 3.6 (3.2, 4.0); 3 months: 3.3 (2.9, 3.7) vs. 3.2 (2.8, 3.6); 6 months: 3.1 (2.7, 3.5) vs. 2.9 (2.5, 3.3); 1 year: 3.0 (2.5, 3.4) vs. 2.9 (2.5, 3.3)</p> <p>NRS Leg pain when active (0-10): 6 weeks: 1.8 (1.4, 2.2) vs. 1.9 (1.5, 2.3); 3 months: 1.7 (1.2, 2.1) vs. 1.9 (1.5, 2.3); 6 months: 1.6 (1.2, 2.0) vs. 1.9 (1.5, 2.3); 1 year: 1.7 (1.3, 2.1) vs. 2.0 (1.5, 2.4)</p> <p>EQ-5D (-0.59 - 1.0): 6 weeks: 0.68 (0.64, 0.72) vs. 0.69 (0.65, 0.72); 3 months: 0.73 (0.70, 0.78) vs. 0.69 (0.65, 0.73); 6 months: 0.74 (0.70, 0.78) vs. 0.76 (0.65, 0.74); 1 year: 0.74 (0.70, 0.78) vs. 0.70 (0.65, 0.74)</p> <p>EQ-VAS (0-100): 6 weeks: 6.8 (6.2, 7.3) vs. 6.7 (6.1, 7.2); 3 months: 7.2 (6.7, 7.8) vs. 6.8 (6.2, 7.3); 6 months: 7.2 (6.6, 7.8) vs. 7.1 (6.7, 7.4); 1 year: 7.4 (7.0, 7.7) vs. 6.6 (6.3, 7.0)</p> <p>Global perceived effect: No. (%): 6 weeks: 22 (18.6) vs. 27 (22.0); 3 months: 26 (21.5) vs. 26 (22.2); 6 months: 39 (33.1) vs. 42 (36.2); 1 year: 14 (30.9) vs. 32 (29.4)</p>	Pre-specified: NR Ascertainment: NR Severity: NR	<p>OR (95% CI)</p> <p>All NS differences</p> <p>AEs resulting in treatment discontinuation: 0.66 (0.48-1.36)</p> <p>All AEs: 0.83 (0.49-1.40)</p> <p>Skin problems: 0.79 (0.35-1.76)</p> <p>Neurological: 0.65 (0.31-1.38)</p> <p>Heartburn: 0.99 (0.06-15.9)</p> <p>Flatulence: 0.55 (0.21-1.44)</p> <p>Abdominal pain: 1.32 (0.29-6.04)</p> <p>Nausea/vomiting: 1.77 (0.50-6.21)</p> <p>Constipation: 4.03 (0.44-36.69)</p> <p>Diarrhea: 0.55 (0.16-1.92)</p> <p>Headache/vertigo: 0.98 (0.28-3.49)</p> <p>Musculoskeletal concerns: 0.42 (0.14-1.25)</p> <p>10 AEs resolved with treatment discontinuation 7 resolved with continuation of study drug</p> <p>2 Serious AEs(death and surgery) were considered unrelated to study drug.</p> <p>Fasting blood glucose, cholesterol and blood pressure levels did not deviate from normal fluctuations during the trial</p>	<p>Total during treatment period: 7 vs. 10</p> <p>Withdrawals due to AE: Glucosamine: 6 vs. 6</p>

Glucosamine chondroitin systematic reviews

Author Year (Quality rating)	Aims	Time period covered	Eligibility criteria	Number of patients
Bjordal, 2007 (Good)	To determine the short-term pain-relieving effects of seven pharmacological agents for OA knee pain	MEDLINE, EMBASE, PedRo, Cochrane Controlled Trials Register 1996 through November 2005	Diagnosis: Knee OA verified by clinical exam and/or by X-ray. If less than 4 trials available for an intervention, trials also including hip OA were considered, if more than 2/3 of their patients had knee OA; Symptom duration: 3 months; Trial designs: Blinded, placebo-controlled parallel groups RCTs; Outcome measures: Pain intensity within 4 weeks of treatment start on WOMAC or on a 100mm VAS for global or walking pain. Pain intensity at 8-12 weeks follow-up; Intervention groups: Identical placebo drug and adequate daily defined drug dosage equal to or exceeding set dosages per drug: paracetamol 4g, diclofenac 100mg, etodolac 400mg, ibuprofen 2400 mg, nabumetone 1500mg, naproxen 1000mg, oxaprozin 1200mg, tiaprofenic acid 600mg, valdecoxib 10mg, celecoxib 200mg, meloxicam 7.5mg, etoricoxib 30mg, lumiracoxib 200mg, rofecoxib 12.5mg, topical diclofenac, piroxicam or meloxicam 1%, ibuprofen gel 3%, triamcinolone 20mg, methylprednisolone 40mg, cortivazol 3.75mg, glucosamine sulfate 1500mg, chondroitin sulfate 800mg, codeine 50mg, oxymorphone 20mg, oxycodone 20mg, morphine sulfate 30mg, tramadol 100mg	14,060 patients for all included drugs. 9964 patients received Oral NSAIDs including coxibs, 749 received topical NSAIDs, 401 received glucosamine sulfate, 362 received chondroitin sulfate

Author Year (Quality rating)	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results	Subgroups
Bjordal, 2007 (Good)	64 RCTs total. 25 RCTs of oral NSAIDs (including coxibs), 9 topical NSAIDs, 7 glucosamine sulfate, 6 chondroitin sulfate	<p>Mean Age: Oral NSAIDs: 62.6 years Topical NSAIDs: 64.2 years Glucosamine sulfate: 58.6 years Chondroitin sulfate: 63.0 years</p> <p>Mean baseline pain on 100mm VAS: Oral NSAIDs: 64.3 Topical NSAIDs: 54.7 Glucosamine sulfate: 57.8 Chondroitin sulfate: 50.7</p>	<p>Trials of included Oral NSAIDs:* 6 celecoxib studies; 2 naproxen studies; 2 diclofenac studies; 3 etodolac studies; 1 diflunisal study; 1 meloxicam study; 2 nabumetone studies; 1 oxaprozin study</p> <p>Trials of included Topical NSAIDs: 7 diclofenac, 2 eltenac, 1 ibuprofen</p> <p>Trials of glucosamine: 7</p> <p>Trials of chondroitin: 6</p>	<p>Best mean difference of change over placebo (100mm VAS): Glucosamine: 4.7 (95% CI 0.3 to 9.1) Chondroitin: 3.7 (95% CI 0.3 to 7.0)</p> <p>Glucosamine and chondroitin did not have effect size or 95% CI exceeding the mean threshold for minimal clinical important improvement, slight improvement, or minimal perceptible improvement</p>	None

* Characteristics of oral NSAID trials of included drugs for the current systematic review. Number of additional trials not reported here because the drugs are not relevant to this review.

Author Year (Quality rating)	Aims	Time period covered	Eligibility criteria	Number of patients
Wandel, 2010 (Good)	To determine the clinical effect of glucosamine, chondroitin, or the two in combination on joint pain and on radiological progression of disease in OA of the hip or knee	MEDLINE, EMBASE, CINAHL, and Cochrane Controlled Trials Register through June 2010.	Randomized trials with an average of at least 100 patients with knee or hip osteoarthritis per arm. Comparisons included chondroitin sulphate, glucosamine sulphate, glucosamine hydrochloride, or the combination of any two with placebo or head to head. Excluded trial arms with sub-therapeutic doses (<800mg/day of chondroitin, <1500mg/day glucosamine).	3803 to the interventions or placebo. Glucosamine sulphate vs. Placebo: 5 trials, 1104 randomized patients; Glucosamine sulphate or hydrochloride vs. Placebo: 1 trial, 205 patients; Chondroitin sulphate vs. Placebo: 3 trials 1229 patients; Glucosamine hydrochloride, chondroitin sulphate, and their combination vs. placebo: 1 trial, 1265 patients

Author Year (Quality rating)	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results	Subgroups
Wandel, 2010 (Good)	10 RCTs: designs not specified	8 trials with knee OA only, one trial with hip or knee OA, one trial with hip OA only. Mean age: 58-66 years % Female: 27-86 (median = 68%) Average duration of symptoms: 6 months- 10 years	6 glucosamine vs. placebo 3 chondroitin vs. placebo 1 glucosamine, chondroitin, combination vs. placebo	<p>Pain Intensity (10cm VAS): Glucosamine vs. Placebo: -0.4 cm (-0.7 to -0.1) Chondroitin vs. Placebo: -0.3 cm (-0.7 to 0.0) Glucosamine and Chondroitin vs. Placebo: -0.5 cm (-0.9 to 0.0)</p> <p>Radiological joint space difference (negative number favors intervention): Glucosamine vs. Placebo: -0.2 mm (-0.3 to 0.0) Chondroitin vs. Placebo: -0.1mm (-0.3 to 0.1) Glucosamine and Chondroitin vs. Placebo: 0.00 mm (-0.2 to 0.2)</p> <p>Adverse Events, OR (95% CI): Glucosamine vs. Placebo: 0.94 (0.59 to 1.47) Chondroitin vs. Placebo: 0.99 (0.49 to 2.00) Glucosamine and Chondroitin vs. Placebo: no data</p> <p>Withdrawals due to AE, OR (95% CI) Glucosamine vs. Placebo: 0.99 (0.61 to 1.50) Chondroitin vs. Placebo: 0.92 (0.56 to 1.51) Glucosamine and Chondroitin vs. Placebo: 0.90 (0.43 to 1.85)</p>	Estimated differences in pain intensity between supplements and placebo were on average 0.5 cm (0.1 to 0.9) higher in industry sponsored trials (p=0.02 for interaction)

Topical NSAID trials

Author Year (Quality Score)	Eligibility criteria	Demographics (age, gender, race)	Interventions (drug, dose, duration)	Allowed other medications/ interventions	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Dickson 1991 (Fair)	Male and female patients between 18 and 86 years of age with well-documented, mild osteoarthritis of the knee	Mean age: 63 years (range 21-86 years) Female: 66% Race: NR	A: Topical piroxicam (0.5%) tid + placebo tablet B: Ibuprofen 400 mg po + placebo gel tid 4 weeks	Paracetamol up to 4 mg allowed during washout and throughout trial; no significant difference between groups	Baseline overall pain during day: 5.0 vs. 5.0	NR/NR/235 (117 topical piroxicam, 118 oral ibuprofen)	39/3/196 (101 topical piroxicam, 95 oral ibuprofen)
Rother 2007(Good)	Minimum of 6 months' history of osteoarthritis with 2 of 3 criteria: 1) morning stiffness < 30 minutes/duration, crepitus on motion and age \geq 40 years; 2) pain rating as \geq 3 on a 5 point Likert scale; 3) oral NASIDs at least 3 days per week in the past 3 months or >25 of the past 30 days AND meeting of three osteoarthritis flare criteria	Mean age: 63 years (range NR)Female: 79%Race: NR	A: 100 mg topical ketoprofen in 4.8 g IDEA-033 (Transfersome) + oral placebo bidB: Celecoxib 100 mg po + placebo gel bid6 weeks	2000 mg paracetamol per day for 3 days any week except 48 hours before study visit	Baseline WOMAC pain score (mean, 0 to 100): 55 vs. 56 Baseline WOMAC stiffness score (mean, 0 to 100): 49 vs. 51 Baseline WOMAC physical function score (mean, 0 to 100): 54 vs. 55 Baseline patient global assessment of osteoarthritis (mean, 0 to 4): 3.9 vs. 3.9	499/NR/397 (138 topical ketoprofen, 132 oral celecoxib)	Topical ketoprofen and oral celecoxib arms only48/1/270 (138 topical ketoprofen, 132 oral celecoxib)

Author Year (Quality Score)	Results	Adverse events assessment: pre-specified, active or passive ascertainment, assessed the severity of adverse events?	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Run-in/ Washout	Class naïve patients only	Notes
Dickson 1991 (Fair)	<p>Topical gel piroxicam vs. oral ibuprofen, at 4 weeks</p> <p>Overall pain during day (median, 1-9 scale): 3.0 vs. 2.0, p=0.56</p> <p>Overall pain during night (median, 1-9 scale): 3.0 vs. 3.0, p=0.54</p> <p>Ability to perform specified activity (median, 1-9 scale): 5.0 vs. 5.0, p=0.33</p> <p>Rescue analgesic use: 69% vs. 62%</p>	<p>Pre-specified: No (general question)</p> <p>Active or passive ascertainment: Active</p> <p>Assessment of severity: Yes</p>	<p>Topical gel piroxicam (n=117) vs. oral ibuprofen (n=118)</p> <p>Any adverse event judged to be definitely or possibly related to study treatment: 26% vs. 23%</p> <p>Upper GI events: 10% vs. 8.5%</p> <p>Other GI events: 2.6% vs. 0.8%</p> <p>CNS events: 6.0% vs. 6.8%</p> <p>Rash events: 0.8% vs. 0.8%</p> <p>Dependent edema: 0% vs. 6.8%</p> <p>Local effects: 1.7% vs. 0.8%</p>	<p>Topical gel piroxicam vs. oral ibuprofen</p> <p>Total withdrawals: 14% vs. 19%</p> <p>Withdrawal due to adverse events: 7.7% vs. 9.9%</p> <p>Withdrawal due to upper GI events: 5.1% vs. 3.4%</p> <p>Withdrawal due to other GI events: 0.9% vs. 0%</p> <p>Withdrawal due to CNS events: 1.7% vs. 2.5%</p> <p>Withdrawal due to rash: 0% vs. 0.8%</p>	7-day washout free of anti-inflammatory medication	No	
Rother 2007 (Good)	<p>Topical ketoprofen + IDEA-033 vs. oral celecoxib, at 6 weeks</p> <p>WOMAC pain score (mean change from baseline, 0 to 100 scale): -19 vs. -21, p not reported</p> <p>WOMAC physical function score (mean change from baseline, 0 to 100 scale): -16 vs. -18, p not reported</p> <p>Patient global assessment excellent (poor, fair, good, or excellent): 12% vs. 11%</p> <p>Patient global assessment good or excellent: 46% vs. 39%</p> <p>Withdrawal due to lack of efficacy: 0.7% vs. 2.3%</p>	<p>Pre-specified: Unclear</p> <p>Active or passive ascertainment: Active</p> <p>Assessment of severity: No</p>	<p>Topical ketoprofen + IDEA-033 (n=138) vs. oral celecoxib (n=132)</p> <p>Any GI event: 9.4% vs. 14%</p> <p>Upper abdominal pain: 1.4% vs. 3.0%</p> <p>Dyspepsia: 0.7% vs. 3.0%</p> <p>Nausea: 1.4% vs. 2.3%</p> <p>Musculoskeletal and connective tissue disorders: 8.7% vs. 14%</p> <p>Respiratory, thoracic and mediastinal: 12% vs. 11%</p> <p>Allergic dermatitis: 1.4% vs. 0.8%</p> <p>Erythema: 21% vs. 14%</p>	<p>Topical ketoprofen + IDEA-033 vs. oral celecoxib</p> <p>Total withdrawals: 18% vs. 17%</p> <p>Withdrawal due to adverse events: 17% vs. 14%</p>	NR/NR	No	

Author Year (Quality Score)	Eligibility criteria	Demographics (age, gender, race)	Interventions (drug, dose, duration)	Allowed other medications/ interventions	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Sandelin 1997 (Fair)	Male and female outpatient patients with radiologically confirmed OA including osteophytes of one or both knees and with pain symptoms for most days of the prior month where analgesics was needed	Mean age: 61 years (range NR) Female: 66% Race: NR	A: Topical eltenac 1% 3 g tid + placebo 1 T po bid B: Diclofenac 50 mg po bid + placebo gel 3 g tid	NR	Bilateral OA: 53% vs. 51% Baseline pain (mean, 0 to 100 VAS): 48 vs. 52 Baseline Lequesne index score (mean, 0 to 24): 9.5 vs. 10	NR/NR/290 (number randomized in each group unclear)	9/0/281 (124 topical eltenac, 89 oral diclofenac)
Simon 2009 (Good)	Male and non-pregnant women aged 40-85 with primary OA of the knee based on a) standard radiological criteria from a recent examination within 3 months; b) pain with regular use of pain meds; c) a flare of pain and a minimum Likert pain score of 8 at baseline	Mean age: 62 years (range NR) Female: 65% Non-white: 22%	A: Topical diclofenac solution (Pennsaid, 1.5% diclofenac sodium in 45.5% DMSO) 40 drops qid + oral placebo B: Oral diclofenac slow release 100 mg + placebo solution qid 12 weeks	Acetaminophen (up to four, 325 mg per day), except 3 days before efficacy assessment Glucosamine, chondroitin, anti-depressants or proton pump inhibitor, or low dose (\leq 325 mg/day) saprin allowed	Bilateral OA: 99% vs. 99% Baseline WOMAC pain score (mean, 0 to 20): 13 vs. 13 Baseline WOMAC physical function score (mean, 0 to 68): 42 vs. 42 Baseline WOMAC stiffness score (mean, 0 to 8): 5.1 vs. 5.2	1396 (overall)/NR/775 (154 to topical diclofenac, 151 to oral diclofenac)	Topical and oral diclofenac arms only 95/4/305 (154 topical diclofenac, 151 oral diclofenac)
Tiso 2010 (Fair)	Subjects from a pain management practice who were \geq 50 years old and \geq 3 months of knee pain	Mean age 58 years Female: 89%	A: 800 mg ibuprofen 3 times daily B: 2 ml of 4% topical ibuprofen applied 4 times per day (320 mg total)	Not specified	Pain duration >12 months: 95% Chronic Grade Pain: I: 5% II: 16% III: 37% IV: 42%	30/22/20	0/1/19

Author Year (Quality Score)	Results	Adverse events assessment: pre- specified, active or passive ascertainment, assessed the severity of adverse events?	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Run-in/ Washout	Class naïve patients only	Notes
Sandelin 1997 (Fair)	Topical eltenac vs. oral diclofenac, average at 2-4 weeks Overall pain (mean, 0-100 VAS): 31 vs. 30 Lequesne Index (mean, 0-24 scale): 6.9 vs. 7.3 Physician rated effect "good" (none, slight, moderate, or good): 18% vs. 30%	Pre-specified: Unclear Active or passive ascertainment: Unclear Assessment of severity: No	Topical eltenac (n=126) vs. oral diclofenac (n=82) Any adverse events: 27% vs. 24% Any GI event: 4.8% vs. 13% CNS events: 9.5% vs. 7.3% Local skin reactions: 13% vs. 1.2% Other: 5.6% vs. 4.9%	Topical eltenac vs. oral diclofenac Total withdrawals: Not reported Withdrawal due to adverse events: 5% vs. 1.2%	NR/NR	No	
Simon 2009 (Good)	Topical diclofenac vs. oral diclofenac, at 12 weeks WOMAC pain score (mean change from baseline, 0-20): - 6.0 vs. -6.4, p=0.43 WOMAC physical function score (mean change from baseline, 0 to 68): -16 vs. -18, p=0.32 WOMAC stiffness score (mean change from baseline, 0 to 8): - 1.9 vs. -2.1, p=0.60 Patient overall health assessment score (mean change from baseline, 0 to 4): - 0.95 vs. -0.88, p=0.96 Patient global assessment of the study knee (mean change from baseline, 0 to 4): -1.4 vs. - 1.4, p=0.44 Withdrawal due to lack of efficacy: 10% vs. 3.3%	Pre-specified: Unclear Active or passive ascertainment: Active Assessment of severity: No	Topical diclofenac (n=154) vs. oral diclofenac (n=151) Any adverse event: 62% vs. 62% Any GI event: 6.5% vs. 24% Abdominal pain: 3.2% vs. 7.3% Dyspepsia: 2.6% vs. 4.0% Nausea: 0% vs. 2.0% Dry skin at application site: 18% vs. 2.6% Contact dermatitis at application site: 2.6% vs. 0.7% Rash: 2.6% vs. 0% Headache: 18% vs. 17% Back pain: 10% vs. 7.3% Arthralgia: 9.1% vs. 7.9%	Topical diclofenac vs. oral diclofenac Total withdrawals: 33% vs. 29% Withdrawal due to adverse events: 10% vs. 13%	NR/NR	No	Has topical diclofenac + oral diclofenac group
Tiso 2010 (Fair)					NR/2 days	No	

Author Year (Quality Score)	Eligibility criteria	Demographics (age, gender, race)	Interventions (drug, dose, duration)	Allowed other medications/ interventions	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Tugwell 2004 (Good)	Men and nonpregnant women 40 to 85 years old, with symptomatic primary OA of the knee and recent (<3 months) x-ray showing osteoarthritis (confirmed by radiologist)	Mean age: 64 years (range NR) Female: 57% Non-white: 6%	A: Topical diclofenac solution (Pennsaid, 1.5% diclofenac sodium in 45.5% DMSO) 50 drops + oral placebo tid B: Diclofenac 50 mg po + topical placebo tid 12 weeks	Aspirin up to 325 mg/day for cardiovascular prophylaxis (use comparable in groups 14% topical and 15% oral)	Mean OA duration: NR Total x-ray score (mean, maximum 27): 6.4 vs. 6.2 Baseline WOMAC pain score (mean, 0 to 500): 288 vs. 289 Baseline WOMAC physical function score (mean, 0 to 1700): 979 vs. 983 WOMAC stiffness score (mean, 0 to 200): 123 vs. 124	1057/NR/622 (311 topical diclofenac, 311 oral diclofenac)	145/10/604 (303 topical diclofenac, 301 oral diclofenac)

Author Year (Quality score)	Results	Adverse events assessment: pre-specified, active or passive ascertainment, assessed the severity of adverse events?	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Run-in/ washout	Class naïve patients only	Notes
Tugwell 2004 (Good)	<p>Topical vs. oral diclofenac, at 12 weeks WOMAC pain score (mean change from baseline, 0-500 scale): -118 vs. -134; difference 16 (-3.4 to 36.1), p=0.10</p> <p>WOMAC physical function score (mean change from baseline, 0-1700 scale): -348 vs. -438; difference 90 (24 to 156), p=0.008</p> <p>WOMAC stiffness score (mean change from baseline, 0-200 scale): -45 vs. -52; p=0.14</p> <p>Pain on walking (mean change from baseline, 0 to 100 scale [based on 1st item of the WOMAC pain subscale): -25 vs. -24; difference 1.7 (-2.9 to 6.4), p NS</p> <p>Patient global assessment (mean change from baseline, 0-100 scale): -27 vs. -32; difference 4.5 (-0.5 to 9.6), p=0.08</p> <p>Number of responders (OMERACT criteria, >=50% improvement in pain or function that was >=20 mm on a 100 mm VAS, or >=20% improvement in at least two of pain, function, or patient global assessment that was >=10 mm on a 100 mm VAS): 66% vs. 70%, p=0.37</p> <p>Withdrawal due to lack of efficacy: 9.0% vs. 3.2%</p>	<p>Pre-specified: Unclear</p> <p>Active or passive ascertainment: Unclear</p> <p>Assessment of severity: Yes</p>	<p>Topical diclofenac (n=311) vs. oral diclofenac (n=311)</p> <p>Any GI events: 35% vs. 48%, p=0.0006</p> <p>Abdominal pain: 12% vs. 22%, p=0.0008</p> <p>Diarrhea: 9% vs. 17%, p=0.001</p> <p>Dyspepsia: 15% vs. 26%, p=0.001</p> <p>Flatulence: 10% vs. 17%, p=0.009</p> <p>Melena: 1% vs. 2%, NS</p> <p>Nausea: 25% vs. 41%, p=0.4</p> <p>Dry skin: 27% vs. 1%; p<0.0001</p> <p>Rash: 12% vs. 2%, p<0.0001</p> <p>Vesiculobullous rash: 5% vs. 0%, p<0.0001</p> <p>Asthma: 0.6% vs. 3%, p=0.02</p> <p>Dizziness: 0.6% vs. 4%, p=0.002</p> <p>Dyspnea: 0% vs. 2%, p=0.01</p>	<p>Topical diclofenac vs. oral diclofenac</p> <p>Total withdrawals: 41% vs. 37%</p> <p>Withdrawal due to adverse events: 21% vs. 25%</p>	<p>NR/washout 3-10 days</p>	<p>No</p>	

Author Year (Quality Score)	Eligibility criteria	Demographics (age, gender, race)	Interventions (drug, dose, duration)	Allowed other medications/ interventions	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Underwood 2008 (Fair)	Literate men and women ≥ 50 years of age with troublesome pain around the knee most days for at least 1 month with knee pain more than three months out of preceding year; consultation with or treatment prescribed by GP for knee pain in the last 3 years.	Mean age: 64 years (range 50-89 years) Female: 56% Non-white: 1%	A: Advice to use a topical NSAID (over-the-counter or prescription), preferably ibuprofen, as needed for knee pain B: Advice to use an oral NSAID, preferably ibuprofen (up to 1.2 g/day), as needed for knee pain 24 months or longer	Not specified	Met ACR criteria for OA: 97% vs. 98% Baseline WOMAC pain score (mean, 0 to 100): 19 vs. 22 Baseline WOMAC stiffness score (mean, 0 to 100): 25 vs. 26 Baseline WOMAC physical function score (mean, 0 to 100): 23 vs. 18 Baseline WOMAC global assessment (mean, 0 to 100): 18 vs. 22	Number assessed and eligible for RCT unclear/282 randomized (138 to advice for topical NSAID, 144 to advice for oral NSAID)	18 at 3 months, 34 at 1 year/NR/264 at 3 months, 248 at 1 year
Zacher 2004	Abstract in English only						

Author Year (Quality score)	Results	Adverse events assessment: pre-specified, active or passive ascertainment, assessed the severity of adverse events?	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Run-in/washout	Class naïve patients only	Notes
Underwood 2008 (Fair)	<p>Advice to use a topical NSAID vs. advice to use an oral NSAID, at 3 months, 1 year, 2 years, and end of study (last value carried forward or 2 years); positive scores favor oral NSAID</p> <p>WOMAC pain score (difference in change from baseline, 0 to 100): -2 (-6 to 2), 1 (-4 to 6), 6 (0 to 12), 5 (0 to 9)</p> <p>WOMAC stiffness score (difference in change from baseline, 0 to 100): -3 (-8 to 2), 0 (-6 to 5), -1 (-8 to 6), -2 (-7 to 4)</p> <p>WOMAC physical function score (difference in change from baseline, 0 to 100): -2 (-5 to 2), 3 (-2 to 7), 5 (-1 to 10), 3 (-2 to 7)</p> <p>WOMAC global assessment (mean difference in change from baseline, 0 to 100): -2 (-5 to 2), 2 (-2 to 6), 4 (-1 to 10), 3 (-1 to 7)</p>	<p>Pre-specified: Yes</p> <p>Active of passive ascertainment: Unclear</p> <p>Assessment of severity: Yes</p>	<p>Advice to use topical NSAID (n=136) vs. advice to use oral NSAID (n=140)</p> <p>Deaths by 24 months: 0% vs. 0%</p> <p>Gastric bleeding by 24 months: 0% vs. 0%</p> <p>Emergency hospital admission (any reason) by 24 months: 7% vs. 4% (difference 3.1%, -2.5 to 8.6%)</p> <p>Cardiovascular hospital admission by 24 months: 2.9% vs. 3.5%</p> <p>Defined GI adverse event (dyspepsia, laboratory evidence of anemia) by or at 12 months: 42% vs. 40% (difference 2.5%, -9 to 14%)</p> <p>New diagnosis of heart failure at 12 months: 1% vs. 0%</p> <p>Increase in systolic blood pressure \geq20 mm Hg at 12 months: 13% vs. 11%</p> <p>Peak expiratory flow reduced by 15% or more at 12 months: 8% vs. 18%; difference -10% (-19 to -1%)</p> <p>Minor GI events: 42% vs. 40%</p> <p>Minor renovascular events: 16% vs. 15%</p> <p>Minor respiratory events: 7% vs. 17%</p> <p>Any minor adverse event: 56% vs. 56%</p>	<p>Advice to use topical NSAID vs. advice to use oral NSAID</p> <p>Missing follow-up data: 12% vs. 12% at 12 months; 42% vs. 36% at 24 months</p> <p>Withdrawal due to adverse events: Not reported</p>	NR/NR	No	<p>Comprehensive data available, also has patient preference data of oral vs. topical as well as cost-effectiveness analyses</p>
Zacher 2004							

Topical NSAID systematic reviews

Author, Year (Quality rating)	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Lin 2004 (Good)	To access the efficacy of topical NSAIDS in the treatment of osteoarthritis	MEDLINE, EMBASE, CINAHL, Scientific Search Index and Cochrane Library, and conference abstracts 1966 to 10/31/2003	RCTs comparing topical NSAIDs with placebo OR oral NSAIDs Studies included those with clinical or radiographical (cross checked by 2 radiologists) evidence of osteoarthritis	n=1983	13 RCTs: double blinded crossovers, double blinded parallel
Mason 2004 (capsicin) (Fair)	To determine the efficacy and safety for topically applied capsaicin for chronic pain from neuropathic or musculoskeletal disorder	MEDLINE, Cochrane Library, EMBASE, and PubMed up to April 2003	16 trials	n=1556	
Mason 2004 (Fair)	To access the efficacy of topical NSAIDS in relieving pain	MEDLINE, EMBASE, PreMedline, Cochrane Library and references supplied by pharmaceutical companies 1966 to April 2003	Double blinded RCTs in which treatments were given to adult patients with moderate to severe chronic pain resulting from musculoskeletal or other painful disorders	n=1502 (efficacy) n=2302 (trials with adverse events)	14 efficacy trials 18 placebo controlled trials

Author, Year (Quality rating)	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results	Subgroups	Comments
Lin 2004 (Good)	Patients with diagnosis of radiographical evidence of osteoarthritis	(A) Topical NSAIDs vs placebo= 9 trials (B) Topical NSAIDs vs oral NSAIDs or placebo=2 trials (C) Topical NSAIDs vs oral NSAIDs=2 trials	(A) Superior in pain reduction in the first two weeks of treatment: effect sizes for weeks 1 AND 2 were 0.41 [95% CI: 0.16 to 0.66] and 0.40 [95% CI: 0.15 to 0.65] respectively; no benefit observed in weeks 3 and 4 (C) Topical NSAIDs vs oral NSAIDs; Week 1 Pooled effect size -0.38 [95% CI -0.66 to -0.10] AND Week 2 -0.19 [-0.47 to 0.09]	Efficacy: pain reduction, topical NSAIDs were superior to placebo in the first two weeks of treatment; topical NSAIDs were less effective than oral NSAIDs numerically at any week and statistically in the first week	Adverse events (A) Rate Ratio: 1.02 (0.62 to 1.68); (C) Rate ratio: 0.99 (.77 to 1.27) Topical NSAIDs had no more side effects than placebo. Compared with oral NSAIDs, fewer patient taking topical NSAIDs had any adverse events, withdrawals due to side effects and GI side effects, but significantly more patients had local side effects such as rash, itch and burning.
Mason 2004 (capsaicin) (Fair)	Patients aged 20 to 95 years with 11 trials of a baseline pain of moderate to severe and 7 allowed concomitant drugs	Capsaicin vs. placebo (A) Pain in neuropathic conditions (B) Pain in musculoskeletal conditions	Relative benefit (95% CI) (A) 4 weeks: 1.5 (1.1 to 2.0) (B) 4 weeks: 1.4 (1.1 to 1.7); 8 weeks: 1.4 (1.2 to 1.7)	Topical capsaicin is better than placebo for the treatment of chronic pain. Local adverse events are common.	Local 3.6 (2.6 to 5.0) Withdrawals 4.0 (2.3 to 6.8)
Mason 2004 (Fair)	Generally, patients were over 40 years of age with predominantly musculoskeletal disorder and with baseline pain of moderate to severe intensity	Pennsaid vs. Placebo (3 trials) WOMAC 1) Pain 2) Stiffness 3) Physical function scale	(A) Topical vs. oral 1.1 (95% CI, 0.9 to 1.3) (B) Local adverse events occurred in 8% in topical vs. oral NSAID, 3%	Efficacy: for 4 or 5 patients with chronic pain treated with topical NSAID, one would benefit who would not have with placebo 95% CI Osteoarthritis of the knee with topical NSAIDs: 2.02 (1.57, 2.60) Topical NSAIDs vs. placebo for chronic pain 1.87 (1.61, 2.17)	RR (95% CI) Local adverse events: 1.0 (0.7 to 1.5) Systematic events: 1.7 (0.96 to 2/85) Withdrawal due to adverse events 0.9 (0.4 to 2.1)

Author, Year (Quality rating)	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Mason 2004 (rubefaciants) (Fair)	To determine the efficacy and safety of topical rubefaciants containing salicylates in acute and chronic pain	MEDLINE, Cochrane Library, EMBASE, and PubMed up to March 2003	3 trials, acute conditions 5 trials, chronic conditions	n=862	Randomized placebo controlled
Moore 1998 (Good)	To review the effectiveness and safety of topical NSAIDs in acute and chronic pain conditions	MEDLINE (1966 September 1996), EMBASE (1981 to September 1996), Oxford Pain Relief Database (1940-1994)	86 reports (A) Acute pain 1) Placebo 2) Active (B) Chronic pain 1) Placebo 2) Active	(A) Acute 1) n= 3556 2) n= 4171 (B) Chronic 1) n= 1161 2) n= 1272	37 RCT in acute 13 RCT in chronic
Ozguney 2008, Narrative, Not SR Review (Poor)					

Author, Year (Quality rating)	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results	Subgroups	Comments
Mason 2004 (rubefacients) (Fair)	Patients age ranged from 14 to 86 years and treatments contained salicylate as the primary ingredient	Topical vs. placebo (A) Pooled relative benefit for acute conditions (B) Pooled relative benefit for chronic conditions	Relative benefit (95% CI) (A) 3.6 (2.4 to 5.6) (B) 1.5 (1.3 to 1.9)	Efficacious in acute pain and moderately to poorly effective in chronic arthritic and rheumatic pain. Longest trial lasted 28 days most lasted 14 days	Acute pain local: 1.1 (0.4 to 3.5)
Moore 1998 (Good)	Studies of acute conditions were conducted in recent soft tissue injury, sprains, or trauma. Studies in chronic conditions were mostly in single joint arthritis and rheumatologic disorders.	Topical vs. placebo (A) Pooled relative benefit for acute conditions (B) Pooled relative benefit for chronic conditions	RR 95% CI (A) 1.7 (1.5 to 1.9) (B) 2.0 (1.5 to 2.7)	Topical NSAIDs are significantly more effective than placebo for pain relief.	Local skin reactions were rate, 3.6% and systemic effects were less 0.5%. Only 0.5% withdrew because of adverse events. Overall, small number of subjects per study.
Ozguney 2008, Narrative, Not SR Review (Poor)					

Author, Year (Quality Rating)	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Towheed 2006 (Fair)	To assess the efficacy of topical diclofenac in patients with osteoarthritis of the knee	MEDLINE (1966 to February 2nd, 2005), EMBASE, CSDR, ACP Journal Club, DARE, CCTR	4 trials, Pennsaid vs. VCP vs. placebo; 2 trials Pennsaid vs. VCP; Pennsaid vs. oral diclofenac	n=1412 (randomized subjects) n=666 (Pennsaid) n=746 randomized to comparator groups n= 970 completed trials	4 RCTs
Zacher 2008 (Good)	To assess the safety and efficacy of topical diclofenac	MEDLINE, Cochrane Library from inception to May 2006	19 Randomized Trials and 15 were vehicle/placebo controlled	over 3,000 patients	
Zhang 1994 (Poor)	To assess the effectiveness of topically applied capsaicin	Institute of Scientific Information Database (BIDS)	14 double-blind RCT	NR	3 RCT

Author, Year (Quality Rating)	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results	Subgroups	Comments
Towheed 2006 (Fair)	Mean trial duration was 8.5 weeks, all patients had osteoarthritis of the knee and in 3 trials specified radiographic criteria used by investigators to establish OA diagnosis	Pennsaid vs. Vehicle Control Placebo (3 trials) (A)WOMAC 1) Pain 2) Stiffness 3) Physical function scale (B) Patient Global Assessment (PGA)	RR 95% CI (A) WOMAC 1) -0.33 (-0.40 to -0.18) 2) -0.30 (-0.45 to -0.15) 3) -0.35 (-0.50 to -0.20) (B) -0.39 (-0.50 to -0.20) (C) Safety	Pennsaid was of equivalent efficacy as oral diclofenac in WOMAC outcomes and was significantly better tolerated than oral diclofenac	(A) Safety, adverse events, localized 1) Skin dryness: 1.74 (1.37 to 2.22) 2) Paresthesias: 0.60 (0.33 to 1.10) 3) Rash: 1.69 (0.96 to 2.95) (B) Systemic (Absolute Risk) 1) GI events: 1.11 (0.74 to 1.68) (B) Any adverse event 1) 1.11 (0.74 to 1.68) 2) 1.11 (1.0 to 1.24)
Zacher 2008 (Good)		NO POOLED RESULTS			
Zhang 1994 (Poor)	NR	Capsaicin vs. placebo (14 trials) (A) Pain in osteoarthritis	OR (95% CI) (A) 4.36 (2.77 to 6.88)	Effective in pain complicated by osteoarthritis	NR

Appendix I. Evidence tables: Glucosamine and Chondroitin Studies

Trials

Author Year	Eligibility criteria	Demographics (Age, gender, race)	Study Design/Type	Interventions (drug, dose, duration)	Run-in/ Washout Period	Allowed other medications/ interventions
Kahan 2009 (Fair)	Male and female outpatients 45-80 years, primary knee OA of the medial tibiofemoral compartment diagnosed according to ACR.	Chondroitin Sulfate: Age: 62.9 ± 0.5 Female: 70% Race: NR Placebo: Age: 61.8 ± 0.5 Female: 67% Race: NR	RCT	A: Chondroitin Sulfates 4&6 800mg sachet daily, every evening with glass of water B: Placebo sachet daily, every evening with glass of water 2 years	24 hours for acetaminophen, 5 days for NSAIDs prior to symptom assessments	Acetaminophen in 500-mg tablets (max dosage 4 gm/day) NSAIDs in cases of acute pain

Author Year	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Results
Kahan 2009 (Fair)	<p>Duration of knee OA: Left knee: 6.1 ± 0.3 vs. 6.5 ± 0.4 Right knee: 6.6 ± 0.4 vs. 6.3 ± 0.4</p> <p>KL grade 1: 17.4% vs. 19.7% KL grade 2: 26.2% vs. 21.6% KL grade 3: 56.4 vs. 58.7%</p> <p>Minimum JSW, mm: 3.73 ± 0.08 vs. 3.81 ± 0.07</p> <p>Pain score, 100 mm VAS: 57.2 ± 0.9 vs. 57.3 ± 1.0</p> <p>WOMAC score, normalized 100mm scales: Total: 40.5 ± 1.2 vs. 41.6 ± 1.2 Pain: 40.0 ± 1.2 vs. 40.5 ± 1.2 Function: 39.2 ± 1.3 vs. 39.0 ± 1.2 Stiffness: 42.3 ± 1.5 vs. 43.5 ± 1.5</p>	1052/NR/622	103 vs. 96 withdrawals/18 vs. 18 lost to fu/ ITT analysis 622	<p>Interaction between time and treatment effect, indicating that the effect of treatment significantly increased over time (P<0.01)</p> <p>Decrease in minimum JSW loss: -0.07 ± 0.03 vs. -0.31 ± 0.04, median effect of treatment 0.14mm (0.06-0.21mm), P<0.0001</p> <p>Percentage of patient with radiographic progression: 28% vs. 41%, p<0.0005. Relative risk reduction: 33% (16%, 46%)</p> <p>Reduction in minimum JSW loss at 2 years: -0.11 ± 0.04mm vs. -0.39 ± 0.04mm. treatment effect= 0.20mm (0.11,0.30 mm), p<0.0001</p> <p>Percentage of responder patients at 6 months: reduction in VAS pain score of at least 40%: 53% vs. 45%, p=0.04 reduction in VAS pain score of at least 60%: 41% vs. 32%, p=0.03 reduction in VAS pain score of at least 40mm: 28% vs. 19%, p=0.01 reduction in VAS pain score of at least 60mm: 9% vs. 4%, p<0.01 decreased WOMAC of at least 40%: 41% vs. 34%, p=0.05</p> <p>patient assessed VAS at 6 months: 42.2 ± 1.8mm vs. 36.6 ± 1.7mm, p<0.02 doctor assessed VAS at 6 months: 39.6 ± 1.6mm vs. 34.8 ± 1.7mm, p<0.04</p>

Author Year	Adverse effects assessment: pre-specified, active or passive ascertainment, measured the severity of adverse effect?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Notes
Kahan 2009 (Fair)	Pre-specified: NR Active or passive ascertainment: NR Severity: NR	Gastrointestinal side effects were the most frequently reported, 6% vs. 5.9% No significant laboratory abnormalities	103 vs. 96 withdrawals. 16 vs. 17 withdrawals due to AE	

Author, Year	Eligibility criteria	Demographics (Age, gender, race)	Study Design/Type	Interventions (drug, dose, duration)	Run-in/ Washout Period	Allowed other medications/ interventions
Mazieres 2007 (Fair)	Male and female outpatients 50-80 years with medial OA, defined according to ACR criteria. Patients with symptomatic knee OA that had lasted for >6 months, with pain during daily activity \geq 40 mm on a 0-100 mm visual analogue scale, a Lequesne's Index Score of between 6 and 12, and Kellgren/Lawrence grade 2 or 3 on an anterior-posterior view in an extended standing position taken within the previous 6 months. Exclusions: secondary knee OA, isolated patella-femoral OA and those requiring knee surgery in the coming year, known hypersensitivities to CS or paracetamol, NSAID use for >50% of the time during the previous 2 months, NSAID use within 48 hours before inclusion or SYSADOA, steroid by any route, intra-articular hyaluronic acid or arthroscopic debridement within 6 months before inclusion	CS: Age: 66 (8.8) Female 71% Race: NR Placebo: Age: 66 (7.7) Female: 69% Race: NR	RCT	A: Chondroitin Sulfate 500mg, twice daily by oral route B: Placebo, twice daily by oral route 24 weeks	NR	Start with paracetamol (up to 4 gm/day). NSAIDs allowed if paracetamol was not effective. NSAIDs not allowed 2 days and paracetamol not allowed 12 hours prior to evaluation visits.
Michel 2005 (Fair)	Male and female patients 40-85 years with clinically symptomatic knee OA (knee pain while standing, walking, and/or on motion for at least 25 of the 30 days prior to study entry) diagnosed according to the ACR clinical and radiographic criteria for OA of the knee. Exclusion criteria: Kellgren/Lawrence grade 4, any causes of secondary OA, traumatic knee lesions, severe comorbidity (severe renal, heart, lung, or neurologic disease), previous joint surgery, intraarticular medications, including corticosteroids into the last month, and the foreseeable prospect of major surgery during the 2-year study period.	Chondroitin Group: Mean age: 62.5 \pm 9.1 Female: 51% Race: NR Placebo Group: Mean age: 63.1 \pm 10.7 Female: 52% Race: NR	RCT	A: Chondroitin Sulfates 4 & 6, 800mg tablet daily B: Placebo 2 years	3 month washout required for potentially longer acting substances such as Chondroitin Sulfate and Glucosamine	Acetaminophen in 500-mg tablets at a maximum dose of 3 gm/day. Secondary rescue with NSAIDs were allowed up to a maximum 5 consecutive days if the primary rescue analgesia with acetaminophen was insufficient. Physical therapy was limited to application of warmth and strengthening exercises. No other interventions allowed

Author, Year	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Results
Mazieres 2007 (Fair)	Duration of disease:6.2 (6.8) vs. 6.6 (7.6)VAS pain during activity: 62 (13) vs. 61 (12)VAS pain at rest: 40 (20) vs. 40 (22)Lequesne's Index: 9.5 (2) vs. 9.4 (2)KL stages 2-3: 69% vs. 59%	322/NR/307 (153 CS, 154 Placebo)	14 vs. 14 withdrawals during treatment period, 12 vs. 11 withdrawals during washout period.307 ITT population	Pain During Activity: VAS, mm; Mean (SD)Week 0: 61 (13) vs. 61 (13)Week 4: 48 (21) vs. 51 (20)Week 12: 40 (23) vs. 42 (21)Week 24: 36 (24) vs. 41 (23)Week 32: 33 (23) vs. 40 (24)Change from baseline to week 24: -26.2 (24.9) mm vs. -19.9 (23.5) mm, p= 0.029Lequesne's Index: Mean (SD):Week 0: 9.5 (2.1) vs. 9.4 (1.8)Week 4: 8.3 (2.8) vs. 8.4 (2.4)Week 12: 7.8 (3.6) vs. 7.9 (3.1)Week 24: 7.2 (3.7) vs. 7.7 (3.3)Week 32: 6.8 (3.9) vs. 7.5 (3.6)Change from baseline to week 24: -2.4 (3.4) vs. -1.7 (3.3), p=0.109.OMERACT-OARSI responders: 68% vs. 56% (p=0.03)Change in pain at rest (VAS; mm): -18.8 (23.8) vs. -16.6 (24.2), NSPatient's global assessment: 3.1 (3.0) vs. 2.5 (3.1), NSInvestigator's global assessment: 3.1 (2.7) vs. 2.5 (3.0), p=0.044Consumption of analgesics (days): 28 (29) vs. 28 (32), NSConsumption of NSAIDs (days): 6.9 (20.2) vs. 9.2 (24.6), NSQOL, mental: 1.2 (10.4) vs. 0.3 (11.3), NSQOL, physical: 5.8 (9.0) vs. 3.8 (10.2), p=0.021Carry over effect: changes at the end of the follow-up (week 32) compared to the end of the treatment period (week 24):Change in pain on activity -1.9 (20.9) vs. -0.4 (18.7), NSChange in Lequesne's index: -0.4 (2.3) vs. -0.2(2.6), NS
Michel 2005 (Fair)	ITT Group: Minimum JSW, mm: 2.41 ± 0.14 vs. 2.35 ± 0.14 Mean JSW, mm: 3.04 ± 0.14 vs. 3.00 ± 0.15 WOMAC score, range 0-10: Total: 2.3 ± 1.6 vs. 2.6 ± 1.7 Pain: 2.5 ± 1.6 vs. 2.7 ± 1.8 Function: 2.1 ± 1.6 vs. 2.5 ± 1.8 Stiffness: 3.0 ± 2.3 vs. 3.5 ± 2.5	341/300/300	40 vs. 41 withdrawals during treatment 300 ITT analysis	A vs. B, at 2 years JSN Minimum: 0.045 ± 0.48 vs. -0.07 ± 0.56, difference: 0.12 (95% CI 0.00 to 0.24), p=0.05 JSN Mean: 0.00 ± 0.53 vs. -0.14 ± 0.61, difference 0.14 (95% CI 0.01 to 0.27), p =0.04 NS changes in WOMAC: Total: -3.9% vs. 2.1% Pain: -11.0% vs -6.2% Stiffness: -7.8% vs. -4.6% Function: -0.8% vs. 5.9%

Author Year	Adverse effects assessment: pre-specified, active or passive ascertainment, measured the severity of adverse effect?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Notes
Mazieres 2007 (Fair)	Pre-specified: No Active ascertainment: requested at visits Severity: NR	Total Number of AEs: 141 vs. 155, majority were gastro-intestinal troubles including dyspepsia, nausea, vomiting, abdominal pain and diarrhea. Patients with at least one AE: 49% vs. 49% Patients with at least on SAE: 6.5% vs. 5.2%, one in each group was considered related to treatment, eczema and urticaria	total withdrawals: 26 vs 25 due to AE: 13 vs. 8	Baseline characteristics show KL grade 2/3 in 69 and 59% of patients. But, inclusion criteria lists KL grade 2/3 as inclusion criteria. Flowchart of patients in study reasons for discontinuation is mis-numbered, used table 5 for discontinuation of treatment due to AEs
Michel 2005 (Fair)	Pre-specified: No Active ascertainment Assessment of severity: No	AEs with frequencies of at least 5% in one of the two study groups: Upper respiratory tract infection: 29% vs. 31% Headache: 7% vs. 9% Abdominal pain: 4% vs. 11% Allergic episode: 6% vs. 6% Cardiac problem: 6% vs. 5% Urinary tract infection: 5% vs. 5%	9 vs. 9 withdrawals due to AE 2 events judged to be related to Chondroitin: abdominal pain and nausea in 1 patient each.	

Author Year	Eligibility criteria	Demographics (Age, gender, race)	Study Design/Type	Interventions (drug, dose, duration)	Run-in/Washout Period	Allowed other medications/interventions
Messier, 2007 (Fair)	Males and females \geq 50 years with radiographic evidence of mild to moderate knee OA, Kellgren-Lawrence grade II-III; radiographic classification criteria or confirmation of mild to moderate radiographic evidence of knee OA from a personal physician; not participating in any other intervention study.	Mean Age Overall NR GH/CS: 70.0 ± 1.28 Placebo: 74.1 ± 1.32 , p0.03 Female: GH/CS: 75.6% Placebo: 65.9% Race, GH/CS vs. Placebo: Caucasian: 68.9% vs. 77.3% African American: 20% vs. 11.4% Asian/Pacific Islander: 6.7% vs. 2.3% Native American: 4.4% vs. 6.8%	RCT with run-in/washout period, Phase 1 treatment. Phase 2 treatment plus exercise.	A: Glucosamine hydrochloride 1500mg/ day and Chondroitin sulfate 1200mg/day taken either once or three times per day B: Placebo taken either once or three times per day 1 year treatment period	2-week discontinuation of all over-the-counter or prescription medications. Rescue medication with acetaminophen up to 4g per day and any other necessary medications unrelated to OA were permitted.	Rescue medication of acetaminophen up to 4g/day
Sawitzke, 2008 GAIT (Good)	Males and females \geq 40 years of age, had knee pain for at least 6 months occurring on the majority of days in the month preceding their enrollment in GAIT, and had Kellgren/Lawrence grade 2 or 3 knee OA determined on a screening AP radiograph of the knee in a weight bearing position. Exclusion: Minimum baseline medial tibiofemoral JSW of <2 mm, predominant lateral compartment OA on any film of the MTP joints, history of significant trauma or surgery to the knee	Age (mean \pm SD years): Glucosamine: 56.7 ± 10.4 CS: 56.4 ± 9.2 Glucosamine + CS: 56.5 ± 9.9 Celecoxib: 58.3 ± 10.7 Placebo: 56.6 ± 8.4 Female (%): Glucosamine: 61.0 CS: 71.8 Glucosamine + CS: 55.9 Celecoxib: 63.8 Placebo: 64.3 Race: NR	Prospective observational study of GAIT enrollees; ancillary study to assess structural changes in knee OA	A: Glucosamine 500mg 3 times daily B: Chondroitin sulfate (400mg 3 times daily) C: Combination of Glucosamine and Chondroitin D: Celecoxib 200mg daily E: Placebo 24 months	NR-check other GAIT pubs	NR- check other GAIT pubs

Author Year	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Results	Adverse effects assessment: pre-specified, active or passive ascertainment, measured the severity of adverse effect?	Total withdrawals; withdrawals due to adverse events	Notes
Messier, 2007 (Fair)		865 screened/435 not interested/341 ineligible 89 randomized	17 withdrawn/89 analyzed using ITT last observation carried forward	Function (WOMAC physical function 0-68) Mean(SE): Baseline: 25.9 (1.7) vs. 21.1 (1.5), p=0.04 6 months: 21.9 (1.1) vs. 22.9 (1.1), NS 12 months: 19.4 (1.2) vs. 20.6 (1.2), NS Pain (WOMAC pain 0-20): Baseline: 7.1 (0.5) vs. 5.9 (0.5), NS 6 months: 6.2 (0.4) vs. 6.2 (0.4), NS 12 months: 6.0 (0.5) vs. 5.18 (0.5), NS 6 minute walk (meters): Baseline: 384.7 (17.6) vs. 398.7 (17.3), NS 6 months: 393.6 (8.0) vs. 396.5 (7.9), NS 12 months: 409.2 (8.7) vs. 410.5(8.6), NS Knee concentric extension strength (N): Baseline: 209.4 (31.2) vs. 163.9 (20.6), NS 6 months: 176.9 (16.3) vs. 202.7 (17.5), NS 12 months: 207.6 (14.1) vs. 209.7 (15.0), NS Knee concentric flexion strength (N): Baseline: 106.0 (16.1) vs. 83.0 (10.9), NS 6 months: 106.1 (7.3) vs. 106.7 (7.8), NS 12 months: 102.9 (7.7) vs. 124.8 (8.3), P=0.05 Balance (foot length): Baseline: 0.52 (0.04) vs. 0.53 (0.03) 6 months: 0.523 (0.014) vs. 0.583 (0.017), P=0.01 12 months: 0.538 (0.017) vs. 0.591 (0.020), P=0.05 During Phase II: Pill compliant GH/CS group had less pain than the non-compliant group (p=0.02) and a non-significant trend in function (p=0.06).	Pre-specified: NR Active or passive: NR Severity: NR	17 withdrawals, 0 due to adverse events 1 AE reported: Hair loss	Groups differ at baseline on age, BMI, gender, annual household income and WOMAC function
Sawitzke, 2008 GAIT (Good)	Kellgren/Lawrence Grade 2, %:80.5 vs. 81.0 vs. 69.2 vs. 72.6 vs. 80.5 Kellgren/Lawrence Grade 3, %:19.5 vs. 19.0 vs. 30.9 vs. 27.4 vs. 19.5	662 GAIT participants consented to this study	A(177 initial): 33/NR/77B (123 initial): 30/NR/71C (128 initial): 40/NR/59D (143 initial): 32/NR/80E (134 initial): 36/NR/70	Mean loss in JSW over 2 years: All NS0.013 vs. 0.107 vs. 0.194 vs. 0.111 vs. 1.166Difference from placebo (negative value = less JSW loss):-0.153 (-0.379, 0.074) vs. -0.059 (-0.287, 0.169) vs. 0.028 (-0.214,0.271) vs. -0.055 (-0.279, 0.170)Disease progression over 2 years, % of patients: All NS18.6 vs. 21.4 vs. 24.4 vs. 20.2 vs. 22.4OR versus placebo for disease progression:0.79 (0.48,1.3) vs. 0.94(0.57,1.55) vs. 1.12(0.67,1.88) vs. 0.87(0.53,1.43)	NR- check earlier GAIT pub	Withdrawals:33 vs 30 vs 40 vs 32 vs 36Technical Loss:9 vs 6 vs 11 vs 10 vs 8Withdrawals due to AE:see earlier GAIT report	

Trials: Glucosamine Compared With Placebo

Author, Year	Eligibility criteria	Demographics (Age, gender, race)	Study Design/ Type	Interventions (drug, dose, duration)	Run-in/ Washout Period
Herrero-Beaumont, 2007 GUIDE trial (Fair)	Male and female outpatients, diagnosed with primary symptomatic knee OA in 1 or both knees according to the American College of Rheumatology criteria. Grade II or III on the Kellgren/Lawrence radiographic system. Discouraged enrollment of obese patients. Excluded patients with inflammatory joint disease.	Age: Mean age NR overall Placebo: 64.5 +/- 7.2 Acetaminophen: 63.8 +/- 6.9 Glucosamine sulfate: 63.4 +/- 6.9 Female: 278/318 (87.4%) Placebo: 89/104 (86%) Acetaminophen: 93/108 (86%) Glucosamine: 96/106 (91%) Race/Ethnicity NR	RCT	A: Glucosamine: 1500 mg glucosamine sulfate, oral solution, once daily. Rottapharm. B: Acetaminophen side comparator: 1 gram tablets 3 times per day C: Placebo 6 month treatment duration	Narcotic, non-narcotic analgesics or anti-inflammatory symptomatic medications including topical agents were discontinued for the duration of at least 5 half-lives or 72 hours, whichever was longer. Recommended washout for corticosteroids was 3 months and was 6 months for glucosamine or other drugs considered specific for OA.
Wilkens, 2010 (Good)	INCLUSION: Nonspecific chronic LBP (defined as the area below the 12th rib and above the gluteal folds); LBP for at least 6 months with summed score of at least 3 out of 24 points on the Roland Morris Disability Questionnaire, older than 25 years of age. Patients with concomitant leg pain were included as long as the LBP pain rating was higher than the leg pain rating. MRI scans no older than 1 year prior to inclusion consisting of at least 1 axial view and 2 sagittal views were required. MRI confirmed degenerative process. At least one of the following MRI criteria: disk signal intensity changes, reduced disk height compared with adjacent superior disk, facet joint changes, modic changes, or high-intensity zone. EXCLUSION: symptomatic intervertebral disk herniation or spinal stenosis, previous lumbar fracture or surgery, pregnancy or breastfeeding, seafood allergy, ongoing psychiatric or somatic disease potentially influencing a patient's pain and use of any type of glucosamine 1 year prior to enrollment.	Age; mean (SD): Total: 48.5 (11.24) Glucosamine: 47.5 (11.5) Placebo: 49.4 (11.0) Female: Total: 121/250 (48.4%) Glucosamine: 54/125 (43.2%) Placebo: 67/125 (53.6%) Race: NR	RCT	A: Glucosamine sulfate 1500mg or placebo administered as three 500-mg capsules per day. Could be taken as one pill 3 times per day or all at once. B: Placebo 6 month treatment period	NR

Author, Year	Allowed other medications/ interventions	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Herrero-Beaumont, 2007 GUIDE trial (Fair)	Ibuprofen 400mg tablets as rescue medication. Physical and/or occupational therapy were allowed if the regimen had been stable for at least 3 months prior to randomization.	<p>Duration of knee OA: 7.4+/-6.0 vs. 6.5 +/-5.3 vs. 7.2+/-5.8</p> <p>Baseline Lequesne index: 11.0+/-3.1 vs. 11.1+/-2.7 vs. 10.8+/-2.6</p> <p>Baseline Kellgren/Lawrence grade: Grade 2: 50% vs. 56% vs. 52% Grade 3: 41% vs. 31% vs. 36% Grade 2/3 unspecified: 9% vs. 12% vs. 11%</p> <p>Baseline WOMAC: Total: 38.3+/-15.2 vs. 40.4+/-14.8 vs. 37.9+/-14.3 Pain: 7.8+/-3.0 vs. 8.0+/-2.9 vs. 7.9+/-3.0 Function: 27.8+/-11.4 vs. 29.4+/-11.0 vs. 27.2+/-10.9</p>	334 screened 325 randomized 7 excluded with no efficacy data 318 ITT population	<p>A: 4 Adverse Events; 7 Lack of efficacy; 5 loss to fu; 12 Protocol violations Analyzed 78 protocol completers. 106 ITT population.</p> <p>B: 12 Adverse Events; 5 Lack of efficacy; 3 loss to fu; 8 protocol violations Analyzed 80 protocol completers. 108 ITT population</p> <p>C: 9 Adverse Events; 8 Lack of efficacy; 5 Loss to fu; 12 Protocol violations Analyzed 70 protocol completers 104 ITT population</p>
Wilkens, 2010 (Good)	Rescue medication: Pain killers or NSAIDs, existing analgesics, or usual LBP therapy (e.g., manipulation, physiotherapy, massage)	<p>Mean (SD) Roland Morris Disability Questionnaire (RMDQ) (0-24): 9.2 (3.9) vs. 9.7 (4.5) Numeric Rating Scale (NRS) (0-10): LBP at rest: 3.7 (2.6) vs. 3.9 (2.4) Leg pain at rest: 1.8 (2.2) vs. 2.0 (2.3) LBP when active: 4.9 (2.5) vs. 5.1 (2.3) Leg pain when active: 2.4 (2.6) vs. 2.7 (2.6) EuroQol-5 Dimensions (EQ-5D) (-0.59 - 1.0): 0.57 (0.3) vs. 0.63 (0.2) EuroQol-Visual analog scale (EQ-VAS) (0-100): 5.8 (2.2) vs. 6.4 (2.0)</p>	473 screened/ 250 randomized and enrolled	Withdrawals during treatment period: 7 vs. 10 Loss to fu: 4 vs. 4 Primary analysis is ITT and includes all 250 randomized patients

Author, Year	Results
Herrero-Beaumont, 2007 GUIDE trial (Fair)	<p>Comparisons to Placebo. No head-to-head.</p> <p>6 month change in Lequesne Index from baseline A: -3.1 (-3.8, -2.3); p=0.032 B: NS: -2.7 (-3.3,-2.1); p=0.18 C: -1.9 (-2.6, -1.2)</p> <p>6 month change in WOMAC from baseline Total: A: -12.9 (-15.6, -10.1); p=0.039 B: NS: -12.3 (-14.9, -9.7); p=0.08 C: -8.2 (-11.3,-5.1) Pain: A: NS: -2.7 (-3.3, -2.1); p=0.12 B: NS: -2.4 (-3.0, -1.8); p=0.41 C: -1.8 (-2.6, -1.1) Function: A: -9.2 (-11.2, -7.2); p=0.022 B: -8.7 (-10.6, -6.8); p=0.049 C: -5.5 (-7.7, -3.3)</p> <p>OARSI-A responders: A: 39.6 (p=0.004) B: 33.3 (P=0.047) C: 21.2</p> <p>OARSI-B, Pain MCII, Function MCII, Pain PASS, Function PASS also reported as secondary outcomes Per-protocol Completers- For all 3 treatments, the degree of improvement in per-protocol completers was higher than that in the ITT population.</p>
Wilkins, 2010 (Good)	<p>Mean SD (95% CI); All results NS:</p> <p>RMDQ (0-24): 6 weeks: 7.0 (6.1, 7.8) vs. 7.1 (6.3, 7.9); 3 months: 5.8 (5.0, 6.6) vs. 6.5 (5.7, 7.3); 6 months: 5.0 (4.2, 5.8) vs. 5.0 (4.2,5.8); 1 year: 4.8 (3.9, 5.6) vs. 5.5 (4.7, 6.4)</p> <p>NRS LBP at rest (0-10): 6 weeks: 2.9 (2.5, 3.3) vs. 2.9 (2.5, 3.3); 3 months: 2.7 (2.4, 3.1) vs. 2.9 (2.5, 3.3); 6 months: 2.5 (2.1, 2.9) vs. 2.4 (2.0, 2.8); 1 year: 2.5 (2.1, 2.9) vs. 2.8 (2.4, 3.1)</p> <p>NRS Leg pain at rest (0-10): 6 weeks: 1.3 (1.0, 1.7) vs. 1.5 (1.2, 1.9); 3 months: 1.4 (1.0, 1.8) vs. 1.7 (1.4, 2.1); 6 months: 1.4 (1.0, 1.7) vs. 1.5 (1.1, 1.8); 1 year: 1.5 (1.1, 1.8) vs. 1.6 (1.3, 2.0)</p> <p>NRS LBP when active (0-10): 6 weeks: 3.7 (3.2, 4.1) vs. 3.6 (3.2, 4.0); 3 months: 3.3 (2.9, 3.7) vs. 3.2 (2.8, 3.6); 6 months: 3.1 (2.7, 3.5) vs. 2.9 (2.5, 3.3); 1 year: 3.0 (2.5, 3.4) vs. 2.9 (2.5, 3.3)</p> <p>NRS Leg pain when active (0-10): 6 weeks: 1.8 (1.4, 2.2) vs. 1.9 (1.5, 2.3); 3 months: 1.7 (1.2, 2.1) vs. 1.9 (1.5, 2.3); 6 months: 1.6 (1.2, 2.0) vs. 1.9 (1.5, 2.3); 1 year: 1.7 (1.3, 2.1) vs. 2.0 (1.5, 2.4)</p> <p>EQ-5D (-0.59 - 1.0): 6 weeks: 0.68 (0.64, 0.72) vs. 0.69 (0.65, 0.72); 3 months: 0.73 (0.70, 0.78) vs. 0.69 (0.65, 0.73); 6 months: 0.74 (0.70, 0.78) vs. 0.76 (0.65, 0.74); 1 year: 0.74 (0.70, 0.78) vs. 0.70 (0.65, 0.74)</p> <p>EQ-VAS (0-100): 6 weeks: 6.8 (6.2, 7.3) vs. 6.7 (6.1, 7.2); 3 months: 7.2 (6.7, 7.8) vs. 6.8 (6.2, 7.3); 6 months: 7.2 (6.6, 7.8) vs. 7.1 (6.7, 7.4); 1 year: 7.4 (7.0, 7.7) vs. 6.6 (6.3, 7.0)</p> <p>Global perceived effect: No. (%): 6 weeks: 22 (18.6) vs. 27 (22.0); 3 months: 26 (21.5) vs. 26 (22.2); 6 months: 39 (33.1) vs. 42 (36.2); 1 year: 14 (30.9) vs. 32 (29.4)</p>

Author Year	Adverse effects assessment: pre-specified, active or passive ascertainment, measured the severity of adverse effect?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Notes
Herrero-Beaumont, 2007 GUIDE trial (Fair)	<p>Pre-specified: For non- lab AEs: No (general question): For lab AEs: Yes, laboratory tests including measurement of serum glucose and liver function tests were preformed at enrollment, 3 months and 6 months of treatment.</p> <p>Active or passive ascertainment: Active-asked a non leading question during clinic visits and drew labs</p> <p>Assessment of severity: Yes, MedDRA</p>	<p>A vs. B vs. C Total AEs: 95 vs. 96 vs. 89</p> <p>Symptoms occurring in at least 3 patients during treatment: Dyspepsia: 5 vs. 2 vs. 4 Abdominal pain: 3 vs. 4 vs. 4 Diarrhea: 3 vs. 4 vs. 4 Respiratory tract infections: 8 vs. 4 vs. 9 Gastroenteritis: 4 vs. 0 vs. 2 Coughing and associated symptoms: 1 vs. 4 vs. 0 Headache: 2 vs. 6 vs. 4 Dizziness: 1 vs. 4 vs. 1 Back pain: 7 vs. 4 vs. 5 Neck pain: 3 vs. 2 vs. 0 Fall: 5 vs. 3 vs. 2 Injury: 2 vs. 4 vs. 0</p> <p>Laboratory: Liver function (transaminases and/or GGT) : 2 vs. 21 vs. 6 Glucose: no change</p>	<p>Withdrawal due to AEs: 4 vs. 12 vs. 9</p>	
Wilkens, 2010 (Good)	<p>Pre-specified: NR Ascertainment: NR Severity: NR</p>	<p>OR (95% CI) All NS differences AEs resulting in treatment discontinuation: 0.66 (0.48-1.36) All AEs: 0.83 (0.49-1.40) Skin problems: 0.79 (0.35-1.76) Neurological: 0.65 (0.31-1.38) Heartburn: 0.99 (0.06-15.9) Flatulence: 0.55 (0.21-1.44) Abdominal pain: 1.32 (0.29-6.04) Nausea/vomiting: 1.77 (0.50-6.21) Constipation: 4.03 (0.44-36.69) Diarrhea: 0.55 (0.16-1.92) Headache/vertigo: 0.98 (0.28-3.49) Musculoskeletal concerns: 0.42 (0.14-1.25) 10 AEs resolved with treatment discontinuation 7 resolved with continuation of study drug 2 Serious AEs(death and surgery) were considered unrelated to study drug. Fasting blood glucose, cholesterol and blood pressure levels did not deviate from normal fluctuations during the trial</p>	<p>Total during treatment period: 7 vs. 10 Withdrawals due to AE: Glucosamine: 6 vs. 6</p>	

Author, Year	Eligibility criteria	Demographics (Age, gender, race)	Study Design/Type	Interventions (drug, dose, duration)	Run-in/ Washout Period
Rozendall, 2008 (Good)	Patients met the American College of Rheumatology clinical criteria for hip osteoarthritis and were able to complete questionnaires in Dutch. Excluded patients who had undergone or were awaiting hip replacement surgery, Kellgren and Lawrence score of 4, renal disease, liver disease, diabetes mellitus, or a disabling comorbid condition that would make visits to the research center impossible, patients receiving glucosamine.	Age: Mean age NR overall Placebo: 63.7 (8.5) Glucosamine sulfate: 63.1 (9.5) Female: Placebo: 70.3% Glucosamine: 68.5% Race/Ethnicity NR	RCT	1500mg oral glucosamine sulfate, administered once daily or as two 750 mg tablets Placebo 24 months treatment duration	NR
Rozendall, 2009 (Good)	Same study as Rozendall, 2008		RCT, subgroup analysis of Rozendall, 2008 data Predefined subgroups: KL=1, KL ≥ 2, localized OA, generalized OA Exploratory subgroups: VAS ≤ 30, VAS > 30, No pain medication, pain medication, no knee OA, knee OA, JSN ≥ 2.5mm, <2.5 mm		

Author Year	Allowed other medications/ interventions	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Rozendall, 2008 (Good)	<p>Baseline Pain Med use: Placebo overall: Daily 18.9% Sometimes: 27.9% None: 53.2%</p> <p>Glucosamine overall: Daily: 28.8% Sometimes: 25.2% None: 46.0%</p> <p>Interventions NR, except Total Hip Arthroplasty was collected and used in analyses.</p>	<p>Kellgren and Lawrence Score (%): 1: 49.5 vs. 53.2 ≥2: 50.5 vs. 46.8</p> <p>Mean minimum JSW (SD), <i>mm</i>: 2.13 (1.00) vs 2.33 (0.90)</p> <p>Mean WOMAC score (SD): Pain: 35.9 (23.0) vs. 32.4 (23.2) Function: 36.0 (24.1) vs. 34.1 (21.7) Stiffness: 44.2 (27.2)</p> <p>Mean pain in past week (SD), <i>mm</i>: 34.3 (26.5) vs. 30.5 (25.2)</p>	<p>Screened: 387 Eligible & Randomized: 222</p>	<p>Withdrawals during treatment period: NR</p> <p>Lost to follow-up: 7 vs 8</p> <p>ITT analysis: 111 vs. 111</p>
Rozendall, 2009 (Good)	Same study as Rozendall, 2008			

Author Year	Results
Rozendall, 2008 (Good)	<p>Primary Outcomes: WOMAC (negative difference favors glucosamine): Pain overall (SE): -1.90 ± 1.6 vs. -0.30 ± 1.6; Unadjusted difference: -1.60 (-5.60, 2.40); Adjusted difference: -1.54 (-5.43, 2.36) Function overall (SE): -1.69 ± 1.3 vs. 0.38 ± 1.3; Unadjusted difference: -2.07 (-5.53, 1.39); Adjusted difference: -2.01 (-5.38, 1.36)</p> <p>JSN, <i>mm</i> (positive difference favors glucosamine sulfate): Minimal: -0.094 (0.32) vs. -0.057 (0.32); Unadjusted difference: -0.038 (-0.130, 0.055); Adjusted difference: -0.029 (-0.122, 0.064) Lateral: -0.180 (0.34) vs. -0.159 (0.36); Unadjusted difference: -0.020 (-0.124, 0.083); Adjusted difference: -0.017 (-0.121, 0.088) Superior: -0.123 (0.36) vs. -0.129 (0.30); Unadjusted difference: 0.006 (-0.090, 0.101); Adjusted difference: 0.016 (-0.079, 0.111) Axial: -0.070 (0.48) vs. -0.079 (0.30); Unadjusted difference: 0.009 (-0.108, 0.124); Adjusted difference: -0.005 (-0.118, 0.108)</p> <p>Secondary Outcomes: WOMAC (Negative difference favors glucosamine): <i>Pain, 3mos.</i> -2.50 (19.2) vs. -1.79 (16.2); Unadjusted difference: -0.71 (-5.47, 4.05); Adjusted difference: 0.06 (-4.11, 4.22). <i>12 mos.</i> -0.54 (19.9) vs. -0.89 (23.3); Unadjusted difference: 0.35 (-5.66, 6.36); Adjusted difference: 1.42 (-3.82, 6.67). <i>24 mos.</i> -1.47 (20.7) vs. 0.88 (26.4); Unadjusted difference: -2.34 (-9.16, 4.48); Adjusted difference: -0.77 (-6.53, 4.98) <i>Function, 3 mos.</i> -3.29 (14.9) vs. -1.08 (12.7); Unadjusted difference: -2.22 (-5.97, 4.05); Adjusted difference: -2.04 (-5.48, 1.40). <i>12 mos.</i> -0.98 (14.9) vs. -0.88 (17.6); Unadjusted difference: -0.11 (-4.63, 4.42); Adjusted difference: 0.11 (-4.14, 4.35). <i>24 mos.</i> -0.84 (19.1) vs. 1.92 (19.7); Unadjusted difference: -2.76 (-8.35, 2.84); Adjusted difference: -1.63 (-6.73, 3.47). <i>Stiffness, 3 mos.</i> -4.59 (22.6) vs. -3.39 (17.7). Unadjusted difference: -1.20 (-6.66, 4.26); Adjusted difference: -0.12 (-4.94, 4.71). <i>12 mos.</i> -1.38 (22.1) vs. -3.43 (21.6); Unadjusted difference: 2.06 (-4.00, 8.12); Adjusted difference: 3.11 (-2.07, 8.28). <i>24 mos.</i> -3.43 (26.2) vs. -2.19 (24.1); Adjusted difference: -1.24 (-8.47, 5.98); Unadjusted difference: 0.66 (-5.27, 6.59).</p> <p>VAS pain also reported.</p>
Rozendall, 2009 (Good)	<p>The predefined subgroup analyses based on radiographic severity of OA and type of OA did not yield differences between GS and placebo in WOMAC pain, function and JSN.</p> <p>The exploratory analyses showed no difference in WOMAC pain, function and JSN.</p> <p>WOMAC Pain (Negative value favors glucosamine): No Knee OA: 0.3 (21.5) vs. 0.1 (26.2); Unadjusted difference: 0.3 (-7.9, 8.5); Adjusted difference: -0.1 (-4.9, 4.7). WOMAC pain: Concomitant Knee OA: -5.8 (18.1) vs. 2.9 (27.1); Unadjusted difference: -8.7 (-21.2, 3.8); Adjusted difference: -5.68 (-12.62, 1.26).</p>

Author Year (Quality Score)	Adverse effects assessment: pre-specified, active or passive ascertainment, measured the severity of adverse effect?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Notes
Rozendall, 2008 (Good)	<p>Pre-specified: yes, used a checklist</p> <p>Active ascertainment; used a checklist at baseline and every 3 months</p> <p>Severity measured: NR</p>	<p>Serious Adverse Events: 4 vs. 2</p> <p>AE resulting in treatment termination: 4 vs. 6</p> <p>Abdominal pain: 14 vs. 10 Stomach symptoms: 25 vs. 19 Intestinal symptoms: 19 vs. 17 Increased blood pressure: 11 vs. 19 Decreased blood pressure: 4 vs. 3 Fatigue: 24 vs. 18 Headache: 16 vs. 26 Vertigo: 16 vs. 18 Cardiac problems: 6 vs. 9 Depressive mood: 10 vs. 6 Allergic episode: 7 vs. 5</p>	<p>Lost to follow up: 7 vs. 8, withdrawal during treatment NR.</p> <p>Withdrawal of treatment due to AE: 4 vs. 6</p>	
Rozendall, 2009 (Good)				See Rozendall, 2008 for study details

Systematic Reviews

Author, Year	Aims	Time period covered	Eligibility criteria	Number of patients
Bjordal, 2007 (Good)	To determine the short-term pain-relieving effects of seven pharmacological agents for OA knee pain	MEDLINE, EMBASE, PedRo, Cochrane Controlled Trials Register 1996 through November 2005	Diagnosis: Knee OA verified by clinical exam and/or by X-ray. If less than 4 trials available for an intervention, trials also including hip OA were considered, if more than 2/3 of their patients had knee OA; Symptom duration: 3 months; Trial designs: Blinded, placebo-controlled parallel groups RCTs; Outcome measures: Pain intensity within 4 weeks of treatment start on WOMAC or on a 100mm VAS for global or walking pain. Pain intensity at 8-12 weeks follow-up; Intervention groups: Identical placebo drug and adequate daily defined drug dosage equal to or exceeding set dosages per drug: paracetamol 4g, diclofenac 100mg, etodolac 400mg, ibuprofen 2400 mg, nabumetone 1500mg, naproxen 1000mg, oxaprozin 1200mg, tiaprofenic acid 600mg, valdecoxib 10mg, celecoxib 200mg, meloxicam 7.5mg, etoricoxib 30mg, lumiracoxib 200mg, rofecoxib 12.5mg, topical diclofenac, piroxicam or meloxicam 1%, ibuprofen gel 3%, triamcinolone 20mg, methylprednisolone 40mg, cortivazol 3.75mg, glucosamine sulfate 1500mg, chondroitin sulfate 800mg, codeine 50mg, oxymorphone 20mg, oxycodone 20mg, morphine sulfate 30mg, tramadol 100mg	14,060 patients for all included drugs. 9964 patients received Oral NSAIDs including coxibs, 749 received topical NSAIDs, 401 received glucosamine sulfate, 362 received chondroitin sulfate
Wandel, 2010 (Good)	To determine the clinical effect of glucosamine, chondroitin, or the two in combination on joint pain and on radiological progression of disease in OA of the hip or knee	MEDLINE, EMBASE, CINAHL, and Cochrane Controlled Trials Register through June 2010.	Randomized trials with an average of at least 100 patients with knee or hip osteoarthritis per arm. Comparisons included chondroitin sulphate, glucosamine sulphate, glucosamine hydrochloride, or the combination of any two with placebo or head to head. Excluded trial arms with sub-therapeutic doses (<800mg/day of chondroitin, <1500mg/day glucosamine).	3803 to the interventions or placebo. Glucosamine sulphate vs. Placebo: 5 trials, 1104 randomized patients; Glucosamine sulphate or hydrochloride vs. Placebo: 1 trial, 205 patients; Chondroitin sulphate vs. Placebo: 3 trials 1229 patients; Glucosamine hydrochloride, chondroitin sulphate, and their combination vs. placebo: 1 trial, 1265 patients

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results	Subgroups
Bjordal, 2007 (Good)	64 RCTs total. 25 RCTs of oral NSAIDs (including coxibs), 9 topical NSAIDs, 7 glucosamine sulfate, 6 chondroitin sulfate	Mean Age: Oral NSAIDs: 62.6 years Topical NSAIDs: 64.2 years Glucosamine sulfate: 58.6 years Chondroitin sulfate: 63.0 years Mean baseline pain on 100mm VAS: Oral NSAIDs: 64.3 Topical NSAIDs: 54.7 Glucosamine sulfate: 57.8 Chondroitin sulfate: 50.7	Trials of included Oral NSAIDs:* 6 celecoxib studies; 2 naproxen studies; 2 diclofenac studies; 3 etodolac studies; 1 diflunisal study; 1 meloxicam study; 2 nabumetone studies; 1 oxaprozin study		
Wandel, 2010 (Good)	10 RCTs: designs not specified	8 trials with knee OA only, one trial with hip or knee OA, one trial with hip OA only. Mean age: 58-66 years % Female: 27-86 (median = 68%) Average duration of symptoms: 6 months- 10 years	6 glucosamine vs. placebo 3 chondroitin vs. placebo 1 glucosamine, chondroitin, combination vs. placebo	Pain Intensity (10cm VAS): Glucosamine vs. Placebo: -0.4 cm (-0.7 to -0.1) Chondroitin vs. Placebo: -0.3 cm (-0.7 to 0.0) Glucosamine and Chondroitin vs. Placebo: -0.5 cm (-0.9 to 0.0) Radiological joint space difference (negative number favors intervention): Glucosamine vs. Placebo: -0.2 mm (-0.3 to 0.0) Chondroitin vs. Placebo: -0.1mm (-0.3 to 0.1) Glucosamine and Chondroitin vs. Placebo: 0.00 mm (-0.2 to 0.2) Adverse Events, OR (95% CI): Glucosamine vs. Placebo: 0.94 (0.59 to 1.47) Chondroitin vs. Placebo: 0.99 (0.49 to 2.00) Glucosamine and Chondroitin vs. Placebo: no data Withdrawals due to AE, OR (95% CI) Glucosamine vs. Placebo: 0.99 (0.61 to 1.50) Chondroitin vs. Placebo: 0.92 (0.56 to 1.51) Glucosamine and Chondroitin vs. Placebo: 0.90 (0.43 to 1.85)	Estimated differences in pain intensity between supplements and placebo were on average 0.5 cm (0.1 to 0.9) higher in industry sponsored trials (p=0.02 for interaction)

* Characteristics of Oral NSAID trials of included drugs for the current systematic review.

Appendix J. Evidence Tables: Topical NSAIDs

Trials of Topical Compared With Oral

Author Year	Eligibility criteria	Demographics (age, gender, race)	Study Design/ Type	Interventions (drug, dose, duration)	Allowed other medications/ interventions
Dickson 1991 (Fair)	Male and female patients between 18 and 86 years of age with well-documented, mild osteoarthritis of the knee	Mean age: 63 years (range 21-86 years) Female: 66% Race: NR	RCT	A: Topical piroxicam (0.5%) tid + placebo tablet B: Ibuprofen 400 mg po + placebo gel tid 4 weeks	Paracetamol up to 4 mg allowed during washout and throughout trial; no significant difference between groups
Rother 2007 (Good)	Minimum of 6 months' history of osteoarthritis with 2 of 3 criteria: 1) morning stiffness < 30 minutes/duration, crepitus on motion and age ≥ 40 years; 2) pain rating as ≥3 on a 5 point Likert scale; 3) oral NASIDs at least 3 days per week in the past 3 months or >25 of the past 30 days AND meeting of three osteoarthritis flare criteria	Mean age: 63 years (range NR) Female: 79% Race: NR	RCT	A: 100 mg topical ketoprofen in 4.8 g IDEA-033 (Transfersome) + oral placebo bid B: Celecoxib 100 mg po + placebo gel bid 6 weeks	2000 mg paracetamol per day for 3 days any week except 48 hours before study visit
Sandelin 1997 (Fair)	Male and female outpatient patients with radiologically confirmed OA including osteophytes of one or both knees and with pain symptoms for most days of the prior month where analgesics was needed	Mean age: 61 years (range NR) Female: 66% Race: NR	RCT	A: Topical eltenac 1% 3 g tid + placebo 1 T po bid B: Diclofenac 50 mg po bid + placebo gel 3 g tid	NR

Author Year	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Results
Dickson 1991 (Fair)	Baseline overall pain during day: 5.0 vs. 5.0	NR/NR/235 (117 topical piroxicam, 118 oral ibuprofen)	39/3/196 (101 topical piroxicam, 95 oral ibuprofen)	Topical gel piroxicam vs. oral ibuprofen, at 4 weeks Overall pain during day (median, 1-9 scale): 3.0 vs. 2.0, p=0.56 Overall pain during night (median, 1-9 scale): 3.0 vs. 3.0, p=0.54 Ability to perform specified activity (median, 1-9 scale): 5.0 vs. 5.0, p=0.33 Rescue analgesic use: 69% vs. 62%
Rother 2007 (Good)	Baseline WOMAC pain score (mean, 0 to 100): 55 vs. 56 Baseline WOMAC stiffness score (mean, 0 to 100): 49 vs. 51 Baseline WOMAC physical function score (mean, 0 to 100): 54 vs. 55 Baseline patient global assessment of osteoarthritis (mean, 0 to 4): 3.9 vs. 3.9	499/NR/397 (138 topical ketoprofen, 132 oral celecoxib)	Topical ketoprofen and oral celecoxib arms only 48/1/270 (138 topical ketoprofen, 132 oral celecoxib)	Topical ketoprofen + IDEA-033 vs. oral celecoxib, at 6 weeks WOMAC pain score (mean change from baseline, 0 to 100 scale): -19 vs. -21, p not reported WOMAC physical function score (mean change from baseline, 0 to 100 scale): -16 vs. -18, p not reported Patient global assessment excellent (poor, fair, good, or excellent): 12% vs. 11% Patient global assessment good or excellent: 46% vs. 39% Withdrawal due to lack of efficacy: 0.7% vs. 2.3%
Sandelin 1997 (Fair)	Bilateral OA: 53% vs. 51% Baseline pain (mean, 0 to 100 VAS): 48 vs. 52 Baseline Lequesne index score (mean, 0 to 24): 9.5 vs. 10	NR/NR/290 (number randomized in each group unclear)	9/0/281 (124 topical eltenac, 89 oral diclofenac)	Topical eltenac vs. oral diclofenac, average at 2-4 weeks Overall pain (mean, 0-100 VAS): 31 vs. 30 Lequesne Index (mean, 0-24 scale): 6.9 vs. 7.3 Physician rated effect "good" (none, slight, moderate, or good): 18% vs. 30%

Author Year	Adverse events assessment: pre-specified, active or passive ascertainment, assessed the severity of adverse events?	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Run-in/ Washout	Class naïve patients only	Notes
Dickson 1991 (Fair)	Pre-specified: No (general question) Active or passive ascertainment: Active Assessment of severity: Yes	Topical gel piroxicam (n=117) vs. oral ibuprofen (n=118) Any adverse event judged to be definitely or possibly related to study treatment: 26% vs. 23% Upper GI events: 10% vs. 8.5% Other GI events: 2.6% vs. 0.8% CNS events: 6.0% vs. 6.8% Rash events: 0.8% vs. 0.8% Dependent edema: 0% vs. 6.8% Local effects: 1.7% vs. 0.8%	Topical gel piroxicam vs. oral ibuprofen Total withdrawals: 14% vs. 19% Withdrawal due to adverse events: 7.7% vs. 9.9% Withdrawal due to upper GI events: 5.1% vs. 3.4% Withdrawal due to other GI events: 0.9% vs. 0% Withdrawal due to CNS events: 1.7% vs. 2.5% Withdrawal due to rash: 0% vs. 0.8%	7-day washout free of anti- inflammatory medication	No	
Rother 2007 (Good)	Pre-specified: Unclear Active or passive ascertainment: Active Assessment of severity: No	Topical ketoprofen + IDEA-033 (n=138) vs. oral celecoxib (n=132) Any GI event: 9.4% vs. 14% Upper abdominal pain: 1.4% vs. 3.0% Dyspepsia: 0.7% vs. 3.0% Nausea: 1.4% vs. 2.3% Musculoskeletal and connective tissue disorders: 8.7% vs. 14% Respiratory, thoracic and mediastinal: 12% vs. 11% Allergic dermatitis: 1.4% vs. 0.8% Erythema: 21% vs. 14%	Topical ketoprofen + IDEA-033 vs. oral celecoxib Total withdrawals: 18% vs. 17% Withdrawal due to adverse events: 17% vs. 14%	NR/NR	No	
Sandelin 1997 (Fair)	Pre-specified: Unclear Active or passive ascertainment: Unclear Assessment of severity: No	Topical eltenac (n=126) vs. oral diclofenac (n=82) Any adverse events: 27% vs. 24% Any GI event: 4.8% vs. 13% CNS events: 9.5% vs. 7.3% Local skin reactions: 13% vs. 1.2% Other: 5.6% vs. 4.9%	Topical eltenac vs. oral diclofenac Total withdrawals: Not reported Withdrawal due to adverse events: 5% vs. 1.2%	NR/NR	No	

Author Year	Eligibility criteria	Demographics (age, gender, race)	Study Design/Type	Interventions (drug, dose, duration)	Allowed other medications/interventions
Simon 2009 (Good)	Male and non-pregnant women aged 40-85 with primary OA of the knee based on a) standard radiological criteria from a recent examination within 3 months; b) pain with regular use of pain meds; c) a flare of pain and a minimum Likert pain score of 8 at baseline	Mean age: 62 years (range NR) Female: 65% Non-white: 22%	RCT	A: Topical diclofenac solution (Pennsaid, 1.5% diclofenac sodium in 45.5% DMSO) 40 drops qid + oral placebo B: Oral diclofenac slow release 100 mg + placebo solution qid 12 weeks	Acetaminophen (up to four, 325 mg per day), except 3 days before efficacy assessment Glucosamine, chondroitin, anti-depressants or proton pump inhibitor, or low dose (≤ 325 mg/day) aspirin allowed
Tugwell 2004 (Good)	Men and nonpregnant women 40 to 85 years old, with symptomatic primary OA of the knee and recent (<3 months) x-ray showing osteoarthritis (confirmed by radiologist)	Mean age: 64 years (range NR) Female: 57% Non-white: 6%	RCT	A: Topical diclofenac solution (Pennsaid, 1.5% diclofenac sodium in 45.5% DMSO) 50 drops + oral placebo tid B: Diclofenac 50 mg po + topical placebo tid 12 weeks	Aspirin up to 325 mg/day for cardiovascular prophylaxis (use comparable in groups 14% topical and 15% oral)

Author Year	Other population characteristics(diagnosis, etc)	Number screened/eligible/enrolled	Number withdrawn/lost to fu/analyzed	Results
Simon 2009 (Good)	Bilateral OA: 99% vs. 99% Baseline WOMAC pain score (mean, 0 to 20): 13 vs. 13 Baseline WOMAC physical function score (mean, 0 to 68): 42 vs. 42 Baseline WOMAC stiffness score (mean, 0 to 8): 5.1 vs. 5.2	1396 (overall)/NR/775 (154 to topical diclofenac, 151 to oral diclofenac)	Topical and oral diclofenac arms only 95/4/305 (154 topical diclofenac, 151 oral diclofenac)	Topical diclofenac vs. oral diclofenac, at 12 weeks WOMAC pain score (mean change from baseline, 0-20): -6.0 vs. -6.4, p=0.43 WOMAC physical function score (mean change from baseline, 0 to 68): -16 vs. -18, p=0.32 WOMAC stiffness score (mean change from baseline, 0 to 8): -1.9 vs. -2.1, p=0.60 Patient overall health assessment score (mean change from baseline, 0 to 4): -0.95 vs. -0.88, p=0.96 Patient global assessment of the study knee (mean change from baseline, 0 to 4): -1.4 vs. -1.4, p=0.44 Withdrawal due to lack of efficacy: 10% vs. 3.3%
Tugwell 2004 (Good)	Mean OA duration: NR Total x-ray score (mean, maximum 27): 6.4 vs. 6.2 Baseline WOMAC pain score (mean, 0 to 500): 288 vs. 289 Baseline WOMAC physical function score (mean, 0 to 1700): 979 vs. 983 WOMAC stiffness score (mean, 0 to 200): 123 vs. 124	1057/NR/622 (311 topical diclofenac, 311 oral diclofenac)	145/10/604 (303 topical diclofenac, 301 oral diclofenac)	Topical vs. oral diclofenac, at 12 weeks WOMAC pain score (mean change from baseline, 0-500 scale): -118 vs. -134; difference 16 (-3.4 to 36.1), p=0.10 WOMAC physical function score (mean change from baseline, 0-1700 scale): -348 vs. -438; difference 90 (24 to 156), p=0.008 WOMAC stiffness score (mean change from baseline, 0-200 scale): -45 vs. -52; p=0.14 Pain on walking (mean change from baseline, 0 to 100 scale [based on 1st item of the WOMAC pain subscale): -25 vs. -24; difference 1.7 (-2.9 to 6.4), p NS Patient global assessment (mean change from baseline, 0-100 scale): -27 vs. -32; difference 4.5 (-0.5 to 9.6), p=0.08 Number of responders (OMERACT criteria, >=50% improvement in pain or function that was >=20 mm on a 100 mm VAS, or >=20% improvement in at least two of pain, function, or patient global assessment that was >=10 mm on a 100 mm VAS): 66% vs. 70%, p=0.37 Withdrawal due to lack of efficacy: 9.0% vs. 3.2%

Author Year	Adverse events assessment: pre-specified, active or passive ascertainment, assessed the severity of adverse events?	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Run- in/Washout	Class naïve patients only	Notes
Simon 2009 (Good)	Pre-specified: Unclear Active or passive ascertainment: Active Assessment of severity: No	Topical diclofenac (n=154) vs. oral diclofenac (n=151) Any adverse event: 62% vs. 62% Any GI event: 6.5% vs. 24% Abdominal pain: 3.2% vs. 7.3% Dyspepsia: 2.6% vs. 4.0% Nausea: 0% vs. 2.0% Dry skin at application site: 18% vs. 2.6% Contact dermatitis at application site: 2.6% vs. 0.7% Rash: 2.6% vs. 0% Headache: 18% vs. 17% Back pain: 10% vs. 7.3% Arthralgia: 9.1% vs. 7.9%	Topical diclofenac vs. oral diclofenac Total withdrawals: 33% vs. 29% Withdrawal due to adverse events: 10% vs. 13%	NR/NR	No	Has topical diclofenac + oral diclofenac group
Tugwell 2004 (Good)	Pre-specified: Unclear Active or passive ascertainment: Unclear Assessment of severity: Yes	Topical diclofenac (n=311) vs. oral diclofenac (n=311) Any GI events: 35% vs. 48%, p=0.0006 Abdominal pain: 12% vs. 22%, p=0.0008 Diarrhea: 9% vs. 17%, p=0.001 Dyspepsia: 15% vs. 26%, p=0.001 Flatulence: 10% vs. 17%, p=0.009 Melena: 1% vs. 2%, NS Nausea: 25% vs. 41%, p=0.4 Dry skin: 27% vs. 1%; p<0.0001 Rash: 12% vs. 2%, p<0.0001 Vesiculobullous rash: 5% vs. 0%, p<0.0001 Asthma: 0.6% vs. 3%, p=0.02 Dizziness: 0.6% vs. 4%, p=0.002 Dyspnea: 0% vs. 2%, p=0.01	Topical diclofenac vs. oral diclofenac Total withdrawals: 41% vs. 37% Withdrawal due to adverse events: 21% vs. 25%	NR/washout 3-10 days	No	

Author Year	Eligibility criteria	Demographics (age, gender, race)	Study Design/ Type	Interventions (drug, dose, duration)	Allowed other medications/ interventions
Underwood 2008 (TOIB study) (Fair)	Literate men and women \geq 50 years of age with troublesome pain around the knee most days for at least 1 month with knee pain more than three months out of preceding year; consultation with or treatment prescribed by GP for knee pain in the last 3 years.	Mean age: 64 years (range 50-89 years) Female: 56% Non-white: 1%	RCT	A: Advice to use a topical NSAID (over-the-counter or prescription), preferably ibuprofen, as needed for knee pain B: Advice to use an oral NSAID, preferably ibuprofen (up to 1.2 g/day), as needed for knee pain 24 months or longer	Not specified
Tiso, 2010 (Fair)	Subjects from a pain management practice who were \geq 50 years old and \geq 3 months of knee pain	Mean age 58 years Female: 89%	RCT	A: 800 mg ibuprofen 3 times daily B: 2 ml of 4% topical ibuprofen applied 4 times per day (320 mg total)	Not specified
Zacher 2004 (No QR)	Abstract in English only				

Author Year (Quality Score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Results
Underwood 2008 (TOIB study) (Fair)	Met ACR criteria for OA: 97% vs. 98% Baseline WOMAC pain score (mean, 0 to 100): 19 vs. 22 Baseline WOMAC stiffness score (mean, 0 to 100): 25 vs. 26 Baseline WOMAC physical function score (mean, 0 to 100): 23 vs. 18 Baseline WOMAC global assessment (mean, 0 to 100): 18 vs. 22	Number assessed and eligible for RCT unclear/282 randomized (138 to advice for topical NSAID, 144 to advice for oral NSAID)	18 at 3 months, 34 at 1 year/NR/264 at 3 months, 248 at 1 year	Advice to use a topical NSAID vs. advice to use an oral NSAID, at 3 months, 1 year, 2 years, and end of study (last value carried forward or 2 years); positive scores favor oral WOMAC pain score (difference in change from baseline, 0 to 100): -2 (-6 to 2), 1 (-4 to 6), 6 (0 to 12), 5 (0 to 9) WOMAC stiffness score (difference in change from baseline, 0 to 100): -3 (-8 to 2), 0 (-6 to 5), -1 (-8 to 6), -2 (-7 to 4) WOMAC physical function score (difference in change from baseline, 0 to 100): -2 (-5 to 2), 3 (-2 to 7), 5 (-1 to 10), 3 (-2 to 7) WOMAC global assessment (mean difference in change from baseline, 0 to 100): -2 (-5 to 2), 2 (-2 to 6), 4 (-1 to 10), 3 (-1 to 7)
Tiso, 2010 (Fair)	Pain duration >12 months: 95% Chronic Grade Pain: I: 5% II: 16% III: 37% IV: 42%	30/22/20	0/1/19	
Zacher 2004 (No QR)				

Author Year	Adverse events assessment: pre-specified, active or passive ascertainment, assessed the severity of adverse events?	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Run-in/ Washout	Class naïve patients only	Notes
Underwood 2008 (TOIB study) (Fair)	Pre-specified: Yes Active of passive ascertainment: Unclear Assessment of severity: Yes	Advice to use topical NSAID (n=136) vs. advice to use oral NSAID (n=140) Deaths by 24 months: 0% vs. 0% Gastric bleeding by 24 months: 0% vs. 0% Emergency hospital admission (any reason) by 24 months: 7% vs. 4% (difference 3.1%, -2.5 to 8.6%) Cardiovascular hospital admission by 24 months: 2.9% vs. 3.5% Defined GI adverse event (dyspepsia, laboratory evidence of anemia) by or at 12 months: 42% vs. 40% (difference 2.5%, -9 to 14%) New diagnosis of heart failure at 12 months: 1% vs. 0% Increase in systolic blood pressure >=20 mm Hg at 12 months: 13% vs. 11% Peak expiratory flow reduced by 15% or more at 12 months: 8% vs. 18%; difference -10% (-19 to -1%) Minor GI events: 42% vs. 40% Minor renovascular events: 16% vs. 15% Minor respiratory events: 7% vs. 17% Any minor adverse event: 56% vs. 56%	Advice to use topical NSAID vs. advice to use oral NSAID Missing follow-up data: 12% vs. 12% at 12 months; 42% vs. 36% at 24 months Withdrawal due to adverse events: Not reported	NR/NR	No	Comprehensive data available, also has patient preference data of oral vs. topical as well as cost-effectiveness analyses
Tiso, 2010 (Fair)				NR/2 days	No	
Zacher 2004 (No QR)						

Systematic Reviews

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
Lin 2004	To access the efficacy of topical NSAIDs in the treatment of osteoarthritis	MEDLINE, EMBASE, CINAHL, Scientific Search Index and Cochrane Library, and conference abstracts 1966 to 10/31/2003	RCTs comparing topical NSAIDs with placebo OR oral NSAIDs Studies included those with clinical or radiographical (cross checked by 2 radiologists) evidence of osteoarthritis	n=1983	13 RCT's: double blinded crossovers, double blinded parallel	Patients with diagnosis of radiographical evidence of osteoarthritis
Mason 2004	To access the efficacy of topical NSAIDs in relieving pain	MEDLINE, EMBASE, Pre Medline, Cochrane Library and references supplied by pharmaceutical companies 1966 to April 2003	Double blinded RCTs in which treatments were given to adult patients with moderate to severe chronic pain resulting from musculoskeletal or other painful disorders	n=1502 (efficacy) n=2302 (trials with adverse events)	14 efficacy trials 18 placebo controlled trials	Generally, patients were over 40 years of age with predominantly musculoskeletal disorder and with baseline pain of moderate to severe intensity
Mason 2004 (capsicin)	To determine the efficacy and safety for topically applied capsaicin for chronic pain from neuropathic or musculoskeletal disorder	MEDLINE, Cochrane Library, EMBASE, and PubMed up to April 2003	16 trials	n=1556		Patients aged 20 to 95 years with 11 trials of a baseline pain of moderate to severe and 7 allowed concomitant drugs

Author Year	Characteristics of identified articles: interventions	Main results	Subgroups	Comments
Lin 2004	(A) Topical NSAIDs vs placebo= 9 trials (B) Topical NSAIDs vs oral NSAIDS or placebo=2 trials (C) Topical NSAIDS vs oral NSAIDS=2 trials	(A) Superior in pain reduction in the first two weeks of treatment: effect sizes for weeks 1 AND 2 were 0.41 [95% CI: 0.16 to 0.66] and 0.40 [95% CI: 0.15 to 0.65] respectively; no benefit observed in weeks 3 and 4 (C) Topical NSAIDs vs oral NSAIDS; Week 1 Pooled effect size -0.38 [95% CI -0.66 to -0.10] AND Week 2 -0.19 [-0.47 to 0.09]	Efficacy: pain reduction, topical NSAIDs were superior to placebo in the first two weeks of treatment; topical NSAIDs were less effective than oral NSAIDS numerically at any week and statistically in the first week	Adverse events (A) Rate Ratio: 1.02 (0.62 to 1.68); (C) Rate ratio: 0.99 (.77 to 1.27) Topical NSAIDs had no more side effects than placebo. Compared with oral NSAIDs, fewer patient taking topical NSAIDs had any adverse events, withdrawals due to side effects and GI side effects, but significantly more patients had local side effects such as rash, itch and burning.
Mason 2004	Pennsaid vs. Placebo (3 trials) WOMAC 1) Pain 2) Stiffness 3) Physical function scale	(A) Topical vs. oral 1.1 (95% CI, 0.9 to 1.3) (B) Local adverse events occurred in 8% in topical vs. oral NSAID, 3%	Efficacy: for 4 or 5 patients with chronic pain treated with topical NSAID, one would benefit who would not have with placebo 95% CI Osteoarthritis of the knee with topical NSAIDs: 2.02 (1.57, 2.60) Topical NSAIDs vs. placebo for chronic pain 1.87 (1.61, 2.17)	RR (95% CI) Local adverse events: 1.0 (0.7 to 1.5) Systematic events: 1.7 (0.96 to 2/85) Withdrawal due to adverse events 0.9 (0.4 to 2.1)
Mason 2004 (capsicin)	Capsaicin vs. placebo (A) Pain in neuropathic conditions (B) Pain in musculoskeletal conditions	Relative benefit (95% CI) (A) 4 weeks: 1.5 (1.1 to 2.0) (B) 4 weeks: 1.4 (1.1 to 1.7); 8 weeks: 1.4 (1.2 to 1.7)	Topical capsaicin is better than placebo for the treatment of chronic pain. Local adverse events are common.	Local 3.6 (2.6 to 5.0) Withdrawals 4.0 (2.3 to 6.8)

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
Mason 2004 (rubefacients)	To determine the efficacy and safety of topical rubefacients containing salicylates in acute and chronic pain	MEDLINE, Cochrane Library, EMBASE, and PubMed up to March 2003	3 trials, acute conditions 5 trials, chronic conditions	n=862	Randomized placebo controlled	Patients age ranged from 14 to 86 years and treatments contained salicylate as the primary ingredient
Towheed 2006	To assess the efficacy of topical diclofenac in patients with osteoarthritis of the knee	MEDLINE (1966 to February 2nd, 2005), EMBASE, CSDR, ACP Journal Club, DARE, CCTR	4 trials, Pennsaid vs. VCP vs. placebo; 2 trials Pennsaid vs. VCP; Pennsaid vs. oral diclofenac	n=1412 (randomized subjects) n=666 (Pennsaid) n=746 randomized to comparator groups n= 970 completed trials	4 RCTs	Mean trial duration was 8.5 weeks, all patients had osteoarthritis of the knee and in 3 trials specified radiographic criteria used by investigators to establish OA diagnosis
Zacher 2008	To assess the safety and efficacy of topical diclofenac	MEDLINE, Cochrane Library from inception to May 2006	19 Randomized Trials and 15 were vehicle/placebo controlled	over 3,000 patients		

Author Year	Characteristics of identified articles: interventions	Main results	Subgroups	Comments
Mason 2004 (rubefaciants)	Topical vs. placebo (A) Pooled relative benefit for acute conditions (B) Pooled relative benefit for chronic conditions	Relative benefit (95% CI) (A) 3.6 (2.4 to 5.6) (B) 1.5 (1.3 to 1.9)	Efficacious in acute pain and moderately to poorly effective in chronic arthritic and rheumatic pain. Longest trial lasted 28 days most lasted 14 days	Acute pain local: 1.1 (0.4 to 3.5)
Towheed 2006	Pennsaid vs. Vehicle Control Placebo (3 trials) (A)WOMAC 1) Pain 2) Stiffness 3) Physical function scale (B) Patient Global Assessment (PGA)	RR 95% CI (A) WOMAC 1) -0.33 (-0.40 to -0.18) 2) -0.30 (-0.45 to -0.15) 3) -0.35 (-0.50 to -0.20) (B) -0.39 (-0.50 to -0.20) (C) Safety	Pennsaid was of equivalent efficacy as oral diclofenac in WOMAC outcomes and was significantly better tolerated than oral diclofenac	(A) Safety, adverse events, localized 1) Skin dryness: 1.74 (1.37 to 2.22) 2) Paresthesias: 0.60 (0.33 to 1.10) 3) Rash: 1.69 (0.96 to 2.95) (B) Systemic (Absolute Risk) 1) GI events: 1.11 (0.74 to 1.68) (B) Any adverse event 1) 1.11 (0.74 to 1.68) 2) 1.11 (1.0 to 1.24)
Zacher 2008	NO POOLED RESULTS			