Appendix A. Pharmacokinetics, Indications and Dosing of Included Drugs

Drug and Trade Name (Trade names provided only for drugs under patent.)	**Half-life or other relevant pharmacokinetic feature**	**Labeled indications**	**Dosing (oral doses)**	**Dose adjustments for special populations**
acetaminophen	Elimination half-life normally 2-4 hours, longer in children and possibly elderly.	Fever;Pain	Pain: 650-1000 mg up to 4g/day	Peds: 10-15 mg/kg/dose up to 5 doses/day
aspirin	Elimination half-life 4.7 to 9 hours Low dose (< 1gm) shortens half-life to 2.5 to 7 hours, high dose of (>10gm) half-life increases to as much as 19 hours	Arthritis; Cerebrovascular accident; Transient ischemia; Coronary artery bypass graft; Disorder of joint of spine; Fever; Juvenile rheumatoid arthritis; Myocardial infarction; Myocardial infarction; Prophylaxis; Osteoarthritis; Pain; Percutaneous coronary intervention; Pleurisy; Systemic lupus erythematosus; Rheumatoid arthritis; Stable angina, chronic; Unstable angina	OA and RA: 3g/day divided into 4-6 doses	Peds: 40-130 mg/kg/day depending on condition
celecoxib (Celebrex®)	Elimination half-life - 11 hrs.	Ankylosing spondylitis; Familial multiple polyposis; syndrome Osteoarthritis; Pain; Primary dysmenorrheal; Rheumatoid arthritis	OA: 200mg/day RA: 200-400 mg/day	Renal impairment: reduce dosage by 50%; Elderly patients (weight <50 kg): initiate at lowest dosage
choline magnesium trisalicylate	Elimination half-life: 9-17 hrs	Rheumatoid arthritis; Osteoarthritis; Acute shoulder pain; Fever	OA and RA: 1,500 mg 2x/day or 3,000 mg 1x/day	Renal impairment: initiate with lowest recommended dosage, monitor closely
diclofenac	Elimination half-life - 2 hours	Ankylosing spondylitis; Extraction of cataract; Inflammatory disorder of the eye; Light intolerance; Pain in eye; Refractive	OA: Delayed-release, 100-150 mg/day in 2-3 doses; Extended-release, 100-200 mg/day RA: Delayed-release, 100-200 mg/day in 3- 4	Renal impairment: initiate with lowest recommended dosage, monitor closely

Drug and Trade Name (Trade names provided only for drugs under patent.)	**Half-life or other relevant pharmacokinetic feature**	**Labeled indications**	**Dosing (oral doses)**	**Dose adjustments for special populations**
		keratoplasty; Osteoarthritis; Pain; Rheumatoid arthritis	doses; Extended-release, 75-225 mg/day	
diflunisal	Elimination half-life: 8 - 12 hrs (dose dependent)	Osteoarthritis; Pain (Mild to Moderate); Rheumatoid arthritis	OA and RA: 500-1000 mg/day in 2 divided doses; max dose/day 1500 mg	Renal impairment and elderly: begin at lowest dose possible and monitor closely
etodolac	Elimination half-life - 6-7 hrs	Juvenile rheumatoid arthritis; Osteoarthritis; Pain, acute; Rheumatoid arthritis	OA and RA initial treatment: immediate release, 300 mg 2-3x/day or 400-500 mg 2x/day OA and RA maintenance: extended release, 400-1000 mg/ day; immediate release, 600-1000 mg/day 2-4x/day with max. dose of 1200 mg/day	Juvenile RA: extended release- 20-30 kg: 400 mg once a day; 31-45 kg: 600 mg once a day; 46-60 kg: 800 mg once a day; greater than 60 kg: 1000 mg once a day
fenoprofen	Elimination half-life - 3 hrs	Migraine; Osteoarthritis; Pain (Mild to Moderate); Rheumatoid arthritis	OA and RA: 300 to 600 mg, divided 3-4x/day to max dose 3200 mg/day	Elderly: smaller dose recommended (300 mg 3x/day) Renal impairment: no dosage adjustment necessary
flurbiprofen	Elimination half-life range- 3.36 to 11.55 hrs	Constricted pupil, intraoperative prophylaxis; Osteoarthritis; Rheumatoid arthritis	OA and RA: 200-300 mg divided 2-4x/day; max 300 mg/day	Renal impairment, liver disease and geriatric patients: start with the lowest recommended dosage; monitor patient closely
ibuprofen	Elimination half-life 1.8 to 2 hrs (1.6 hrs peds); prolonged in patients with cirrhosis	Fever; Juvenile rheumatoid arthritis; Osteoarthritis; Pain, Minor; Pain (Mild to Moderate); Primary dysmenorrheal; Rheumatoid arthritis	OA and RA: 1200-3200 mg/day divided in 3-4 doses	Renal impairment: initiate with the lowest recommended dosage, monitor patient closely
indomethacin	Elimination half-life 4.5 hrs, 3.2 hrs in elderly	Ankylosing spondylitis; Bursitis of shoulder – Pain, acute – Shoulder pain; Gouty arthritis, acute; Osteoarthritis;	OA and RA: 25-50 mg 2-3x/day max 200 mg/day, 100 mg/dose; sustained-release product, 75 mg 1-2/day	Severe renal impairment: (CrCL less than 15 mL/min), liver disease (Child-Pugh Class III), elderly & peds: initiate with lowest recommended dosage, monitor patient closely

Drug and Trade Name (Trade names provided only for drugs under patent.)	**Half-life or other relevant pharmacokinetic feature**	**Labeled indications**	**Dosing (oral doses)**	**Dose adjustments for special populations**
		Pain, acute – Shoulder pain – Tendinitis; Patent ductus arteriosus; Rheumatoid arthritis		
ketoprofen	Elimination half-life – 2 to 4 hours. Controlled release, the elimination half-life is 5.4 +/- 2.2 hours. The half-life increases in elderly and in patients with decreased creatinine clearances	Fever; Osteoarthritis; Pain, Minor; Pain (Mild to Moderate); Primary mpairment al; Rheumatoid arthritis	OA and RA: immediate-release: 150-300 mg/day divided 3-4x; extended-release: 100-200 mg 1x/day	Mild renal impairment(CrCl >25 mL/min) max 150 mg/day; Moderate renal impairment (CrCl l<25 mL/min) max 100 mg/day; Geriatric(> 75 yrs) initiate with doses of 75-150 mg/day; Liver disease and serum albumin less than 3.5 g/dL maximum initial dose 100 mg/day
ketorolac	Elimination half-life – 5.6 hours. Elderly – 4.3 to 7.6 hours; Hepatic dysfunction – 1.6 to 7.6 hours; Renal impairment – 3.4 to 18.9 hours Pediatric (4-8yrs) **–** 6.1 hours	Extraction of cataract – Inflammatory disorder of the eye; Light intolerance – Pain in eye – Refractive keratoplasty; Pain, acute (Moderate to Severe); Seasonal allergic conjunctivitis	Pain, acute (Moderate to Severe): <65 yrs initiate with 20 mg followed by 10 mg every 4-6 hours, max 40 mg/day	Peds: use lowest effective dose for shortest possible duration >65 yrs or weight <50kg or renal mpairment: 10 mg every 4-6 hours as needed, max 40 mg/day
meclofenamate sodium	Elimination half-life : 0.8 – 5.3 hrs	Dysmenorrhea; Menorrhagia; Osteoarthritis; Pain; Rheumatoid arthritis	OA and RA: 200 – 400 mg/day in 3 to 4 equally divided doses, max 400 mg/day	Elderly and renal impairment: lowest effective dose for shortest possible duration
mefenamic acid	Elimination half-life: 2 - 3 hrs	Dysmenorrhea; Pain	Pain (children >14yrs and adults): 500mg initially, followed by 250 mg every 6 hours; use beyond one week is not recommended	Renal impairment: do not use Peds: use not studied
meloxicam	Elimination half-life: 15-20 hrs	Juvenile rheumatoid arthritis, polyarticular - Pauciarticular juvenile rheumatoid arthritis; Osteoarthritis; Rheumatoid arthritis	OA and RA: 7.5 mg 1x/day day, max 15 mg 1x/day	Elderly, renal impairment, liver disease (Child-Pugh Class III): initiate with the lowest recommended dosage, monitor patient closely,
nabumetone	Elimination half-life unknown	Osteoarthritis; Rheumatoid arthritis	OA and RA: initial 1000 mg/day;	Renal impairment and liver disease: monitor closely

Drug and Trade Name (Trade names provided only for drugs under patent.)	**Half-life or other relevant pharmacokinetic feature**	**Labeled indications**	**Dosing (oral doses)**	**Dose adjustments for special populations**
			maintenance 1000-2000 mg/day divided 1-2 times	and reduce dosage if necessary
naproxen	Elimination half-life: 12-15 hrs	Ankylosing spondylitis; Bursitis; Fever; Gout, acute; Juvenile rheumatoid arthritis; Osteoarthritis; Pain; Pain, Minor; Primary dysmenorrheal; Rheumatoid arthritis; Tendinitis	OA and RA: 250-500 mg 2x/day mAX 1500 mg/day for up to 6 months; over-the-counter dosing, do not take longer than 10 days	Juvenile RA: 10 mg/kg/day given in 2 divided doses; Renal impairment and liver disease: monitor patient closely and reduce dosage if necessary
oxaprozin	Elimination half-life: 24-69 hours	Juvenile rheumatoid arthritis; Osteoarthritis; Rheumatoid arthritis	OA and RA: 1200 mg 1x/day, max 1800 mg/day or 26 mg/kg/day	Juvenile RA: 22-31 kg, 600 mg 1x/ day; 32-54 kg, 900 mg 1x/day; >55 kg 1200 mg 1x/day Renal impairment or weight <50kg: initial, 600 mg 1x/day monitor closely
piroxicam	Elimination half-life: 30-86 hrs	Osteoarthritis; Rheumatoid arthritis	OA and RA: 20 mg/day 1x/day or divide and give 2x/day	Renal impairment or liver disease: monitor patient closely and reduce dosage if necessary
rofecoxib (Vioxx®)	Elimination half-life: 17 hrs	Migraine, with or without aura, acute treatment; Osteoarthritis Pain Primary dysmenorrhea Rheumatoid arthritis	OA: 12.5 mg 1x/day, max 25 mg/day RA: 25 mg 1x/day	Hepatic impairment and elderly: lowest possible dose up to 12.5mg/day for hepatic patients Peds: 0.6mg/kg/day to max of 25 mg/day
salsalate	Elimination half-life: 1 hr	Inflammatory disorder of musculoskeletal system, Rheumatic; Osteoarthritis; Rheumatoid arthritis	OA and RA: 3000 mg/day in 2-3 divided doses	Elderly: lower dosages may be required for elderly patients Peds: safety and efficacy not established in pediatric patients
sulindac	Elimination half-life: 7.8 hrs	Bursitis of shoulder - Pain, acute - Shoulder pain; Gouty arthritis, acute; Osteoarthritis; Pain, acute - Shoulder pain – Tendinitis; Rheumatoid arthritis	OA and RA: 150 mg 2x/day max 400 mg/day	Renal impairment and liver disease: monitor closely and reduce dosage if necessary
tolmetin	Elimination half-life: 5 hrs	Juvenile rheumatoid arthritis; Osteoarthritis; Rheumatoid arthritis	OA and RA: initial, 400 mg 3x/day for 1-2 weeks OA and RA:	Renal impairment: initiate with the lowest recommended dosage, monitor closely and reduce dosage if necessary

Drug and Trade Name (Trade names provided only for drugs under patent.)	**Half-life or other relevant pharmacokinetic feature**	**Labeled indications**	**Dosing (oral doses)**	**Dose adjustments for special populations**
			maintenance,200-600 mg 3x/day max 1800 mg/day	Juvenile RA: 2 yrs and older- initial, 20 mg/kg/day divided in 3 or 4 doses; maintenance, 15-30 mg/kg/day divided in 3 or 4 doses
topical capsaicin	n/a	Arthritis; Diabetic neuropathy; Postherpetic neuralgia	Arthritis: apply thin film 3-5x/day	Peds (>2 yrs): apply thin film 3-4x/day
valdecoxib (Bextra®)	Elimination half-life: 8-11 hrs	Osteoarthritis; Rheumatoid arthritis; Dysmenorrhoea.	OA and RA: 10 mg 1x/day	Moderate hepatic impairment (Child-Pugh Class B): treat with the lowest possible dosage not exceeding 10 mg with close monitoring. Avoid use in patients with severe liver dysfunction.

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
Rofecoxib	0.05
Nimesulide	0.04

*Expressed as the ratio of the 50% inhibitory concentration of cycloogenase-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. Comparable NSAID Dose Levels

Non-selective 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
Flubriprofen	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
Rofecoxib/Vioxx	12.5mg qd	25mg qd	50mg qd for max of 5 days (acute pain)
Valdecoxib/Bextra	10mg qd	10mg qd	20mg bid (primary dysmenorrhea only)

*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 D. Exact Search Strings

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 meclofenamate 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)

Appendix E. Quality Assessment Methods

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are rated fair quality. As the "fair quality" category is broad, 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. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - 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
    - Not reported
2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
            - On-site computer based system with a randomization sequence that is not readable until allocation
            - Other approaches sequence to clinicians and patients
        - Inferior approaches to concealment of randomization:
        - Use of alternation, case record numbers, birth dates or week days
        - Open random numbers lists
            - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
        - Not reported

3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors 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? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?
2. How many patients were recruited?
3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)
4. What was the funding source and role of funder in the study?
5. Did the control group receive the standard of care?
6. What was the length of followup? (Give numbers at each stage of attrition.)

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?
2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)
3. Were the events investigated specified and defined?
4. Was there a clear description of the techniques used to identify the events?
5. Was there non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?
6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?
7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?
2. How similar is the population to the population to whom the intervention would be applied?
3. How many patients were recruited?
4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)
5. What was the funding source and role of funder in the study?

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results and adverse events.

5. Are the primary studies summarized appropriately?

   The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

   For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Appendix F. Evidence Table1. 01 [1]. Trials of NSAIDs vs NSAIDs

Author year	Subjects	Comparison		Number of subjects*	Duration (weeks)	Aspirin permitted?	Efficacy measures	Withdrawals**		Other outcomes
		Meloxicam (mg)	NSAID (mg)					Meloxicam	NSAID	
Dequeker (SELECT) †	OA hip, knee, hand, or spine	7.5	piroxicam 20	8656	4	unclear	pain, PGA, withdrawals	1.7%	1.6%	No difference
Furst	RA	7.5, 15, 22.5	diclofenac 150	894	12	no	PGA, pain, painful/tender joints, physical functioning	25.7% (7.5 mg); 24.5% (15 mg); 20.9% (22.5 mg)	14.4%	No differences
Goei The	OA knee	7.5	diclofenac 100	258	6	yes	pain during active movement, PGA, acetaminophen use	3.9%	2.3%	No difference, trend favored meloxicam
Hawkey (MELISSA)	OA hip, knee, hand, or spine	7.5	diclofenac 100	9323	4	unclear	pain, PGA, withdrawals	**1.7%**	**1.0%**	No difference, trend slightly favored meloxicam
Hosie 1996	OA hip or knee	7.5	diclofenac 100	336	24	unclear	pain, quality of life	4%	4%	No difference
Hosie 1997	OA hip or knee	15	piroxicam 20	455			overall pain, pain on movement, joint stiffness, global efficacy and quality of life			No difference
Linden	OA hip	15	piroxicam 20		6			-	-	No difference
Valat	OA lumbar spine	7.5	diclofenac 100	229	2	unclear	pain on motion	0.0%	0.0%	No difference
Wojtulweski	RA	7.5	naproxen 750	379	24	no	PGA, several others	**23.6%**	**14.4%**	No difference, trend favored naproxen

* Excludes subjects randomized to placebo

**If underlined, for lack of efficacy; otherwise for all reasons

†design identical to Hawkey et al

Bold type - statistically significant; OA - osteoarthritis; PGA - patient global assessment; RA - rheumatoid arthritis

Appendix F. Evidence Table1. 01 [1]. Trials of NSAIDs vs NSAIDs

Internal Validity										
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**
Dequeker (SELECT)	method NR	NR	yes	no	unclear, reported as double-blind	unclear, reported as double-blind	yes	no/no/no/no	no	no
Furst	method NR	NR	yes	yes	unclear, reported as double-blind	unclear, reported as double-blind	unclear, reported as double-blind	no/no/no/no	no	no
Hawkey (MELISSA)	method NR	NR	yes	yes	unclear, reported as double-blind	unclear, reported as double-blind	unclear, reported as double-blind	no/no/no/no	no	unclear, only mean values reported
Hosie 1996	method NR	NR	yes	yes	unclear, reported as double-blind	unclear, reported as double-blind	unclear, reported as double-blind	no/no/no/no	no	yes
Linden	method NR	NR	yes	yes	unclear, reported as double-blind	unclear, reported as double-blind	unclear, reported as double-blind	no/no/no/no	no	no
Valat	method NR	NR	yes	yes	unclear, reported as double-blind	unclear, reported as double-blind	unclear, reported as double-blind	no/no/no/no	no	yes
Wojtulewski	method NR	NR	yes	yes	unclear, reported as double-blind	unclear, reported as double-blind	unclear, reported as double-blind	no/no/no/no	no	yes

Appendix F. Evidence Table1. 01 [1]. Trials of NSAIDs vs NSAIDs

External Validity								
Author Year	**Post-randomization exclusions**	**Quality Rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**
Dequeker (SELECT)	yes (n=630)	fair	NR/NR/9286	NR	NR/NR	no	NA	Boehringer Ingelheim
Furst	NR	fair	NR/NR/894	NR	NR/12hrs (acetaminophen)	no	yes	Boehringer Ingelheim
Hawkey (MELISSA)	NR	fair	NR/NR/10,051	Active peptic ulcer; hypersensitivity to analgesics, antipyretics or NSAIDs; asthma; nasal polyps; angioneurotic oedema or urticaria following NSAID administration; concomitant anticoagulants; litium, methotrextate, other NSAIDs or analgesic agents; significant impairment of renal function; severe liver injury; hemotological disorder; pregnant or breastfeeding; any disease which could interfere with the evaluation of efficacy or tolerabilityl corticosteroid treatment within 2 mos of study; prior replacement of, trauma to, or infection of evaluated joint; previous participation in this or other clinical study within previous month.	NR/washout 3 days	no	NA	NR
Hosie 1996	NR	fair	NR/NR/336	Pregnant, lactating or of childbearing potential not using contraception; concomitant clinically unstable disease; clinically relevant lab test abnormalities; clinical evidence of peptic ulceration within previous 6 mos; hypersensitivity to analgesics, antipyretics and/or NSAIDs; required or recently received treatment with any drug or procedure that may interact or obscure the action of the study medication.	NR/washout 3 days	no	NA	NR

Appendix F. Evidence Table1. 01 [1]. Trials of NSAIDs vs NSAIDs

External Validity								
Author Year	**Post-randomization exclusions**	**Quality Rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**
Linden	yes (n=29)	fair	NR/NR/285	NR	NR/washout 3-7 days	no	NA	NR
Valat	no	fair	NR/NR/232	Symptoms of invertebrate disk herniation with pressure on the nerve roots; former surgery, fracture or trauma in the area of the lumbar spine; severe cardias, hepatic, renal, hematological or metabolic disease, cancer of mental disturbance; any disease that could potentially interfere with the evaluation of safety or efficacy; treatment of the currenty lumbar spine osteoarthritis flare with other NSAIDs (without appropriate washout) muscle relazants or physical therapy; previous concomitant treatment with corticosteroids or with more than 4g/day acetaminophen; evidence of peptic ulcer during the previous 6 mos; bronchial asthma inducible by NSAIDs; known hypersensitivity to analgesics; pregnant or lactating women and women of child-bearing potential who were not using adequate contraception.	NR/washout 3-7 days	no	NA	NR
Wojtulewski	NR	fair	NR/NR/379	Previous participation in meloxicam trial; clinical evidence of peptic ulceration; presence of any other rheumatological or non-rheumatological disease which would interfere with the evaluation of efficacy and safety.	NR/washout 3-11 days	no	NA	NR

Appendix F. Evidence Table 02[1]. Trials of celecoxib vs NSAIDs

Author year	Subjects	Celecoxib doses (mg)	NSAIDs (mg)	Number of subjects*	Duration (weeks)	Aspirin permitted?	Efficacy measures	Results
Bensen/Zhao	OA of the knee with flare	50, 100, or 200 bid	naproxen 500 bid	1004	12	Yes	PGA, WOMAC, withdrawals	No difference
Goldstein	OA and RA with no ulcer on EGD; many had a history of GI disease	200 bid	naproxen 500 bid	537	12	Yes	PGA, withdrawals	No difference
Kivitz	OA	100-400 mg daily	naproxen 1000 mg daily	1061	12	Yes	PGA, WOMAC	No difference
McKenna	OA of the knee with flare	100 bid	diclofenac 50 tid	400	6	Yes	Index joint pain, WOMAC	No difference
Silverstein (CLASS)	OA and RA	400 bid	ibuprofen 800 tid or diclofenac 75 bid	7968	24	Yes	No efficacy measures reported except withdrawal	Not reported

*Excludes subjects randomized to placebo

PGA - patient global asssessment; WOMAC - Western Ontario and McMaster Universities Osteoarthritis Index; OA - osteoarthritis;

RA -rheumatoid arthritis; EGD - esophagogastroduodenoscopy; GI - gastrointestinal

Appendix F. Evidence Table 02[1]. Trials of celecoxib vs NSAIDs

Internal Validity										
Author	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**
Bensen/Zhao	method NR	NR	yes	yes	NR	NR	NR	no/no/no/no	no	yes
Goldstein	yes	NR	yes	yes	NR	NR	NR	no/no/no/no	no	yes
Kivitz	yes	NR	yes	yes	unclear, reported as "double-masked"	unclear, reported as "double-masked"	yes	no/no/no/no	no	yes
McKenna (pooled analysis of three trials)	method NR	NR	yes	yes	NR	NR	NR	no/no/no/no	no	yes
Silverstein (CLASS)	yes	yes	yes	yes	yes	unclear	yes	no/no/no/no	no	no

Appendix F. Evidence Table 02[1]. Trials of celecoxib vs NSAIDs

External Validity								
Author	**Post-randomization exclusions**	**Quality Rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**
Bensen/Zhao	no	fair	NR/NR/1003	Concomitant GI, renal hepatic or coagulation disorder; malignancy; esophageal of gastroduodenal ulceratiion w/in 30 days; inflammatory arthritis, gout acute trauma of the knee; known hypersensitivity to NSAIDs or sulfonamides.	run-in NR/2-7day washout	no	NA	GD Searle
Goldstein	no	fair	NR/NR/537	Inflammatory arthritis other than OA/RA; gout; GI disease; upper GI ulceration within 30 days of study; naproxen use within 30 days of study; endoscopically confirmed ulcer (>/= 3mm)	run-in NR/1-7day washout	no	NA	GD Searle; Pfizer
Kivitz	yes (n=1)	good	NR/NR/1061	Pregnancy; oral, intramuscular, intra-articular, or soft-tissue injections of corticosteroids within 4 wks of study; know hypersensitivity to COX-2s, sulfonamides or NSAIDs; any other investigational medication within 30 days of study; any NSAID or analgesic use within 48 hrs of baseline assessment; concomitant GI, renal, hepatic or coagulation disorder; malignancy within 5 years; esophageal/GI ulceration within 30 days; inflammatory arthritis; gout; acute joint trauma at hip; anticipated need for surgery during study period.	run-in NR/ 2-4 day washout	no	NA	Pharmacia; Pfizer
McKenna (pooled analysis of three trials)	no	fair	NR/NR/1940	Recent treatment with disease-modifying drugs, oral corticosteroids or corticosteroid injections; presence of other rhuematic condition; acute trauma of the joints, peptic ulceration, GI bleeding, inflammatory bowel disease, renal or hepatic failure, significant coagulation defect; malignancy.	NR/NR	no	NA	NR (Pharmacia?)
Silverstein (CLASS)	yes (n=89)	good	NR/NR/8059	Active GI, renal hepatic or coagulation disorder; malignancy within 5 yrs; esophageal or gastroduodenal ulceration within 30 days of study; know hypersensitivity to COX-2s, sulfonamides, ibuprofen or diclofenac; pregnant or lactating.	NR/NR	no	NA	Pharmacia

Evidence Table 03[1]. Trials of rofecoxib vs NSAIDs

Author year	Subjects	Comparison		Number of subjects*	Duration (weeks)
		Rofecoxib dose (mg)	NSAIDs (mg)		
Acevado	OA, negative FOBT	12.5	diclofenac 50/misoprostol 200 mcg bid	483	6
Bombardier (VIGOR)	RA, negative FOBT	50	naproxen 500 bid	8076	52
Cannon (035)	OA of knee or hip and flare (for NSAID users) or acetominophen user.	12.5, 25	diclofenac 50 tid	784	52
Chrubasik	Low back pain	12.5	Assalix 1 qid †	228	4
Day	OA of knee or hip and flare (for NSAID users) or acetominophen user.	12.5, 25	ibuprofen 800 tid	735	6
Geusens 2002	RA	25, 50	naproxen 500 bid	1023	12
Hawkey	OA with no ulcer on EGD	25, 50	ibuprofen 800 tid	581	24
Kivitz 2004	OA of knee	12.5	nabumetone 1000	1042	6
Laine	OA with no ulcer or esophagitis on EGD	25, 50	ibuprofen 800 tid	565	24
Lisse	OA of the knee, hip, hand, or spine	25	naproxen 500 tid	5557	12
Myllykangas-Luosujarvi	OA of knee or hip	12.5	naproxen 500 bid	944	6
Niccoli	OA of the hand, hip or knee	25	diclofenac 50 mg tid	90	2
Saag	OA of knee or hip and flare (for NSAID users) or acetominophen user. Excluded aspirin 81mg users.	12.5, 25	ibuprofen 800 tid	667	6
Saag	OA of knee or hip and flare (for NSAID users) or acetominophen user. Excluded aspirin 81mg users.	12.5, 25	diclofenac 50 tid	693	52
Truitt	OA of knee or hip	12.5, 25	nambumetone 1500 qd	341	6

Appendix F. Evidence Table 03[1]. Trials of rofecoxib vs NSAIDs

Author year	Aspirin permitted?	Efficacy measures	Withdrawals**		Outcomes
			Rofecoxib dose (mg)	NSAIDs (mg)	
Acevado	No	PGA	7%	10.80%	No difference
Bombardier (VIGOR)	No	PGA	6.30%	6.50%	No difference
Cannon (035)	No	WOMAC, PGA, pain while walking	13.9% (12.5 mg) 21.8% (25 mg)	16%	Trend favoring diclofenac for 2 of 3 primary measures
Chrubasik	Yes	Pain	21%	18.0%	No difference
Day	No	WOMAC, PGA, pain while walking	3.5% (12.5 mg) 2.8% (25 mg)	3%	No difference in 3 primary endpoints, but trend favored rofecoxib 25 mg for 2 of the 3.
Geusens 2002	No	Pain	nr	nr	No difference
Hawkey	No	PGA	3% (12.5 mg) 1.6% (25 mg)	5%	No difference
Kivitz 2004	Yes	PGART, WOMAC, SF-36	17.50%	20.7%	Rofecoxib superior for PGART, WOMAC, and
Laine	No	PGA	3% (12.5 mg) 2.1% (25 mg)	4.9%	No difference
Lisse	No	PGA, SF-36	11.30%	12.9%	No difference
Myllykangas-Luosujarvi	No	PGA, WOMAC	27.20%	28.4%	No difference
Niccoli	nr	PGA, pain	nr	nr	No difference
Saag	No	WOMAC, PGA, pain while walking	7.8% (12.5 mg) 4.0% (25 mg)	8.6%	No difference
Saag	No	WOMAC, PGA, pain while walking	12.1% (12.5 mg) 11.2% (25 mg)	7.0%	No difference
Truitt	No	PGA, WOMAC	1.7% (12.5 mg) 0% (25 mg)	1.7%	No differences

OA - osteoarthritis; FOBT - fecal occult blood test; PGA - patient global assessment;PGART Patient Global Response to Therapy Questionnaire
WOMAC - Western Ontario and McMaster Universities Osteoarthritis Index; EGD - esophagogastroduodenoscopy; RA - rheumatoid arthritis
* Excludes subjects randomized to placebo
** If underlined, for lack of efficacy; otherwise, for all reasons
†Willow bark extract containing 15% salicin, total dose 240mg of salicin a day

Appendix F. Evidence Table 03[1]. Trials of rofecoxib vs NSAIDs

Internal Validity										
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**
Acevado	yes	yes	yes	yes	NR	NR	yes	no/no/no/no	no	yes
Bombardier (VIGOR)	method NR	NR	yes	yes	NR	NR	NR	no/no/no/no	no	no
Cannon (035)	yes	NR	yes	yes	NR	NR	NR	no/no/no/no	448/784 (57.1%) completed study - although no SS differences among the study groups in withdrawal rates	yes
Chrubasik	yes	NA	yes	yes	NA	NA	NA	no/no/no/no	no	no
Day	yes	yes	yes (placebo group smaller in number with similar characteristics)	yes	NR	NR	yes	no/no/no/no	no	unclear; mean % changes reported only
Geusens 2002	method NR	unclear - stratified according to concomitant corticosteroid use	yes (naproxen group smaller than placebo and rofecoxib groups: 114 vs 289/306/286	yes	NR	NR	NR	no/no/no/no	no	no
Hawkey	method NR	allocation stratified by the presence or absence of history of GI events	yes	yes	NR	NR	yes	no/no/no/no	no	no

Appendix F. Evidence Table 03[1]. Trials of rofecoxib vs NSAIDs

Internal Validity										
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**
Kivitz 2004	method NR	NR	yes	yes	NR	NR	yes	no/no/no/no	no	unclear for efficacy; yes for safety
Laine	method NR	allocation stratified by the presence or absence of history of GI events	yes	yes	yes	NR	yes	no/no/no/no	no	no
Lisse	yes	yes	yes	yes	NR	NR	yes	no/no/no/no	no	no
Myllykangas-Luosujarvi	yes	NR	yes	yes	NR	NR	yes	no/no/no/no	no	unclear; only mean percentages reported
Niccoli	method NR	NR	yes	yes	NR	NR	NR	no/no/no/no	no	unclear; only mean values reported
Saag (2 studies)	yes	yes	yes	yes	NR	NR	yes	no/no/no/no	no	no for efficacy, yes for safety

Appendix F. Evidence Table 03[1]. Trials of rofecoxib vs NSAIDs

External Validity								
Author Year	**Post-randomization exclusions**	**Quality Rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**
Acevado	NR	good	NR/NR/483	Inflammatory or post-traumatic arthritis; GI associated diarrhea; infectious disease; malabsorption; uncontrolled diabetes or other serious conditions; bleeding disorder; allergic to NSAIDs/paracetamo; positive test for fecal occult blood; previous use of misoprostol; regular aspirin users; users of corticosteroids; history of sustained use of GI medication.	NR	no	NA	Merck Research Labs
Bombardier (VIGOR)	NR	fair	9539/NR/8076	History of inflammatory arthritis other than RA; upper GI surgery or inflammatory; estimated creatinine clearance of 30 ml or less/minute; an unstable medical condition; hisotyr of cancer or alcohol or drug abuse within five years of study; history of cerebrovascular events within two years of study; history of MI or coronary bypass in year before study; morbid obesity; patients who required or who had been receiving any of the following drugs: aspirin, ticlopidine, anticoagulants, cyclosporine, misprostol, sucralfate, PPIs, histamine H2-receptor agonists.	3-14 day NSAID washout	no	NA	Merck Research Labs

Appendix F. Evidence Table 03[1]. Trials of rofecoxib vs NSAIDs

External Validity								
Author Year	**Post-randomization exclusions**	**Quality Rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**
Cannon (035)	NR	fair	1,128/NR/784	Pregnancy or menopausal; significant renal impariment; clinically significant abnormalities on physical of lab exams at baseline; positive results n fecal occult blood test; class III/IV angina or uncontrolled CHF, uncontrolled hypertension, stroke or transient ischemic attack within 2 yrs of study; active hpeatic disease; recent neoplastic disease; allergy to acetaminophen or NSAIDs; required use of aspirin, corticosteroids, warfarin, ticlopidine.	NR	no	NA	Merck Research Labs
Chrubasik	NR	fair	NR/NR/228	Any recent trauma; age >50 or <20; history of cancer or risk factors for spinal infection; unexplained weight loss or recent fever or chills; pain exacerbation when supine; severe nocturnal pain; perineal anesthesia; bladder dysfunction; severe or progressive neurological deficit in a lower extremity.	none	no	NA	NR
Day	yes (n=14)	fair	1023/NR/809	Significant renal impairment; clinically signficant abnormal results of physical exam or lab screening; positive fecal occult blood test; malabsorption; class III/IV angina or CHF; uncontrolled hypertension; stroke or transient ischemic attack within 2 yrs of study; recent neoplastic disease; allergy of acetaminophen of NSAIDs; required use os aspirin, corticosteriods, warfarin sodium, ticlopidine.	yes - varied depending on NSAID use	no	yes	Merck & Co

Appendix F. Evidence Table 03[1]. Trials of rofecoxib vs NSAIDs

External Validity								
Author Year	**Post-randomization exclusions**	**Quality Rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**
Geusens 2002	yes (n=35)	fair/poor	1344/NR/1023	Presence of: systemic lupus, spondylarthropathy, polymyalgia rheumatica, gout, Paget's disease, active GI bleeding or ulceration, fecal occult blood, uncontrolled diabetes, MI, angioplasty, coronary bypass surgery within one year, stroke within 2 yrs, active hepatitis, malignancy, hepatic abnomalities, allergy to acetaminophen, aspirin, NSAIDs.	NR	no	yes	Merck Research Labs
Hawkey	NR	fair	1045/NR/775	Previous upper GI surgery; inflammatory bowel disease; elevated creatinine levels; fecal occult blood; unstable medical disease; malignancy within 5 yrs, pregnancy; CV events within 2 yrs; bleeding diathesis; anticoagulant therapy; use of corticosteroids, ticlopidine or aspirin.	2 wks NSAIDs	no	yes	Merck Research Labs
Kivitz 2004	no	fair	1495/NR/1042	Concurrent medical /arthritic disease; use of corticosteroids, misoprostol, sucralfate, histamine blockers, antacids, PPIs, analgesics, warfarin, ticlopidine, high-dose aspirin, appetite suprossants, other meds for chronic diseases.	yes - varied depending on NSAID use	no	yes	Merck & Co
Laine	no	fair/poor	1102/NR/742	Previous upper GI surgery; inflammatory bowel disease; elevated creatinine levels; fecal occult blood; unstable medical disease; malignancy within 5 yrs; CV events within 2 yrs; bleeding diathesis; anticoagulant therapy; use of corticosteroids, ticlopidine or aspirin.	2 wks NSAIDs	no	yes	Merck & Co
Lisse	yes (n=29)	fair	6018/NR/5557	Existence of potentially confounding concurrent disease (based on investigator opinion)	NR	no	NA	Merck & Co

Appendix F. Evidence Table 03[1]. Trials of rofecoxib vs NSAIDs

External Validity								
Author Year	**Post-randomization exclusions**	**Quality Rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**
Myllykangas-Luosujarvi	no	fair	1189/NR/944	Inflammatory or post-traumatic arthritis; uncontrolled diabetes or hypertension; angina or CHF; malabsorption; morbid obesity; history of inherited bleeding disorder; elevated creatinine levels; positive test for fecal occult blood; use of corticosteroids, misoprostol, H2 blockers, antacids, PPIs, warfarin, ticlopidine, aspirin >100 mg/day or low-dose aspirin for cardioprophylaxis; history od ulcer or upper GI bleeding.	yes - length NR	no	NA	Merck & Co
Niccoli	no	fair	96/NR/90	Patients who appeared unreliable/uncooperative; severe CV, hepatic or renal disorders; GI bleeding or peptic ulcer; history of hypersensitivity to NSAIDs; concomitant drugs use such as antihistamines, antibiotics, other NSAIDs, corticosteroids, mucolytics, anticoagulants, antiplatelets or other potentially nephrotoxic drugs; pregnant or lactating; previous abnormalities in renal function.	NR	no	NA	NR
Saag (2 studies)	no	good	2065/NR/1429	Use of corticosteroids, topical analgesics, low-dose aspirin, regular antacid, H2 blocker, PPIs, warfarin, or ticlopidine; significant renal impairment; active GI bleeding; GI malabsorption syndrome; class III/IV angina or CHF; uncontrolled hypertension; stroke; transient ischemic attack; active hepatic disease; allergy to acetaminophen or NSAIDs.	NR	no	NA	Merck & Co

Evidence Table 04[1]. VIGOR vs CLASS Trials

a) Evidence table												
Trial		**Sites**		**Patients**		**Aspirin use**		**Definition of significant GI events**	**Number screened/ enrolled**		**Number analyzed**	**Withdrew for lack of efficacy (Coxib group / NSAID groups)***
VIGOR (rofecoxib 50mg qd)		301 centers, 22 countries		RA, over 50		Not allowed		Perforation, obstruction, upper GI bleeding, or symptomatic ulcer	9539/8076		8076	6.3% / 6.5%
CLASS (celecoxib 400mg bid)		386 centers, US and Canada		RA or OA, 18 or older		20%		Perforation, obstruction, upper GI bleeding	9764/8059		7968	12.6% / 14.8%
* In VIGOR, there was no difference												
b) Comparison of outcomes												
		VIGOR NSAID group**		**CLASS NSAID group†**		**VIGOR NNT**		**CLASS NNT †**				
ulcers		0.030		0.011		62		265				
perforation		0.001		0.000		no effect		no effect				
obstruction		0.000		0.000		no effect		no effect				
bleeding from an ulcer		0.008		0.008		268		199				
Complicated confirmed UGI events		0.009		0.008		191		199				

RA - rheumatoid arthritis; GI - gastrointestinal; OA - osteoarthritis; NNT - number needed to treat; UGI - upper gastrointestinal

**average 9 months of followup

† adjusted to replicate 9 months of followup

Evidence Table 05[1]. GI Safety in observational studies

Author, Year Sample size	Population	Duration (days)	Celecoxib mean dose (mg)	Rofecoxib mean dose (mg)	NSAIDs dose (mg)	Aspirin permitted	Outcome
Garcia-Rodriguez 2001 UK General Practice Research Database Cases: 2,105	Patients with codes for upper GI complications	Mean NR	n/a	n/a	Dosage NR	NR	Codes for upper GI complications (bleed/perforation in stomach or duodenum; clinical diagnosis of peptic ulcer with referral to consultant or admitteospd to a hital); Adjusted relative risk (95% CI)
Hippisley-Cox 2005 Case-control QRESEARCH database (8/1/00-7/31/04) Cases: 9407	Aged ≥ 25 with first ever upper GI event and ≥ 3 yrs of recorded medical data	Unclear	NR	NR	(A) Selective NSAIDs (B) Ibuprofen (C) Diclofenac (D) Naproxen (E) Non-selective	NR	Complicated GI event (those involving hemorrhage, perforation, or surgery): Adjusted Odds Ratio (95% CI)
Kasliwal 2006National Health Service prescription data (England)Rofecoxib n=15,268Celecoxib n=17,458	Patients for whom a completed questionnaire was returned among GP-dispensed prescriptions for rofecoxib between July and November 1999 (mean age=62.5 years) and for celecoxib between May and December 2000 (mean age=62.2 years)	Events occuring whilst taking drug or within 7 days of stopping drug during 9 months since start of treatment; when not known if patient was taking drug at the time of the event, only those events that had occurred within 30 days after treatment was started were included	NR	NR	n/a	Aspirin and antiplatelet/anticoagulant agentsRofecoxib=35.3%Celecoxib=21.9%p<0.0001	Complicated upper GI conditions (perforations/bleeding)

Appendix F. Evidence Table 05[1]. GI Safety in observational studies

Author, Year Sample size	Population	Duration (days)	Celecoxib mean dose (mg)	Rofecoxib mean dose (mg)	NSAIDs dose (mg)	Aspirin permitted	Outcome
Laporte 2004Hospitals in Spain and ItalyCases=2,813	Patients aged > 18 years admitted with primary diagnosis of acute upper GI bleeding	NR	n/a	NR	(A) Diclofenac(B) Ibuprofen(C) Indomethacin(D) Ketoprofen(E) Ketorolac(F) Meloxicam(G) Naproxen(H) Nimesulide(I) Piroxicam	NR	Upper GI bleeding (odds ratio, 95% CI)
Layton 2003a National Health Service prescription data n=34,355	Patients exposed to meloxicam between 12/1996 and 3/1997 (mean age=60.4 yrs) and rofecoxib between 5/2000 and 12/2000 (mean age 62.5)	270	n/a	NR	Meloxicam	NR	Complicated upper GI conditions (perforations/bleeding) (Adjusted Rate Ratio, 95% CI)
Layton 2003aNational Health Service prescription datan=36,545	Patients exposed to meloxicam between 12/1996 and 3/1997 (mean age=60.4 yrs) and celecoxib between 5/2000 and 12/2000 (mean age 62.2)	264	≤ 200 mg taken by 83.9% pts with complicated upper GI events	n/a	Meloxicam	NR	Perforations/bleeding
Mamdani 2002 Cohort Ontario healthcare administrative database n=143,969	Aged ≥ 66 (mean=75.7), NSAID-naïve	141	NR >200 mg: 19%	NR >25 mg: 8%	Nonselective NSAIDs Diclofenac+misoprostol	13.50%	Upper GI hemorrhage (adjusted risk ratio, 95% CI, NNH)

Appendix F. Evidence Table 05[1]. GI Safety in observational studies

Author, Year Sample size	Population	Duration (days)	Celecoxib mean dose (mg)	Rofecoxib mean dose (mg)	NSAIDs dose (mg)	Aspirin permitted	Outcome
Mann 2004 43 long-term care and assisted living facilities receiving consultative pharmacy services by Cornerstone Pharmacy Services n=1,198	Use of NSAID or COX-2 inhibitor therapy from 1/2002-2/2003; mean age=81.2	352	NR	NR	(A) Ibuprofen(B) Naproxen(C) Nabumetone(D) Meloxicam(E) Salsalate	26.2% patients	Hospitalization due to GI bleed
Norgard 2004 County Hospital Discharge Registry of North Jutland County/Pharmaco-Epidemiological Prescription Database of North Jutland Cases: 780	First incident cases of upper gastrointestinal bleeding in patients with previous upper gastrointestinal disorders	Mean NR	NR	NR	NR	NR	First incident upper gastrointestinal bleeding (adjusted odds ratio)
Weideman 2004 Dallas Veterans Affairs Medical Center N=16,286	Patients who received naroxen or etodolac between 1/1/99 and 12/31/01; mean age=56.4 years; 89.5% male	NR	n/a	n/a	(A) Etodolac ≥ 800 mg (average=885 mg) (B) Naproxen ≥ 1000 mg (average=1054 mg)	≤ 325 mg	Clinically significant upper GI event (perforation, obstruction, bleeding, symptomatic ulcer) (Adjusted odds ratio; 95% CI)

Appendix F. Evidence Table 05[1]. GI Safety in observational studies

Author, Year Sample Size	Reference comparison	Celecoxib	Rofecoxib	NSAIDs	Subgroup information?	Notes
Garcia-Rodriguez 2001 UK General Practice Research Database Cases: 2,105	Nonuse	n/a	n/a	Etodolac: 2.2 (0.4-11.3) Ibuprofen: 2.5 (1.9, 3.4) Ketoprofen: 3.3 (1.9, 5.9) Nabumetone: 3.4 (1.1, 10.6) Tenoxicam: 3.4 (0.9, 13.1) Meloxicam: 3.8 (0.8, 17.2) Naproxen: 4.0 (2.8, 5.8) Diclofenac: 4.6 (3.6, 5.8) Flurbiprofen: 4.6 (2.0, 10.9) Indomethacin: 5.2 (3.2, 8.3) Piroxicam: 6.2 (3.7, 10.1)	Dose: All individual NSAIDs presented an RR < 4 when administered at low/medium doses and a greater RR with increasing dose	Etodolac, nabumetone, meloxicam: risk estimates compatible with average NSAID; data were scarce and this resulted in wide CI's
Hippisley-Cox 2005 Case-control QRESEARCH database (8/1/00-7/31/04) Cases: 9407	No NSAID use	1.25 (0.91, 1.72)	1.79 (1.42, 2.26)	(A) 1.72 (1.29, 2.29) (B) 1.58 (1.37, 1.83) (C) 2.07 (1.82, 2.35) (D) 1.97 (1.48, 2.61)	<u>Rofecoxib</u> Aspirin use: 2.98 (2.24, 3.99) No aspirin use: 1.22 (0.97, 1.54)	# pts taking celecoxib was low

Appendix F. Evidence Table 05[1]. GI Safety in observational studies

Author, Year Sample Size	Reference comparison	Celecoxib	Rofecoxib	NSAIDs	Subgroup information?	Notes
Kasliwal 2006National Health Service prescription data (England)Rofecoxib n=15,268Celecoxib n=17,458	Celecoxib	n/a	RR (95% CI)Crude: 1.52 (1.02, 2.27)Adjusted for age, age2 and sex: 1.58 (0.96, 2.58)Adjusted for NSAIDs prescribed within 3 months before starting coxib: 1.55 (1.02, 2.38)Adjusted for age, age2, sex, NSAIDs prescribed within 3 months before starting coxib: 1.60 (0.95, 2.70)	n/a	Increased risk of bleeding with age and use of concomitant drugs that increase risk of bleeding	
Laporte 2004Hospitals in Spain and ItalyCases=2,813	Nonuse	n/a	7.2 (2.3, 23.0)	(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)	Risk increased with dose, history of peptic ulcer and/or upper GI bleeding, and use of antiplatelet drugs	Excluded patients on anticoagulants
Layton 2003a National Health Service prescription data n=34,355	Meloxicam	n/a	0.91 (0.59, 1.42	n/a	Significant association with age, but not sex or past medical history of upper GI problems	

Appendix F. Evidence Table 05[1]. GI Safety in observational studies

Author, Year Sample Size	Reference comparison	Celecoxib	Rofecoxib	NSAIDs	Subgroup information?	Notes
Layton 2003aNational Health Service prescription datan=36,545	Meloxicam	Adjusted RR=0.56, 95% CI 0.32, 0.96	n/a	n/a		
Mamdani 2002 Cohort Ontario healthcare administrative database n=143,969	(A) Treatment vs nonuse (B) Nonselective NSAIDs vs COX-2 (C) Diclofenac+misoprostol vs COX-2 (D) Rofecoxib vs celecoxib	(A) 1.0 (0.7, 1.6) (B) 4.4 (2.3, 8.5) (C) 3.2 (1.6, 6.5)	(A) 1.9 (1.3, 2.8); NNH=1389 (B) 1.9 (1.0, 3.5) (C) 1.4 (0.7, 2.7) (D) vs celecoxib 1.9 (1.2, 2.8)	Nonselective NSAIDs vs nonuse: 4.0 (2.3, 6.9); NNH=403 Diclofenac+misoprostol vs nonuse 3.0 (1.7, 5.5); NNH=592	Age, gender, and history of GI hemorrhage had no effect	Has income, previous GI hemorrage info
Mann 200443 long-term care and assisted living facilities receiving consultative pharmacy services by Cornerstone Pharmacy Servicesn=1,198	None - crude rates only	6/679 (0.9%)	6/279 (2.2%)	(A) 0(B) 5/63 (7.9%)(C) 1/22 (4.5%)(D) 0(E) Salsalate (1/17 (5.6%)		% patients:Anticoagulant use=11.3%Cigarette smoking=4.6%Poor quality; no adjustment for baseline differences
Norgard 2004 County Hospital Discharge Registry of North Jutland County/Pharmaco-Epidemiological Prescription Database of North Jutland Cases: 780	Nonuse	1.3 (0.7, 2.8)	2.1 (1.2, 3.5)	"Other NSAIDs": 3.3 (2.4, 4.4)	Rofecoxib associated with significantly higher risk of GI bleed in men (OR 2.1; 95% CI 1.0, 4.6), but not women (OR 2.0; 95% CI 0.9, 4.4)	

Appendix F. Evidence Table 05[1]. GI Safety in observational studies

Author, Year Sample Size	Reference comparison	Celecoxib	Rofecoxib	NSAIDs	Subgroup information?	Notes
Weideman 2004 Dallas Veterans Affairs Medical Center N=16,286	n/a	n/a	n/a	Etodolac vs Naproxen: <u>Not taking aspirin</u> All: 0.24 (95% CI 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	

Appendix F. Evidence Table 06[1]. CV Safety in observational studies

Author, Year Data source Sample size	Population	Exposure (days)	Celecoxib dose (mg)	Rofecoxib dose (mg)	Other NSAIDs dose (mg)	Aspirin permitted	Outcome
Andersohn 2006 UK General Practice Research Database (GPRD) Cases=3,643	Diagnosis of AMI, death from AMI, or sudden death from coronary heart disease (CHD); aged ≥ 40 years; ≥ 1 NSAID prescription between June 1, 2000 and October 31, 2004; with a practice with ensured quality standards of data recording for ≥ 1 year	Average=542 days; exposure defined as quantity of prescribed tablets by the number of tablets to be taken daily; "current"=NSAID prescription lasting into 14-day period before index date; "recent" = supply ended 15-183 days before index date; "past" = supply ended between 184 days and 1 year before index	Mean NR	Mean NR	Etoricoxib Valdecoxib Diclofenac Ibuprofen Naproxen	NR	Diagnosis of AMI, death from AMI, or sudden death from coronary heart disease (CHD) (Adjusted RR; 95% CI)
Graham 2005 State of California Kaiser Permanente health care database Cases=8,143	Age 18-84 years who filled ≥ 1 prescription for celecoxib, rofecoxib or any other non-selective NSAID; ≥ 12 months of health plan coverage before index prescription date; 1/1/99-12/31/01; mean age=66.9; 62% male	Mean=113 days before event	NR	(A) all doses(B) ≤ 25 mg(C) > 25 mg	(A) Ibuprofen(B) Naproxen(C) Other NSAIDs	Random sample of n=817 cases participated in phone interview and 23% reported using cc aspirin	Acute MI requiring admission or sudden cardiac death

Appendix F. Evidence Table 06[1]. CV Safety in observational studies

Author, Year Data source Sample size	**Population**	**Exposure (days)**	**Celecoxib dose (mg)**	**Rofecoxib dose (mg)**	**Other NSAIDs dose (mg)**	**Aspirin permitted**	**Outcome**
Harrison-Woolrych 2005 New Zealand Intensive Medicines Monitoring Programme (IMMP) *Interim* analysis of 11,149 of 58,849 for who follow-up was complete	All patients who received a prescription between 12/1/00 and 11/30/01; patients who changed medicines were included in both groups	Duration to event (through 11/30/04); period to last follow-up questionnaire; date of stopping medication; or expiration of final prescription	100 mg=7.1% 200 mg=81.6% 400 mg=10.9% Other=0.4%	12.5=24.3% 25 mg=64.5% 50 mg=11% Other=0.2%	n/a	NR	Thrombotic cardiovascular events identified from several different sources (questionnaires, hospital admission data, spontaneous reports, prescription data, national morbidity and mortality databases) (Hazard Ratio adjusted for age)
Hippisley-Cox 2005Case-controlQRESEARCH database (8/1/00-7/31/04)Cases: 9218	All patients aged 25 to 100 with a first ever MI; **63.1% male**	NR	NR	NR	(A) Other selective NSAIDs(B) Ibuprofen(C) Diclofenac(D) Naproxen(E) Other non-selective NSAIDs	yes, but proportion NR	First ever MI (Adjusted odds ratio, 95% CI)
Hudson 2005Database of hospital discharge summaries (4/1/00-3/31/02)n=1866	Aged > 66 with known heart failure (no hospitalizations in last 3 years)	352	NR	NR	Any NSAID	Yes, in 1006 (53.9%)	Hazard Ratio, 95% CI(A) Recurrent HF (B) Death(C) Death OR recurrent HF (Primary outcome)

Appendix F. Evidence Table 06[1]. CV Safety in observational studies

Author, Year Data source Sample size	Population	Exposure (days)	Celecoxib dose (mg)	Rofecoxib dose (mg)	Other NSAIDs dose (mg)	Aspirin permitted	Outcome
Johnson 2005 Denmark National Health Service registries Cases=10,280	First diagnosis of MI; living in counties for ≥ 1 year; aged ≥ 20 years (mean age=69.6 years); 60.4% male; 1/1/00-12/31/03	NR	NR	NR	(A) Naproxen (B) other nonaspirin NSAID	6.9% high dose	Acute MI (Relative risk, 95% CI)
Kasliwal 2006 National Health Service prescription data (England) Rofecoxib n=15,268 Celecoxib n=17,458	Patients for whom a completed questionnaire was returned among GP-dispensed prescriptions for rofecoxib between July and November 1999 (mean age=62.5 years) and for celecoxib between May and December 2000 (mean age=62.2 years)	Events occuring whilst taking drug or within 7 days of stopping drug during 9 months since start of treatment; when not known if patient was taking drug at the time of the event, only those events that had occurred within 30 days after treatment was started were included	NR	NR	n/a	Aspirin and antiplatelet/anticoagulant agents Rofecoxib=35.3% Celecoxib=21.9% p<0.0001	(a) Cardiovascular TE (b) Cerebrovascular TE (c) Peripheral venous (DVT/PE)
Kimmel 2005Hospitals in 5-county region (telephone interview)Cases: 1718	Persons aged 40 to 75 years hospitalized for first, nonfatal MI	NR	NR	NR	(A) Ibuprofen or diclofenac(B) Naproxen	33.60%	Nonfatal MIOdds ratio (95% CI)

Appendix F. Evidence Table 06[1]. CV Safety in observational studies

Author, Year Data source Sample size	Population	Exposure (days)	Celecoxib dose (mg)	Rofecoxib dose (mg)	Other NSAIDs dose (mg)	Aspirin permitted	Outcome
Langman 2004 MediPlus (UK) database of general clinical practices N=18,737	Men or women aged ≥ 50 years that were new users of any drug-of-interest (with ≥ 1 prescription) during the period 1/1/00 - 12/31/00	180	n/a	NR	(A) diclofenac (B) ibuprofen (C) naproxen	NR	Initiation of antihypertensive medication (odds ratio, 95%) CI)
Layton 2003 National Health Service prescription data N=34,355	Patients exposed to meloxicam 12/96-3/97 (n=19,087); rofecoxib 7/99-9/99 (n=15,268)	270	NR	NR	Meloxicam	NR	Thromboembolic events: (A) cardiovascular (B) cerebrovascular (C) peripheral venous thrombotic
Levesque 2005 Computerized health insurance and vital statistics databases of Quebec, Canada n=59724	≥ 66 years of age prescribed an NSAID or COX-2 who've never had an MI	844.8	(A) All (B) Low: ≤ 200 mg (C) High: >200 mg	(A) All (B) Low: ≤ 25 mg (C) High: > 25 mg	(A) Naproxen (B) Meloxicam	22.50%	Acute MI, fatal or nonfatal
Mamdani 2003 Ontario healthcare administrative database N=166,964	NSAID-naïve patients aged ≥ 66 years of age prescribed an NSAID or COX-2	165.6	NR	NR	(A) Naproxen (B) Nonnaproxen nonselective NSAIDs	14.70%	Incidence of hospitalization for acute MI
Mamdani 2004 Ontario healthcare administrative database 4/17/00-3/31/01 N=145097	NSAID-naïve patients aged ≥ 66 years of age prescribed an NSAID or COX-2	140	NR	NR	Non-selective NSAID users	NR	Admission for CHF (risk ratio, 95% CI)

Appendix F. Evidence Table 06[1]. CV Safety in observational studies

Author, Year Data source Sample size	Population	Exposure (days)	Celecoxib dose (mg)	Rofecoxib dose (mg)	Other NSAIDs dose (mg)	Aspirin permitted	Outcome
Ray 2002Tennessee Medicaid program database1/1/99-6/30/01	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	NR	NR	(A) ≤ 25 mg(B) > 25 mg	(A) Ibuprofen(B) Naproxen	NR	Serious CHD (hospital admission for AMI or death from CHD)
Schlienger 2002 UK General Practice Research Database (GPRD) Cases=3,315	First-time diagnosis of acute myocardial infarction (AMI) between January 1, 1992 and October 31, 1997; ≤ 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	NR	n/a	n/a	Ibuprofen Diclofenac Piroxicam Ketoprofen Indomethacin Flubiprofen Naproxen	Yes	First-time diagnosis of acute myocardial infarction (AMI) (Adjusted Odds Ratio; 95% CI)

Appendix F. Evidence Table 06[1]. CV Safety in observational studies

Author, Year Data source Sample size	Population	Exposure (days)	Celecoxib dose (mg)	Rofecoxib dose (mg)	Other NSAIDs dose (mg)	Aspirin permitted	Outcome
Shaya 2005 Medicaid database N=6,250	Enrollees who received ≥ 1 prescription for an NSAID between 1/1/00 and 6/30/02; 70% female; 50% African American; 70% were aged 50 years or younger	≥ 60 prior to event	NR	NR	Other NSAIDs (excluding naproxen)	NR	Cardiovascular thrombotic events (odds ratio, 95% CI)
Solomon 2002 New Jersey Medicaid or Medicare and Pharmaceutical Assistance for the Aged and Disabled programs	Patient hospitalized with a main diagnosis of AMI with continuous use of the aforementioned benefit programs for ≥ 180 days before index date; excluded patients with any diagnoses that might have been managed with aspirin	6 months prior to index date was primary exposure of interest	n/a	n/a	Naproxen, ibuprofen, ketorolac, indomethacin, sulindac, oxaprozin, diclofenac, fluriprofen, etodolac, ketoprofen, nabumetone, piroxicam, fenoprofen, tolmetin; dosages NR	No	Acute MI - Odds Ratio (95% CI)
Solomon 2004 Chart review of prescription drug benefit program participants Cases=10,895	Low-income, elderly, Medicare beneficiaries who had at least 1 healthcare visit in each 6-month period; mean age > 80 years	1-30 days 31-90 days > 90 days	≤ 200 mg >200 mg	≤ 25 mg > 25 mg	(A) Naproxen (B) Ibuprofen (C) Other NSAIDs	NR	Acute MI

Appendix F. Evidence Table 06[1]. CV Safety in observational studies

Author, Year Data source Sample size	Population	Exposure (days)	Celecoxib dose (mg)	Rofecoxib dose (mg)	Other NSAIDs dose (mg)	Aspirin permitted	Outcome
Solomon 2004 Medicare Prescription Drug Benefit Program databases through Pennslyvania Pharmaceutical Assistance Contract for the Elderly (PACE) or the New Jersey Pharmaceutical Assistance Program for the Aged and Disabled (PAAD) (both programs for elderly individuals with low-moderate income levels) Cases=3,915	Active users of prescription drug benefit program for 2 consecutive years out of the 3-year period (1998-2000) with no prior diagnosis of hypertension and no use of antihypertensive medications; mean age=79	Short=1-30 Long=31-90	Low: ≤ 200 mg High: >20 mg	Low: ≤ 25 mg High: > 25 mg	Nonspecific NSAID	NR	New onset hypertension and the filling of at least 1 antihypertensive medication prescription
Velentgas 2005 Insurance claims/administrative records of UnitedHealthcare N=424,584	Patients aged 40-64 who received at least one dispensing of rofecoxib, celecoxib, naproxen, ibuprofen, or diclofenac in oral tablet or capsul from 1/1/99 to 6/30/01	Mean=5.1 months	200 mg (modal)	25 mg (modal)	Naproxen 1000 mg (modal)	NR	Primary: Combined endpoint of acute coronary syndrome and myocardial infarction (adjusted rate ratio)

Appendix F. Evidence Table 06[1]. CV Safety in observational studies

Author, Year Data source Sample size	Reference comparison	Celecoxib	Rofecoxib	NSAIDs	Subgroup information?	Notes
Andersohn 2006 UK General Practice Research Database (GPRD) Cases=3,643	Nonuse	1.56 (1.23, 1.98)	1.33 (1.06, 1.67)	Etoricoxib: 2.02 (1.08, 3.80) Valdecoxib: 4.26 (0.60, 30.27) Diclofenac: 1.36 (1.17, 1.58) Ibuprofen: 1.00 (0.83, 1.21) Naproxen: 1.16 (0.86, 1.58)	Risk increased with dose for celecoxib, etoricoxib, and rofecoxib. No significant interaction with age, gender, or presence of risk factors	
Graham 2005State of California Kaiser Permanente health care databaseCases=8,143	Celecoxib	n/a	(A) 1.59 (1.10, 2.32)(B) 1.47 (0.99, 2.17)(C) 3.58 (1.27, 10.11)	(A) 1.26 (1.00, 1.60)(B) 1.36 (1.06, 1.75)(C) 1.35 (1.06, 1.72)	3.8% taking anticoagulants	
Harrison-Woolrych 2005 New Zealand Intensive Medicines Monitoring Programme (IMMP) *Interim* analysis of 11,149 of 58,849 for who follow-up was complete	Rofecoxib	0.94 (95% CI 0.51, 1.70)	n/a	n/a	No dose effect	
Hippisley-Cox 2005 Case-controlQRESEARCH database (8/1/00-7/31/04) Cases: 9218	No use	1.21 (0.96, 1.54)	1.32 (1.09, 1.61)	(A) 1.27 (1.00, 1.61)(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	Adjusted for smoking, obesity, deprivation, aspirin

Appendix F. Evidence Table 06[1]. CV Safety in observational studies

Author, Year Data source Sample size	Reference comparison	Celecoxib	Rofecoxib	NSAIDs	Subgroup information?	Notes
Hudson 2005Database of hospital discharge summaries (4/1/00-3/31/02)n=1866	COX-2	NSAIDs vs celecoxib:(A) 1.21 (0.92, 1.60)(B) 1.54 (1.17, 2.04)(C) 1.26 (1.00, 1.57)	NSAIDs vs rofecoxib: (A) 1.04 (0.80, 1.36)(B) 1.07 (0.82, 1.39)(C) 0.99 (0.80, 1.22)	n/a	NR	
Johnson 2005 Denmark National Health Service registries Cases=10,280	Nonuser	Current user: 1.25 (0.97, 1.62); new user: 2.13 (1.45, 3.13)	Current user: 1.80 (1.47, 2.21); new user: 2.52 (1.45, 3.13)	(A) Current user: 1.50 (0.99, 2.29); new user: 1.65 (0.57, 4.83) (B) Current user: 1.68 (1.52, 1.85); new user: 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	
Kasliwal 2006 National Health Service prescription data (England) Rofecoxib n=15,268 Celecoxib n=17,458	Celecoxib	n/a	aRR (95% CI) (adjusted for age, age2, sex, and concomitant use of the combination of aspirin and/or antiplatelet/anticoagulant agents (a) 1.04 (0.50, 2.17) (b) 1.43 (0.86, 2.38) (c) 0.36 (0.01, 1.34)	n/a	(a) increased risk associated with age, sex, cc aspirin use, cc antiplatelet/anticoagulant agents (b) increased risk with all but sex (c) increased risk with the cc meds	
Kimmel 2005Hospitals in 5-county region (telephone interview)Cases: 1718	Nonselective NSAIDS	(A) 0.77 (0.40, 1.48) (in aspirin and nonaspirin users - like CLASS)(B) 0.81 (0.37, 1.77)	(B) 3.30 (1.37, 8.40) (among nonaspirin users - like VIGOR)(A) 2.04 (1.16, 3.60)	n/a		

Appendix F. Evidence Table 06[1]. CV Safety in observational studies

Author, Year Data source Sample size	Reference comparison	Celecoxib	Rofecoxib	NSAIDs	Subgroup information?	Notes
Langman 2004 MediPlus (UK) database of general clinical practices N=18,737	Rofecoxib	n/a	Combined non-selective NSAIDs vs rofecoxib: Overall=0.93 (0.73, 1.18); chronic and persistent users=1.07 (0.71-1.61)			
Layton 2003 National Health Service prescription data N=34,355	Meloxicam	n/a	vs meloxicam: (A) 1.38 (0.71, 2.67) (B) 1.68 (1.15, 2.46) (C) 0.29 (o.11, 0.78)	n/a	Significant association between age, sex and time, respectively, and event rates	Only adjusted for age and sex
Levesque 2005 Computerized health insurance and vital statistics databases of Quebec, Canada n=59724	NSAID nonusers	(A) 0.99 (0.85, 1.16) (B) 0.98 (0.83, 1.17) (C) 1.00 (0.78, 1.29)	(A) 1.24 (1.05, 1.46) (B) 1.21 (1.02, 1.43) (C) 1.73 (1.09, 2.76)	Naproxen 1.17 (0.75, 1.84) Meloxicam 1.06 (0.49, 2.30)	aspirin mitigates risk for low- but not high-dose rofecoxib use	
Mamdani 2003 Ontario healthcare administrative database N=166,964	General non-NSAID using population (adjusted risk ratio, 95% CI)	0.9 (0.7, 1.4)	1.0 (0.8, 1.4)	(A) 1.0 (0.6-1.7) (B) 1.2 (0.9, 1.4)		
Mamdani 2004 Ontario healthcare administrative database 4/17/00-3/31/01 N=145097	COX-2	Non-selective NSAID vs celecoxib: 1.4 (1.0, 1.9)	Non-selective NSAID vs rofecoxib: 1.5 (1.1, 2.1)	vs non-NSAID users: 1.4 (1.0-1.9)	History of heart failure admission w/I past 3 years increased risk	
Ray 2002Tennessee Medicaid program database1/1/99-6/30/01	Nonusers	0.96 (0.76-1.21)	(A) 1.03 (0.78, 1.35)(B) 1.70 (0.98, 2.95)	(A) 0.91 (0.78, 1.06(B) 0.93 (0.82, 1.06)	NR	

Appendix F. Evidence Table 06[1]. CV Safety in observational studies

Author, Year Data source Sample size	Reference comparison	Celecoxib	Rofecoxib	NSAIDs	Subgroup information?	Notes
Schlienger 2002 UK General Practice Research Database (GPRD) Cases=3,315	Nonuse	n/a	n/a	Ibuprofen: 1.17 (0.87, 1.58) Diclofenac: 1.38 (1.08, 1.77) Piroxicam: 1.65 (0.78, 3.49) Fenbufen: 2.06 (0.80, 5.30) Ketoprofen: 1.39 (0.77, 2.51) Indomethacin: 1.03 (0.58, 1.85) Fluriprofen: 2.26 (0.93, 5.46) Naproxen: 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 N=6,250	Other NSAIDs (excluding naproxen)	1.19 (0.93, 1.51)	0.99 (0.76, 1.30)	n/a		
Solomon 2002New Jersey Medicaid or Medicare and Pharmaceutical Assistance for the Aged and Disabled programs	Nonuser (control)	n/a	n/a	Comparison of specific NSAID use only reported for: Naproxen: OR 0.84 (0.72-0.98)Etodolac: OR 1.28 (1.00-1.64)Fenoprofen: OR 1.95 (1.16, 3.30)Ibuprofen: OR 1.02 (0.88, 1.18)	No dose- or duration-response relationship	
Solomon 2004 Chart review of prescription drug benefit program participants Cases=10,895	NSAID	(A) 0.95 (0.74, 1.21) (B) 0.98 (0.76, 1.26)	(A) 1.17 (0.90, 1.52) (B) 1.21 (0.92, 1.58)	n/a	Dose had an effect for rofecoxib but not celecoxib; couldn't adjust for aspirin use	

Appendix F. Evidence Table 06[1]. CV Safety in observational studies

Author, Year Data source Sample size	Reference comparison	Celecoxib	Rofecoxib	NSAIDs	Subgroup information?	Notes
Solomon 2004 Medicare Prescription Drug Benefit Program databases through Pennslyvania Pharmaceutical Assistance Contract for the Elderly (PACE) or the New Jersey Pharmaceutical Assistance Program for the Aged and Disabled (PAAD) (both programs for elderly individuals with low-moderate income levels) Cases=3,915	(A) nonspecific NSAID (B) no NSAID	(A) 0.9 (0.7, 1.1) (B) 1.0 (0.9, 1.2)	(A) 1.4 (1.1, 1.9) (B) 1.6 (1.3, 2.0)	n/a	Dose, duration had no effect; but presence of renal disease, liver disease, or congestic heart failure appeared in increase risk for rofecoxib users	
Velentgas 2005Insurance claims/administrative records of UnitedHealthcareN=424,584	Ibuprofen or diclofenac	Current: 1.03 (0.83, 1.27)Recent: 0.91 (0.70, 1.17)	Current: 1.35 (1.09, 1.68)Recent: 1.15 (0.88, 1.50)	NaproxenCurrent: 1.15 (0.93, 1.39)Recent: 0.86 (0.70, 1.04)	No dose-relationship; increased risk for males and for individuals with a cardiac history, peripheral arterial disease, diabetes, beta blocker use, nitrate use	

Appendix F. Evidence Table 07[1]. Trials of etoricoxib and lumiracoxib (Safety only)

Author Year (Quality Score)	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment
Etoricoxib studies					
Baraf, et al 2004 fair (abstract only)	Knee, hip, hand or spine OA patients	etoricoxib 90 mg/day vs diclofenac 50 mg tid	NR	use of "routine" medications allowed - definition of "routine" not specified	Primary: discontinuations due to clinical or lab GI AEs Secondary: patient global assessment using 4-point Likert scale
Curtis, et al 2005	<40 yrs with clinical and radiographic evidence of knee OA for at least 6 mos	etoricoxib 30, 60 or 90 mg/day dicofenac 150 mg/day	Discontinuation of previous therapy; time-frame not specified	NR	Efficacy: WOMAC and Investigator Global Assessment of Disease Status Safety: Clinical AEs determined by investigator
van der Heijde, et al 2004	AS patients meeting modified NY criteria; >18 yrs; diagnosis ≥ 6 mos prior to study; previous NSAID responder; routine NSAID use (25 of 30 days preceding study); use of approved antirheumatic therapy at a stable does for 3-6 mos; experiencing AS flare	etoricoxib 90 or 120 mg/day naproxen 1000 mg/day	NSAID washout, time not specified	acetaminophen	Primary endpoints: VAS and Bath Ankylosing Spondylitis Functional Index Secondary endpoints: patient's assessment using 4 pt Likert
Lumiracoxib					

Appendix F. Evidence Table 07[1]. Trials of etoricoxib and lumiracoxib (Safety only)

Author Year (Quality Score)	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment
Schnitzer, et al 2004 TARGET study good	Patients ≥ 50 yrs with hip, knee or hand OA according to ACR criteria or radiographically confirmed cervical or lumbar spine OA	lumiracoxib 400 mg/day naproxen 500 mg bid ibuprofen 800 mg tid 52 wks	NR	1) paracetamol ≤2g/day 2) up to 2 two-week periods of systemic corticosteroid therapy 3) one hyaluronic acid injection 4) up to 3 corticosteriod injections at least 8 wks apart and more than 4 wks prior to study assessment 5) up to 2 non-consecutive 3 wk courses of low-dose (equivalent of famotidine 30 mg/day) H2 receptor antagonists at least 4 wks between courses 6) up to 8 antacid tablets/day*	Primary endpoint of study: time-to-event distribution of definite or probable upper GI complications in patients not taking low-dose aspirin Secondary GI endpoint: time-to-event in patients taking low-dose aspirin and time-to-event of other GI events including 1) complicated and symptomatic upper GI ulcers; 2) symptomatic upper GI ulcers; 3) major episodes of GI bleeding; 4) evidence of anemia* CV endpoint: time-to-event of Antiplatelet Trialists' Collaboration (APTC) endpoint (composite of nonfatal MI, nonfatal stroke or CV-related death, adjucated as confirmed or probable)* Renal endpoint: time-to-event of clinically relevant lab abnormalities, defined as serum creatinine elevations ≥100% from baseline and/or proteinuria ≤ 3g/L* Hepatic endpoint: time-to-event of elevations in ALT > 5 x ULN and/or AST > 5 x ULN with total bilirubin elevations > 30 mg/L, adjucated as probably or possibly related to study medication* Tolerability endpoint: all serious and non-serious AEs, lab measures, time to discontinuation for any reason and time to discontinuation due to AEe*

Appendix F. Evidence Table 07[1]. Trials of etoricoxib and lumiracoxib (Safety only)

Author Year (Quality Score)	Timing of Outcome Assessment	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Etoricoxib studies					
Baraf, et al 2004 fair (abstract only)	Baseline and months 1, 4, 8, 12	mean age 64 yrs gender NR ethnicity NR		NR/ NR/ 7111	NR/ NR/ NR
Curtis, et al 2005	During active-comparator phase (wks 6-52) assessed at wks 6, 8, 14, 20, 26, 34, 42, 52	mean age 61.8 yrs 72% women 89% white	67.4% of patients ARA Function Class II	NR/ 617/ 550	262/ NR/ 550
van der Heijde, et al 2004	Baseline and wks 2, 4, 6, 8, 16, 26, 34, 43, 52	mean age 43.6 yrs 22.2% women ethnicity NR	History of iritis 33.6%; chronic peripheral arthritis 40.1%; corticosteroid use 25.3%; concomitant DMARD use 22.25%	500/ 387/ 374* (number of patients who entered second long-term phase of study wks 6-52)	90/NR/374
Lumiracoxib					
Schnitzer, et al 2004 TARGET study good	Study visits at wks 4. 13. 26. 39, 52 and 4 wks post-study Patient assessed pain using 5-point Likert scale at wks 13, 26, 39, 52; physician and patient assessed disease activity using 5-point Likert scale	mean age 63.5 yrs 76% women ethnicity NR		21,787/ 18,325/ 18,244	7161/ 40/ 18,244

Appendix F. Evidence Table 07[1]. Trials of etoricoxib and lumiracoxib (Safety only)

Author Year (Quality Score)	Results	Notes
Etoricoxib studies		
Baraf, et al 2004 fair (abstract only)	Cumulative discontinuations due to GI events lower with etoricoxib v diclofenac - 9.4 v 19.2 events/100 patient yrs (RR 0.5 95% CI: 0.43, 0.58; p < 0.001)	
Curtis, et al 2005	A higher percentage of diclofenac patients (22.5%) reported GI symptoms and discontinuted (4%) due to GI symptoms vs all etoricoxib doses (13.1% and 0% at 30mg/day, 14.7% and 1 % at 60 mg/day, 13.5% and 1.4% at 90 mg/day respectively) Only other AE which showed difference was lower extremity edema: higher with etoricoxib- 30 mg/day 4.5%; 60 mg/day 3.9%; 90 mg/day 3.4% and lowest with diclofenac 2.0%	
van der Heijde, et al 2004	Rates of serious AEs were similar (7.6%, 7.2% and 7.7% for etoricoxib 90mg, 120mg and naproxen 1000mg respectively) However, 2% of patients experienced serious CV AEs - all were etoricoxib patients (4, 90mg/day; 1, 120 mg/day)	
Lumiracoxib		
Schnitzer, et al 2004 TARGET study good	GI: Risk of any upper GI AE - lumiracoxib v NSAIDS (naproxen and ibuprofen) in aspirin and non-aspirin patients: .32 lumiracoxib patients v .91 NSAID patients HR 0.34 (0.22-0.52) CI 95%; p < 0.0001. CV: No SS differences, however lower risk of MI with naproxen v lumiracoxib (HR 1.77 (0.82-3.84); p=0.1471) and higher risk of MI with ibuprofen v lumiracoxib (HR 0.66 (0.21-2.09); p = 0.4833) Renal: No SS difference b/t lumiracoxib and NSAIDs for renal endpoint or serious liver AEs. SS difference in transaminase concentrations 3x above upper limit of normal between lumiracoxib and NSAIDs (HR 3.97 (2.96-5.32); p<0.0001) Transaminase concetrations were reversed upon drug discontinuation.	Supratherapeutic dose of lumiracoxib used (2-4 x greater than typical OA dosage) *Farkouh ME. Kirshner H. Harrington RA. Ruland S. Verheugt FW. Schnitzer TJ. Burmester GR. Mysler E. Hochberg MC. Doherty M. Ehrsam E. Gitton X. Krammer G. Mellein B. Gimona A. Matchaba P. Hawkey CJ. Chesebro JH. TARGET Study Group. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial.[see comment]. Lancet. 364(9435):675-84, 2004 Aug 21-27.* provides a more detailed analysis of CV events, however same data is used.

* reported in: Hawkey CJ. Farkouh M. Gitton X. Ehrsam E. Huels J. Richardson P. Therapeutic arthritis research and gastrointestinal event trial of lumiracoxib - study design and patient demographics. Alimentary Pharmacology & Therapeutics. 20(1):51-63, 2004 Jul 1.

Appendix F. Evidence Table 07[1]. Trials of etoricoxib and lumiracoxib (Safety only)

Author Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Etoricoxib studies						
Curtis, et al 2005	yes	yes	yes	yes	unclear ("study staff" reported as blinded)	unclear ("study staff" reported as blinded)
van der Heijde, et al 2004	yes	yes	yes	yes	NR	NR
Lumiracoxib						
Schnitzer, et al2004TARGET study	yes	yes	yes	yes	yes	yes

Appendix F. Evidence Table 07[1]. Trials of etoricoxib and lumiracoxib (Safety only)

Author Year	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Funding
Etoricoxib studies							
Curtis, et al 2005	yes	no/yes/no/no	no	unclear, only mean percentages reported	no	fair	Merck & Co.
van der Heijde, et al 2004	yes	no/no/no/no	no	no	no	fair	NR
Lumiracoxib							
Schnitzer, et al2004TARGET study	yes	no/no/no/no	no	no for efficacy; yes for safety	no	good	Novartis Pharma AG, Switzerland

Appendix F. Evidence Table 07[1]. Trials of etoricoxib and lumiracoxib (Safety only)

Author Year	Number screened/ eligible/enrolled	Exclusion criteria	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding
Etoricoxib studies						
Curtis, et al 2005	NR/NR/550	Significant renal impairment; clinically significant abnormalities on screening physical or lab examinations; class III/IV angina or uncontrolled CHF; uncontrolled hypertension; stroke or tranisient ischemic heart disease within 2 yrs; active hepatic disease; recent neoplastic disease; acute meniscal injury to the study joint within 2 yrs; arthroscopy in study joint within 6 mos; weight in excess of 280 lbs; allergy to acetaminophen or NSAIDs; use of systemic corticosteroids, warfarin, low-dose aspirin, ticlopidine, intra-articular steroids; previous AE associated with topical analgesic use.	NR/NR	no	NA	Merck & Co.

Appendix F. Evidence Table 07[1]. Trials of etoricoxib and lumiracoxib (Safety only)

Author Year	Number screened/ eligible/enrolled	Exclusion criteria	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding
van der Heijde, et al 2004	NR/NR/374	Concurrent rheumatic disease that could confound efficacy; pts with acute peripheral articular disease; chronic peripheral arthritis; use of corticosteroid therapy within 1 mo; use of analgesics within 3 days through wk 6 of study; use of non-study NSAID or COX-2.	NR/washout length not specified	no	NA	NR
Lumiracoxib						
Schnitzer, et al2004TARGET study	21,787/NR/18,325	Use of PPIs, misoprostol or full-dose H2 agonists; active upper GI ulceration in previous 30 days; upper GI bleeding within 1 yr; history of gastroduodenal perforation or obstruction; history of MI, stroke, coronary bypass graft, invasive coronary revascularization, new-onset angina within previous 6 mos; ECG evidence of recent silent MI; severe CHF.	NR/NR	no	NA	Novartis Pharma AG, Switzerland

Appendix F. Evidence Table 08[1]. Systematic reviews of NSAIDs

Author Year	(1) Aims	(2) Time period covered	(3) Eligibility criteria	(4) Number of patients	(5) Characteristics of identified articles: study designs	(6) Characteristics of identified articles: populations
Rostom 2005	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
Rubenstein 2005	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
Towheed 2004	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.

Appendix F. Evidence Table 08[1]. Systematic reviews of NSAIDs

Author Year	(1) Aims	(2) Time period covered	(3) Eligibility criteria	(4) Number of patients	(5) Characteristics of identified articles: study designs	(6) Characteristics of identified articles: populations
Watson2004	To determine difference in efficacy of NSAIDs in treatment of knee OA.	1966 - November, 1996 MEDLINE1980-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.

Appendix F. Evidence Table 08[1]. Systematic reviews of NSAIDs

Author Year	(7) Characteristics of identified articles: interventions	(8) Main results
Rostom 2005	18 NSAID v placebo; 33 diclofenac studies; 12 ibuprofen studies; 14 naproxen studies; 5 meloxicam studies; 8 rofecoxib studies; 5 celecoxib studies; 1 valdecoxib study.	Safety: Among all comparisons, no NSAID had higher rates of renal serious adverse events, hospitalizations or death. Diclofenac and rofecoxib both showed higher rates of amniotransferase 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%)
Rubenstein 2005	6 studies: unspecified NSAIDs (including any of the folowing: 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.	Safety: 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 hospitaliztion 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.
Towheed 2004	Placebo v: etodolac, tenoxicam, ketoprofen, diacerhein Head to head: flurbiprofen v sulindac diclofenac v naproxen proquazone v naproxen piroxicam v naproxen diclofenac v ibuprofen sulindac v ibuprofen carprofen v diclofenac piroxicam v indomethacin naproxen v indomethacin tenoxicam v 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. Safety 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.

Appendix F. Evidence Table 08[1]. Systematic reviews of NSAIDs

Author Year	(7) Characteristics of identified articles: interventions	(8) Main results
Watson2004	Etodolac (600 mg and 800 mg) v diclofenac (100-150 mg), naproxen (1000 mg), piroxicam (20 mg), indomethacin (150 mg), nabumetone (1500 mg)Nabumetone (1000 mg) v diclofenac (100 mg)Tenoxicam (20 mg) v piroxicam (20 mg)Tenoxicam (20 mg) v diclofenac (150 mg)Flurbiprofen (150 mg) v diclofenac (150 mg)Naproxen (750 mg) v diclofenac (150 mg)	EfficacyWithdrawal 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 inequivalent 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, inequivalent dose comparisons resulted in questionable validity of results.Physical function: Only one trial showed a SS difference in favor of tenoxicam v diclofenac (OR 3.93 CI: 95% 1.07-14.44)

Appendix F. Evidence Table 08[1]. Systematic reviews of NSAIDs

Author Year	(9) Subgroups	(10) Comments
Rostom 2005	Use of high dose of diclofenac (>100mg/day) was associated with a higher proportion of patients having amniotransferase elevation >3x ULN. No SS differences for other subgroups (high dose rofecoxib; longer duration for all comparators including placebo)	Assessed adverse events only
Rubenstein 2005	not reported	Assessed adverse events only
Towheed 2004	not reported	SR limited by lack of standardization of OA diagnosis and OA outcomes Results suggest that best NSAID varies widely depending on a particular patient
Watson2004	not reported	Poor methodology resulted in little SS evidence favoring one NSAID over anotherOnly 5 of 16 trials compared equivalent dosing of trial and comparators

Appendix F. Evidence Table 08[1]. Systematic reviews of NSAIDs

Author Year	(1) Is there a clear review question?	(2) Were there explicit inclusion/ exclusion criteria reported relating to selection of the primary studies?	(3) Is there evidence of a substantial effort to search for all relevant research?	(4) Was the literature search strategy stated?	(5) Is the validity of included studies adequately assessed?	(6) Is sufficient detail of the individual studies presented?	(7) Are there any important studies missing?	(8) Are the primary studies summarized appropriately?	(9) Quality rating
Rostom 2005	yes	yes	yes	yes	yes	yes	no	yes	good
Rubenstein 2005	yes	yes	yes	yes	yes	yes	no	yes	good
Towheed 2004	yes	yes	yes	yes	yes	yes	no	yes	good
Watson 2004	yes	yes	yes	yes	yes	yes	no	yes	good

Appendix F. Evidence Table 09[1]. COX-2s vs NSAIDs - tolerability

Trial	Focus	Subjects	Coxib dose	NSAIDs (mg)	Number of subjects*	Duration (weeks)
Celecoxib						
Ekman	efficacy and tolerability	Ankle sprain	400 mg daily	ibuprofen 2400 mg daily	445	10 days
Bertin	efficacy and tolerability	Acute shoulder pain	400 mg daily	naproxen 100 mg daily	203	14 days
Dougados	efficacy	Ankylosing spondylitis with flare	100 bid	ketoprofen 100 bid	170	6
McKenna	efficacy and tolerability	OA of the knee with flare	100 bid	diclofenac 50 tid	400	6
Bensen/Zhao	efficacy	OA of the knee with flare	200 bid	naproxen 500 bid	1004	12
Goldstein	endoscopic ulcers	OA and RA with no ulcer on EGD	200 bid	naproxen 500 bid	537	12
Simon/Zhao	efficacy and endoscopic ulcers	RA with flare and no ulcer on EGD	100, 200, or 400 bid	naproxen 500 bid	918	12
Emery	endoscopic ulcers	RA	200 bid	diclofenac 75 bid	655	24
Silverstein (CLASS)	serious GI events	OA and RA	400 bid	ibuprofen 800 tid or diclofenac 75 bid	7968	24
Kivitz	efficacy and tolerability	OA	100-400 mg daily	naproxen 100 mg daily	1061	12
Simon	efficacy and tolerability	RA	100-400 mg bid	naproxen 500 mg bid	1149	12
Etoricoxib						
Baraf 2004						
Curtis 2005						
van der Heijde 2004						
Lumiracoxib						
Schnitzer 2004						

Appendix F. Evidence Table 09[1]. COX-2s vs NSAIDs - tolerability

Trial	Focus	Subjects	Coxib dose	NSAIDs (mg)	Number of subjects*	Duration (weeks)
Rofecoxib						
Niccoli	tolerability	OA of hand, hip or knee	25 mg	diclofenac 50 tid	90	2
Acevado	adverse events	OA, negative FOBT	12.5 mg	diclofenac 50 mg/misoprostol 200 mcg bid	483	6
Saag	efficacy and tolerability	OA of knee or hip with flare (for NSAID users) or acetominophen user. Excluded aspirin 81mg users.	25 mg	ibuprofen 800 tid	667	6
Day	efficacy and tolerability	OA of knee or hip with flare (for NSAID users) or acetominophen user	25	ibuprofen 800 tid	735	6
Truitt	efficacy and tolerability	OA knee or hip with flare, >80 years old	25	nabumetone 1500	250	6
Myllykangas-Luosujarvi	efficacy and tolerability	OA of the knee or hip	12.5	naproxen 500 bid	944	6
Lisse	efficacy and tolerability	OA of the knee, hip, hand, or spine	25	naproxen 500 bid	5557	12
Hawkey	tolerability	RA	50	naproxen 500 bid	660	12
Hawkey	endoscopic ulcers	OA with no ulcer on EGD	25	ibuprofen 800 tid	581	18
Laine (044)	endoscopic ulcers	OA with no ulcer or esophagitis on EGD	25, 50	ibuprofen 800 tid	565	24
Bombadier (VIGOR)	serious GI events	RA, negative FOBT	50	naproxen 500 bid	8076	52
Cannon (035)	efficacy	OA of knee or hip with flare (for NSAID users) or acetominophen user	25	diclofenac 50 tid	784	52
Saag	efficacy and tolerability	OA of knee or hip with flare (for NSAID users) or acetominophen user. Excluded aspirin 81 mg users.	25	diclofenac 50 tid	693	52

Appendix F. Evidence Table 09[1]. COX-2s vs NSAIDs - tolerability

Trial	Focus	Subjects	Coxib dose	NSAIDs (mg)	Number of subjects*	Duration (weeks)
Valdecoxib						
Makarowski	efficacy and tolerability	OA of the hip	5, 10	naproxen 500 bid	349	12
Pavelka	efficacy and tolerability	RA	20, 40	diclofenac 75 mg SR bid	722	26

GI - gastrointestinal; HTN - hypertension; CHF - congestive heart failure; NR - not reported; OA - osteoarthritis;
EGD - esophagogastroduodenoscopy; RA - rheumatoid arthritis; FOBT-fecal occult blood test; LFT - liver function test
*Excludes subjects randomized to
placebo
**inadequately reported
§ Reported GI adverse events leading to discontinuation, but did not report total GI adverse events
†statistically significant
‖mean change (%); ¦only side effects not causing withdrawal

Appendix F. Evidence Table 09[1]. COX-2s vs NSAIDs - tolerability

Trial	Withdrawals due to adverse events		Total adverse events		GI adverse events		Elevated creatinine, HTN, CHF, or edema		Comment
Celecoxib	coxib	NSAID	coxib	NSAID	coxib	NSAID	coxib	NSAID	
Ekman	<1%	0%	24.0%	27.0%	Total GI nr	Total GI nr	nr	nr	
Bertin	nr	nr	40.4%	44.7%	20.2%	25.2%	nr	nr	
Dougados	6.3%	1.1%	68.0%	60.0%	32.2%	33.8%	nr	nr	
McKenna	7.0%	11.0%	50.0%	54.0%	18.0%	25.0%	5.0%	3.0%	**
Bensen/Zhao	10.0%	8.0%	65.0%	63.0%	24.0%	32.0%	4.0%	1.0%	
Goldstein	7.0%	9.0%	70.0%	70.0%	34.0%	40.0%	nr	nr	
Simon/Zhao	5.5%	5.3%	62%-68%	65.0%	26.0%	31.0%	2.0%	2.0%	
Emery	nr	nr	68.0%	73.0%	36.0%	48.0%	nr	nr	5 NSAID patients admitted for adverse events. Lower hematocrits and higher LFTs in the NSAID group.
Silverstein (CLASS)	18.4%	20.6%	48.5%	56.8%	31.4%†	36.8%	5%†	6.6%	
Kivitz	8% (100 mg); 13% (200 mg); 12% (400 mg)	14%	58% (100 mg); 66% (200 mg); 62% (400 mg)	63.0%	17% (100mg); 29% (200mg); 30% (400mg)	35.0%	Edema 1% (100mg); 1% (200mg); 5% (400mg)	Edema 3%	
Simon	5% (100mg); 7% (200mg); 6% (400mg)	5%	68% (100mg); 63% (200 mg); 62% (400mg)	65.0%	28% (100mg); 25% (200mg); 26% (400mg)	31.0%	Edema1% (100mg); 2% (200mg); 2% (200mg)HTN0% (100mg); <1% (200mg); <1% (400mg)	Edema2%HTN<1%	
Etoricoxib									
Baraf 2004									

Appendix F. Evidence Table 09[1]. COX-2s vs NSAIDs - tolerability

Trial	Withdrawals due to adverse events		Total adverse events		GI adverse events		Elevated creatinine, HTN, CHF, or edema		Comment
Curtis 2005									
van der Heijde 2004									
Lumiracoxib									
Schnitzer 2004									
Rofecoxib									
Niccoli	11.7%	3.2%	33.3%¦	26.6%¦	nr	nr	24%‖, nr, nr, nr	5.7%‖, nr, nr, nr	
Acevado	4.1%	9.1%	52.9%†	73.0%	28.9%	48.5%	nr	nr	
Saag	no difference (numbers not given)		nr	nr	3.5%	3.2%	5.3%	2.3%	
Day	3.7%	8.4%	53.3%	51.8%	higher for NSAID (numbers not given)		no difference (numbers not given)		
Truitt	8.9%	7.0%	nr	nr	nr	nr	incompletely reported; probably no difference.		
Myllykangas-Luosujarvi	nr	nr	43.3%	48.2%	13.4%†	24.1%	nr; 1.9%; nr; 3.4%(lower extremity), 0.2% (peripheral)	nr; 1.7%; nr; 2.3%(lower extremity), 1.4% (peripheral)	
Lisse	nr	nr	30.0%	30.0%	5.9%§†	8.1%§	nr, 2.9%, nr, 3.5%	nr, 2.4%, nr, 3.8%	
Hawkey	5%†	9.1%	62.1%	66.4%	3.7%§	6.8%§	nr, 6.4%, 0.5%, 1.4%	nr, 0.9%, 0.0%, 0.0%	
Hawkey	5.6%	9.8%	80.1%	80.0%	no difference		nr	nr	
Laine (044)	10.3%	14.0%	78.3%	74.7%	nr	nr	nr	nr	
Bombadier (VIGOR)	16,4%	16.1%			3.5%§†	4.9%	1.2%	0.9%	

Appendix F. Evidence Table 09[1]. COX-2s vs NSAIDs - tolerability

Trial	Withdrawals due to adverse events		Total adverse events		GI adverse events		Elevated creatinine, HTN, CHF, or edema		Comment
Cannon (035)	12.5%	15.3%	84.0%	86.2%	no difference (numbers not given)		no differences		
Saag	significantly higher for NSAID (numbers not given)		nr	nr	5.2%	8.3%	no difference (numbers not given)		Discontinuation for elevated ALT higher in NSAID group.
Valdecoxib									
Makarowski	9%	12.70%	53%	60.20%	no difference		nr	nr	
Pavelka	9.8%, 10.5%	15.20%	67%, 65%	73.0%	39.4%†, 40.1%	49.4%	nr	nr	

Appendix F. Evidence Table 10[1]. Systematic reviews of COX-2 inhibitors

Author Year	(1) Aims	(2) Time period covered	(3) Eligibility criteria	(4) Number of patients	(5) Characteristics of identified articles: study designs	(6) Characteristics of identified articles: populations
Celecoxib reviews						
Garner 2004 (Celecoxib for RA)	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.
Ashcroft 2001	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.
Rofecoxib reviews						

Appendix F. Evidence Table 10[1]. Systematic reviews of COX-2 inhibitors

Author Year	(1) Aims	(2) Time period covered	(3) Eligibility criteria	(4) Number of patients	(5) Characteristics of identified articles: study designs	(6) Characteristics of identified articles: populations
Juni 2004	To establish whether robust evidence, aside from the published findings of the VIGOR trial, on the adverse effects of rofecoxib was available prior to September, 2004.	from "inception" of database through September, 2004 MEDLINE EMBASE, CINAHL and CCTR	RCTs in adults with chronic musculoskeletal disorders that compared rofecoxib with other NSAIDs or placebo and cohort and case-control studies of CV risk and naproxen.	25,273	18 RCTs - 12 OA, 5 RA, 1 low back pain. 3 trails had 2 arms, 7 had 3 arms, 8 had four arms. 11 observational studies.	No restrictions based on age or sex.
Garner 2004 (Rofecoxib for RA)	To assess the efficacy and toxicity of rofecoxib in treating RA.	1966 - December, 2000 MEDLINE 1980 - December 2000 EMBASE CDSR, CCTR though Issue 4: 2000 HTA database (no date supplied)	Parallel design, placebo-controlled and comparative RCTs evaluating efficacy and/or toxicity of rofecoxib in RA. Outcome criteria had to be available to evaluate efficacy and/or toxicity, such as OMERACT outcomes.	8,734	2 RCTs: 1 parallel-group double-blinded placebo controlled and 1 parallel-group double-blinded active comparator	Both trials assessed patients diagnosed with RA with no restrictions based on age or sex.
Garner2004(Rofecoxib for OA)	To establish the efficacy and safety of rofecoxib in the management of OA.	1966-August, 2004MEDLINE1980-week 36, 2004EMBASECCTR through Issue 3: 2004	Published RCTs of parallel design that used any accepted method to assess OA severity or progression.	21551	26 published RCTs: 25 parallel- group double-blinded and 1 single-blinded study.	Patients with OA with no restrictions based on age or sex.
Valdecoxib reviews						

Appendix F. Evidence Table 10[1]. Systematic reviews of COX-2 inhibitors

Author Year	(1) Aims	(2) Time period covered	(3) Eligibility criteria	(4) Number of patients	(5) Characteristics of identified articles: study designs	(6) Characteristics of identified articles: populations
Eisen 2005	To compare incidence of upper GI disturbances (abdominal pain, dyspepsia or nausea) with valdecoxib, nonspecific NSAIDs and placebo in patients with OA and RA.	All included studies were published in 2002. Method of identifing included studies was not specified.	Not reported	4,394	5 randomized, double-blind 12-week phase III trials; Three OA studies and 2 RA studies were included.	Patients were eligible if the met ACR criteria for RA or OA. Reasons for patient exclusion included serious concomitant GI, renal, hepatic or coagulation disorders, malignancy or diagnosis with other forms of inflammatory or secondary non-inflammatory arthritis.
Etoricoxib (included for safety only)						
Ramey, et al2005	To determine the incidence of upper GI perforations, symptomatic gastroduodenal ulcers and upper GI bleeding (PUBs) in etoricoib users compared to NSAID users	Trials completed by June 2003	NR	5441	10 RCTs 9 active-comparator and placebo-controlled, one active-comparator only	OA (4 studies), RA (3 studies), ankylosing spondylitis (1 study), endoscopy trials (2 12-wk studies)

Appendix F. Evidence Table 10[1]. Systematic reviews of COX-2 inhibitors

Author Year	(1) Aims	(2) Time period covered	(3) Eligibility criteria	(4) Number of patients	(5) Characteristics of identified articles: study designs	(6) Characteristics of identified articles: populations
Lumiracoxib (included for safety only)						
Matchaba, et al 2005	To determine the risk of CV events with lumiracoxib through meta-analysis	dates NR	All clinical studies >1wk and <52wks in Novartis Lumiracoxib Clinical Trial Database included	34,668	22 RCTs: 21 published trials, including 8 placebo-controlled and 1 unpublished (also placebo-controlled)	OA (15 trials) and RA (7 tri patients
Multiple COX-2s (reported adverse events only)						
Kearney, et al 2006	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.

Appendix F. Evidence Table 10[1]. Systematic reviews of COX-2 inhibitors

Author Year	**(7) Characteristics of identified articles: interventions**	**(8) Main results**
Celecoxib reviews		
Garner 2004 (Celecoxib for RA)	1 study celecoxib (200mg 2x/day) v diclofenac (75mg 2x/day) 1 study celecoxib (400mg 2x/day) v diclofenac (75 mg 2x/day) or ibuprofen (800mg 3x/day) 1 study celecoxib (200mg 2x/day) v naproxen (500mg 2x/day) 1 study celecoxib at varied doses (40mg, 200mg or 400mg 2x/day each) v placebo 1 study celecoxib at varied doses (100mg, 200mg or 400mg 2x/day each) v naproxen (500 mg 2x/day) or placebo	Efficacy Celecoxib v 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.)Percentage 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 v diclofenac: Withdrawals due to lack of efficacy were essentially the same for both interventions (8% for celecoxib and 7% for diclofenac). Percentage 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 v 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%. Percentage of patients showing improvement: 100 mg - 40%; 200mg - 44% and 51%; 400mg - 39% and 52%; placebo - 29% for both studies.There was no statistically significant difference between 40mg and placebo. Safety Celecoxib v 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 v 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 v 19% of diclofenac patients (RR 0.5 (95% CI: 0.4, 0.8)). Two diclofenac patients required hospitalization due to gastric erosions/ulcer. Celecoxib v placebo: For one study, only number of patients withdrawn due to AEs was reported. There was no signifcant difference amongst doses or v 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%.) No clinically significant GI events were reported.

Appendix F. Evidence Table 10[1]. Systematic reviews of COX-2 inhibitors

Author Year	**(7) Characteristics of identified articles: interventions**	**(8) Main results**
Ashcroft 2001	Various doses of celecoxib ranging from 50mg - 400 mg/day v naproxen (500mg), diclofenac (75mg) or ibuprofen (800 mg)	Celecoxib v diclofenac (200 mg v 75mg 2x/day) One study found no difference b/t celecoxib v 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 v modified-relsease diclofenac 75mg 2x/day. RR 0.24 (95% CI: 0.16-0.40) Celecoxib v ibuprofen (200mg v 800mg 3x/day) Fewer ulcers were found at 12wks w/celecoxib RR 0.30 (95% CI: 0.20-0.46) Celecoxib v naproxen (doses 100mg - 800mg v 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 v 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)
Rofecoxib reviews		
Juni 2004	Rofecoxib at various doses ranging from 12.5mg to 50mg v diclofenac (150mg), ibuprofen (2400mg), nabumetone (1000mg or 1500mg, naproxen (1000mg) or placebo	All serious CV event risk based on available comparisons: 85 AEs in rofecoxib groups, 38 in control groups. RR 1.55 (95%: CI 1.05-2.29) MI risk based on all comparisons: 52 AEs in rofecoxib groups, 12 in control groups.RR 2.24 (95% CI: 1.24-4.02) Stroke risk for all available comparisons: 25 AEs in rofecoxib group, 19 in control groups. RR 1.02 (95% CI: 0.54-1.93) Cardioprotective effect of naproxen: Meta-analysis of 11 studies showed RR 0.86 (95% CI: 0.75-0.99) No difference compared to non-naproxen NSAIDs RR 0.86 (95% CI: 0.75-0.99) For both analyses there was considerable between-study hetereogeneity (I^2 68% and 43% respectively) Studies funded by Merck indicated larger cardioprotective effects (p=0.001 and p=0.056, respectively, by test of interaction.)

Appendix F. Evidence Table 10[1]. Systematic reviews of COX-2 inhibitors

Author Year	(7) Characteristics of identified articles: interventions	(8) Main results
Garner 2004 (Rofecoxib for RA)	1 8-week trial rofecoxib 5mg, 25mg or 50mg/day v placebo; 1 trial 50mg/day rofecoxib v 500mg naproxen 2x/day. Trial duration 4 weeks to 13 months.	Efficacy Rofecoxib v placebo: No SS difference between 5mg rofecoxib and placebo (10.1% and 14.2% respectively.) ACR 20 responders who received 25mg or 50mg (48% and 53% of patients, respectively) was statistically significantly more than those patients receiving placebo (35%) RR 1.39 CI:1.07, 1.80 and RR 1.55 CI: 1.20, 1.99 respectively.) There were fewer withdrawls due to lack of efficacy in patients taking 25mg (6.4%) or 50mg (6.8%) v placebo (14.3%) RR 0.45 CI: 0.23, 0.89 and RR 0.48 CI 0.24 and 0.94 respectively) and overall at 25 mg (15.2%,) 50mg (16.1%) and placebo (22.0%) (RR 0.69 CI: 0.44, 1.09 and RR 0.72 CI: 0.47, 1.15.) Rofecoxib v naproxen: No statistically significant differences between comparators for withdrawals due to lack of efficacy: rofecoxib withdrawals 6.3% v naproxen withdrawals 6.5% (RR 0.97 CI: 0.82, 1.14) Safety Rofecoxib v placebo: There was no statistically significant difference in the number of withdrawals due to AEs for all doses of rofecoxib and placebo (placebo - 3.0%, 5 mg - 3.2%, 25 mg - 4.7% and 50 mg - 6.2%) except that more patients experienced rash at 50mg. Rofecoxib v naproxen:WIthdrawal rates due to AEs were similar for rofecoxib (16.4% of patients) v naproxen (16.1%) (RR 1.02 CI: 0.92, 1.12)
Garner2004(Rofecoxib for OA)	Rofecoxib v:-NSAIDsdiclofenac (3 RCTs)ibuprofen (4 RCTs)nabumetone (3 RCTs)naproxen (3 RCTs)nimesulide (2 RCTs)diclofenac+misoprostol (1 RCT)-Other Cox-2scelecoxib and paracetamol (2 studies)celecoxib (10 studies)valdecoxib (1 study)-Placebo (12 RCTs)	EfficacyRofecoxib v NSAIDs: Study design greatly effected the ability to pool data regarding rofecoxib v various NSAIDs. For diclofenac, ibuprofen, naproxen, nabumetone, diclofenac+misoprostol, and nimesulide all studies showed that efficacy was not statistically significantly greater for rofecoxib and the comparator, however nearly all the studies suffered from inconsistent methodologies and data reporting.Rofecoxib v Cox-2s: There was no SS difference between withdrawals due to lack of efficacy between rofecoxiib 25mg and celecoxib 200mg at 6 wks. RR: 0.76 CI: 0.47, 1.24). Patient global response pooled data indicated that patients taking 25mg rofecoxib v celecoxib had good-excellent improvement (RR 1.14 CI: 1.05, 1.24)Rofecoxib v placebo: The result of meta-analysis showed that rofecoxib was superior to placebo for most outcome measures (e.g. WOMAC, patient/investigator ratings.) NNT with rofecoxib v placebo to achieve improvement in patient global assessment was 5 (95% CI: 4, 6)Safety1) GI eventsRofecoxib v NSAIDs: Rates of GI events difficult to interpret due to methodology of included studies and lack of reported data. The only statistically significant difference relating to GI events was that rofecoxib caused less GI pain than diclofenac (0.8% in the rofecoxib group and 5% in the diclofenac group.) Naproxen caused more withdrawals due to GI events. Endoscopic evidence indicates that rofecoxib at 25mg and 50mg caused fewer gastric ulcers and fewer duodenal ulcers at 25mg when compared to ibuprofen.Rofecoxib v placebo: The risk of GI AE was not significantly increased with rofecoxib for most studies, however one study reported increased GI events at doses of 25mg RR 3.39 CI: 1.47, 7.84) Endoscopic evaluation at 18wks showed no difference in ulcers or erosions escept that rofecoxib caused fewer large ulcers/erosions (> 5mm) RR 0.42 CI: 0.20, 0.86.2) CV eventsRofecoxib v NSAIDs: Many studies did not report specific data on CV events. One study of rofecoxib v diclofenac reported withdrawal due to CV events (hypertension: 3/231, palpitation 4/232, TIA 3/230) RR 1.0 (95% CI: 0.2, 4.9) for diclofenac v RR 1.3 (95% CI: 0.3, 5.8) for rofecoxib. For rofecoxib v naproxen, one withdrawal due to CHF was reported in the rofecoxib group of the Naproxen 901 studies. The ADVANTAGE study report 5 patients with MI in the rofecoxib group v 1 in the naproxen group (RR 4.98 CI: 0.58, 42.57) and 6 strokes in the rofecoxib group v 0 in the naproxen group (RR 1.22 CI: 0.89,

Appendix F. Evidence Table 10[1]. Systematic reviews of COX-2 inhibitors

Author Year	(7) Characteristics of identified articles: interventions	(8) Main results
		1.68.) Higher rates of CV events occured in patient with pre-existing hypertention.Rofecoxib v placebo: Two trials that reported withdrawals due to CV events showed no SS difference between rofecoxib withdrawals and placebo withdrawals.3) Other AEsRofecoxib v NSAIDs: Rofecoxib seems to be associated with increased systolic blood pressure compared to celecoxib, diclofenac and naproxen. One study also reported an increase in diastolic blood pressure. Other reported AEs include oedema (v diclofenac, RR 19.20 CIL 1.17, 314.55), hypertension (v diclofenac 15.54 CI: 0.93, 258.58) and weight gain (v diclofenac RR 19.20 CI: 1.17, 314.55)Rofecoxib v placebo: Overall risk of AEs was statistically significantly higher at 6wks at 12.5mg. RR 3.95 CI: 1.05, 14.63
Valdecoxib reviews		
Eisen 2005	OA patients were randomly assigned to one of five treatment groups - placebo, valdecoxib (5, 10 or 20 mg) or nonspecific NSAID (500 mg naproxen, 800 mg ibuprofen, or 75 mg diclofenac.) RA patients were randomly assigned to one of five treatment groups - placebo, valdecoxib (10, 20 or 40 mg) or naproxen (500 mg.)weeks. Low-dose aspirin (< 325 mg/day) and acetaminophen (< 2 g/day) were permitted as concomitant medications. Prednisone up to 10 mg/day was permitted for RA patients.	Cumulative 12-wk incidence of any moderate to severe upper GI AE based on Kaplan-Meier time-to-event estimates were: NSAIDs (n=1185): 15.0 (12.8-17.2) Valdecoxib (n=2236): 9.0 (7.7-10.4) Placebo (n=973): 10.5 (7.3-13.7) Pooled analysis demonstrated decrease in dyspepsia and inprovement in GI tolerability for valdecoxib v NSAIDs.
Etoricoxib (included for safety only)		
Ramey, et al2005	For all PUBs, etoricoxib v NSAIDs RR 0.48% (95% CI).32, 0.73; p<0.001	Effect in favor of etoricoxib remained across the following subgroups: age; history of PUB; GPA users; gender; disease (OA or RA) and ethnicity

Appendix F. Evidence Table 10[1]. Systematic reviews of COX-2 inhibitors

Author Year	**(7) Characteristics of identified articles: interventions**	**(8) Main results**
Lumiracoxib (included for safety only)		
Matchaba, et al 2005	15 studies lumiracoxib (200-1200mg) v celecoxib (200mg), diclofenac (75 mg bid), ibuprofen (800mg tid), naproxen (500mg bid) or rofecoxib (25 mg), 8 studies lumiracoxib (100-400mg) v placebo	For all comparisons, no SS difference was found in CV event rates with lumiracoxib v comparator. Lumiracoxib compared less favorably with naproxen (0.37% event rate with lumiracoxib v 0.22% event rate with naproxen) but again did not meet statistical significance.
Multiple COX-2s (reported adverse events only)		
Kearney, et al 2006		NA

Appendix F. Evidence Table 10[1]. Systematic reviews of COX-2 inhibitors

Author Year	(9) Subgroups	(10) Adverse events	(11) Comments
Celecoxib reviews			
Garner 2004 (Celecoxib for RA)	Celecoxib v placebo No effect for H. pylori status, concurrent aspirin or corticosteriod use, history of GI tract bleeding and ulcers. No other subgroup analysis reported	Celecoxib v diclofenac Total AEs: 68% v 73% RR 0.9 (95% CI: 0.9, 1.0) GI: 36% v 48% RR 0.8 (95% CI: 0.6, 0.9) Peripheral oedema: 3% v 2% Hypertension: 1% v 2% Celecoxib v 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 v 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)	Study design problems with both CLASS and VIGOR studies
Ashcroft 2001	Not reported	Celecoxib v diclofenac Risk of endoscopically detected ulcer - pooled analysis: RR 0.24 (95% CI: 0.16-0.40) Celecoxib v ibuprofen Risk of endoscopically detected ulcer - RR 0.30 (95% CI: 0.20-0.46) Celecoxib v 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 v 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)	
Rofecoxib reviews			

Appendix F. Evidence Table 10[1]. Systematic reviews of COX-2 inhibitors

Author Year	**(9) Subgroups**	**(10) Adverse events**	**(11) Comments**
Juni 2004	Not reported	MI - RR (95% CI) Rofecoxib: 12.5mg: 2.71 (0.99-7.44) 25mg: 1.37 (0.52-3.61) 50mg: 2.83 (1.24-6.43) Naproxen: 2.93 (1.36-6.33) non-Naproxen NSAIDs: 1.55 (0.55-4.36) Placebo: 1.04 (0.34-3.12)	Restricitve inclusion criteria resulted in few study participants with history of CV disease. Other studies (Ray et al, 2002) looking at rofecoxib use in routine clinical settings report that 40% of rofecoxib patients had hisotry of CV disease resulting in an eight-fold increase in MI (11.6 v 1.45 per 1000 patient years)
Garner 2004 (Rofecoxib for RA)	Patients with previous GI events showed a lower rate of GI events in patients treated with rofecoxib (RR 0.4 CI: 0.2, 0.8) v those with no previous events (RR 0.5 CI: 0.3, 0.7). For patients with very low risk (<65 years of age, H. pylori negative, no history if clinical GI event and not taking glucocoticoids) the RR of clinical GI events was signficantly lower (RR 0.1 CI: 0.02, 1.0)	Rofecoxib v placebo Withdrawals due to GI events: 0% placebo, 1.3% rofecoxib 5mg/day, 1.8% rofecoxib 25 mg/day, 0% rofecoxib 50mg/day. No PUBs reported. Lower extremity oedema: 1.2% placebo, 1.3% rofecoxib 5mg/day, 2.3% rofecoxib 25 mg/day, 2.5% rofecoxib 50mg/day Hypertension: 1.2% placebo, 0% rofecoxib 5 mg/day, 2.9% rofecoxib 25 mg/day. 3.1% rofecoxib 50mg/day Renal: Little reported data, however 1 patient in both 25mg and 50mg groups withdrew due to elevated serum creatinine level Rofecoxib v naproxen Upper GI events incidence: 1.4% rofecoxib, 3.0% naproxen RR 0.43 CI: 0.24, 0.77 Severe GI events incidence: 0.4% rofecoxib, 0.9% naproxen (RR 0.43 CI 0.24, 0.77). Renal AEs: 1.2% rofecoxib, 0.9% naproxen (RR 1.4 CI: 0.9, 2.1) CV events were higher in the rofecoxib group at unspecified doses. CV death rate was 0.2% for both rofecoxib and naproxen. MI rate was 0.45% for rofecoxib v 0.1% for naproxen (RR 5.0 CI: 1.5, 13.2)	In rofecoxib v placebo study, AEs were only reported if experience >3% of patients in any group. Also, no data on mortality was presented in the rofecoxib v placebo study.

Appendix F. Evidence Table 10[1]. Systematic reviews of COX-2 inhibitors

Author Year	(9) Subgroups	(10) Adverse events	(11) Comments
Garner2004(Rofecoxib for OA)	Rofecoxib v naproxen-One study analyzed patients receiving concomitant low-dose aspirin which showed no SS difference in GI events	Rofecoxib v diclofenac:Total AEs: Fewer withdrawals due to AEs for 12.5mg and 25mg of rofecoxib (RR 0.71 CI: 0.52, 0.97 and RR 0.70 CI: 0.51, 0.95 respectively). No SS differences for withdrawals due to GI or CV AEs. SS fewer liver function disturbances reported with rofecoxib, but there are no numerical data supplied to support this.Rofecoxib v ibuprofen:GI: Fewer gastric ulcers 25mg RR: 0.15 CI: 0.09, 0.25 and 50mg RR: 0.23 CI: 0.14, 0.36. Fewer duodenal ulcers at 25mg RR 0.24 CI: 0.09, 0.63 but no SS difference at 50mg. Other AEs ambiguously reported.Rofecoxib v naproxen:GI: Study data pooled for 2 of 4 studies. Fewer GI events reported in rofecoxib group for two studies (63/471 v 114/473 RR: 0.55 CI: 0.42, 0.73) No PUBs in rofecoxib group, 3 in naproxen group (RR 0.14 CI: 0.01, 2.77) Serious AEs: 6/17 serious AEs considered drug-related. One CHF in rofecoxib group, 5 other serious AEs in naproxen group. Other discontinuations for hypertension (2/471 v 0/473; RR 5.02 CI: 0.24, 104.31) and oedema (3/471 v 0/473; RR 7.03 CI: 0.36, 135.77)Rofecoxib v nabumetonePooled analysis showed no difference in total or serious AEs (RR 1.09 CI: 0.99, 1.20 and RR 1.28 CI: 0.57, 2.89 respectively)Rofecoxib v placeboSS AEs were for total withdrawals in rofecoxib group 12.5 mg at 6/8 wks. (RR: 2.18 CI: 1.34, 3.55) and 50mg at 12wks (RR 2.04 CI: 1.24, 3.36)	Lack of adequate reporting of outcomes and lack of consideration of variations in NSAID toxicity in many of the included studies severly hampered the ability to draw conclusions regarding efficacy and safety.
Valdecoxib reviews			
Eisen 2005	Not reported	AEs estimated using Kaplan-Meier time-to-event analysis Valdecoxib (n=2236) abdominal pain: 4.2 (3.3-5.2) dyspepsia: 3.9 (3.0-4.8) nausea: 2.7 (1.9-3.5) NSAIDs (n=1185) abdominal pain: 6.9 (5.3-8.4) dyspepsia: 6.8 (5.2-8.3) nausea: 4.0 (12.8-17.2) Placebo (n=973) abdominal pain: 4.1 (2.6-5.7) dyspepsia: 3.8 (2.4-5.2) nausea: 4.8 (2.0-7.6)	Patients taking <5mg of valdecoxib were excluded from the final results - final number of participants was 4394.
Etoricoxib (included for safety only)			

Appendix F. Evidence Table 10[1]. Systematic reviews of COX-2 inhibitors

Author Year	(9) Subgroups	(10) Adverse events	(11) Comments
Ramey, et al2005			
Lumiracoxib (included for safety only)			
Matchaba, et al 2005	No subgroup analysis		quality of included studies not considered in meta-analysis
Multiple COX-2s (reported adverse events only)			
Kearney, et al 2006	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.

Appendix F. Evidence Table 10[1]. Systematic reviews of COX-2 inhibitors

Author Year	(1) Is there a clear review question?	(2) Were there explicit inclusion/ exclusion criteria reported relating to selection of the primary studies?	(3) Is there evidence of a substantial effort to search for all relevant research?	(4) Was the literature search strategy stated?	(5) Is the validity of included studies adequately assessed?	(6) Is sufficient detail of the individual studies presented?	(7) Are there any important studies missing?	(8) Are the primary studies summarized appropriately?	(9) Quality rating
Celecoxib reviews									
Garner 2004 (Celecoxib for RA)	yes	yes	yes	yes	yes	yes	no	yes	good
Ashcroft 2001	yes	yes	yes	partially	yes	yes	no (2001 publication)	yes	good
Rofecoxib reviews									
Juni 2004	yes	yes	yes	partially	yes	yes	no	yes	good
Garner 2004 (Rofecoxib for RA)	yes	yes	yes	yes	yes	yes	no	yes	good
Garner 2004 (Rofecoxib for OA)	yes	yes	yes	yes	yes	yes	no	yes	good
Valdecoxib reviews									
Eisen 2005	yes	yes	no	no	no	yes	no	yes	fair
Etoricoxib (included for safety only)									
Ramey, et al 2005	yes	no	no	no	no	yes	no	yes	fair

Appendix F. Evidence Table 10[1]. Systematic reviews of COX-2 inhibitors

Author Year	**(1) Is there a clear review question?**	**(2) Were there explicit inclusion/ exclusion criteria reported relating to selection of the primary studies?**	**(3) Is there evidence of a substantial effort to search for all relevant research?**	**(4) Was the literature search strategy stated?**	**(5) Is the validity of included studies adequately assessed?**	**(6) Is sufficient detail of the individual studies presented?**	**(7) Are there any important studies missing?**	**(8) Are the primary studies summarized appropriately?**	**(9) Quality rating**
Lumiracoxib (included for safety only)									
Matchaba, et al 2005	yes	yes	yes	no	no	yes	no	yes	fair
Multiple COX-2s (reported adverse events only)									
Kearney, et al 2006	yes	yes	yes	yes	no	yes	no	yes	good

Appendix F. Evidence Table 11[1]. Systematic reviews of acetaminophen

Author Year	(1) Aims	(2) Time period covered	(3) Eligibility criteria	(4) Number of patients	(5) Characteristics of identified articles: study designs	(6) Characteristics of identified articles: populations	(7) Characteristics of identified articles: interventions
Lee, 2004	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.	1 study compared actetaminophen to placebo, and 5 compared acetaminophen to NSAIDs. Acetaminophen dose ranged from 2600 mg/d (1 study) to 4000 mg/d (5 studies). 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.
Towheed, 2005 Cochrane review: most recent substantive update 9/16/02	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	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.

Appendix F. Evidence Table 11[1]. Systematic reviews of acetaminophen

Author Year	(1) Aims	(2) Time period covered	(3) Eligibility criteria	(4) Number of patients	(5) Characteristics of identified articles: study designs	(6) Characteristics of identified articles: populations	(7) Characteristics of identified articles: interventions
Wegman, 2004	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 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 design9 guidelines	All trials included patients with knee OA, and two included those with hip or knee OA.	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 trail period from which data were drawn was 49 $\pm$ 25 days, with a range of 24 - 84 days.
Zhang, 2004	To assess the best available evidence for efficacy of paracetamol (acetaminophen) in the treatment of osteoarthiritis (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).	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.

Appendix F. Evidence Table 11[1]. Systematic reviews of acetaminophen

Author Year	(8) Main results
Lee, 2004	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%) 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, arthotec, rofecoxib 12.5 mg, naproxen) Physician global assessment: not reported Patient global assessment: 37/94 (39%) vs 54/96 (56%)
Towheed, 2005 Cochrane review: most recent substantive update 9/16/02	Pain reduction 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. Overall Western Ontario and McMaster Universities OA Index (WOMAC) In the 2 placebo controlled trials, no significant difference between paracetamol and placebo (pooled ES 0.14, 95% CI -0.06-0.34). 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). Clinical response rate 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). 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. Patient preference for NSAIDs or paracetamol 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).
Wegman, 2004	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.

Appendix F. Evidence Table 11[1]. Systematic reviews of acetaminophen

Author Year	(8) Main results
Zhang, 2004	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) 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.

Appendix F. Evidence Table 11[1]. Systematic reviews of acetaminophen

Author Year	(9) Subgroups	(10) Adverse events	(11) Comments
Lee, 2004	Not reported	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. 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%). 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%)	Results do not account for differences in baseline pain Most trials had short follow-up periods. 1 included trial was an abstract only (Altman 1999)

Appendix F. Evidence Table 11[1]. Systematic reviews of acetaminophen

Author Year	(9) Subgroups	(10) Adverse events	(11) Comments
Towheed, 2005 Cochrane review: most recent substantive update 9/16/02	Not reported	Paracetamol vs placebo GI discomfort: 5/55 (9.1%) vs 6/55 (10.9%) Nausea: 1/25 (4.0%) vs 0/25 (0) Headache: 2/55 (3.6%) vs 2/55 (3.6%) Dizziness: 1/55 (1.8%) vs 7/55 (12.7%) NSAIDs overall vs paracetamol GI discomfort: 108/704 (15.3%) vs 82/702 (11.7%) RR 1.35 (95%CI 1.05-1.75) Nausea: 29/491(5.9%) vs 23/492 (4.7%) Headache: 27/581(4.6%) vs 32/580 (5.5%) Dizziness: 5/288 (1.7%) vs 3/282 (1.1%) Conventional NSAIDs vs paracetamol GI discomfort: 105/416 (25.2%) vs 76/420 (18.1%) RR 1.39, 95% CI 1.07-1.80 Nausea: 15/203 (7.4%) vs 8/210 (3.8%) Headache: 5/293 (1.7%) vs 8/298 (2.7%) Dizziness: - Coxibs vs paracetamol GI discomfort: 3/288 (1.0%) vs 6/282 (2.1%) RR 0.65, 95% CI 0.17-2.52 Nausea: 14/288 (4.9%) vs 15/282 (5.3%) Headache: 22/288 (7.6%) vs 24/282 (8.5%) Dizziness: 5/288 (1.7%) vs 3/282 (1.1%)	Only the 2 placebo controlled studies considered baseline pain levels Most trials had short follow-up periods of approximately 6 weeks 1 included trial was an abstract only (Shen 2003) One RCT was an "n of 1" design
Wegman, 2004	Not reported	Dropouts due to adverse eventsAll 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

Appendix F. Evidence Table 11[1]. Systematic reviews of acetaminophen

Author Year	(9) Subgroups	(10) Adverse events	(11) Comments
Zhang, 2004	Not reported	Not reported	Main results based on 3 trials with a total n of 589 Baseline pain levels not accounted for in analysis

Appendix F. Evidence Table 11[1]. Systematic reviews of acetaminophen

Author Year	(1) Is there a clear review question?	(2) Were there explicit inclusion/exclusion criteria reported relating to selection of the primary studies?	(3) Is there evidence of a substantial effort to search for all relevant research?	(4) Was the literature search strategy stated?	(5) Is the validity of included studies adequately assessed?	(6) Is there sufficient detail of the individual studies presented?	(7) Are there any important studies missing?	(8) Are the primary study summarized appropriately?
Lee 2004	Yes	yes	yes	yes	yes	yes	Amadio 1983, Bradley 1992, Zoppi 1995	Yes
Towheed 2005	yes	yes	yes	yes	yes	yes	March 1994 awaiting assessment, Bradley 1992, Solomon 1974, Zoppi 1995 not included. Specific information on excluded studies not provided	Baseline pain levels not controlled. Specific data on how pooled SMDs were derived was not provided on tables
Wegman 2004	yes	yes	yes	yes	yes	yes, although not much detail on study designs	Amadio 1983 March 1994 Zoppi 1995 Specific information on excluded studies not provided.	yes Baseline pain levels not controlled
Zhang 2004	yes	yes	yes	yes	Not sure - method of randomization not assessed, and only randomization, masking & withdrawal considered	One was abstract only	Altman 1999 Bradley 1992 Solomon 1974 Specific information on excluded studies not provided.	An "n of 1" study included, as well as an abstract only study

Appendix F. Evidence Table 12[1]. Topical NSAIDs trials

Author Year (Quality Score)	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/ Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Tugwell 2004	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)	Topical diclofenac solution (Pennsaid, 1.5% diclofenac sodium + 45.5% DMSO) tid Oral diclofenac 50 mg po tid 12 weeks	3-10 days	Aspirin up to 325 mg/day for cardiovascular prophylaxis	Pain and physical function (WOMAC VA3.1 OA Index) Patient Global Assessment (100 mm VAS) Stiffness by WOMAC stiffness dimension Responder defined as >50% improvement in pain or function of >20 mm on VAS or >20% improvement in at least two of pain, function, or patient global assessment of >10 mm on VAS All assessments at baseline and week 12
Bookman 2004	Primary OA in at least 1 knee, verified radiologically with previous 6 months and at least moderate pain in 2 weeks before randomization	Topical diclofenac solution (Pennsaid, 1.5% diclofenac sodium + 45.5% DMSO) qid DMSO solution qid Placebo solution qid 4 weeks	1-week washout for patients on NSAIDs	Aspirin up to 325 mg/day for cardiovascular prophylaxis Acetaminophen up to 650 mg qid except during 24 hours prior to baseline and final WOMAC assessments	Patient Global Assessment of arthritis (0=very good to 4=very poor): Weekly Western Ontario and McMaster Universities Osteoarthritis (WOMAC): Daily Pain on walking (first question of WOMAC pain dimenstion): Daily

Appendix F. Evidence Table 12[1]. Topical NSAIDs trials

Author Year (Quality Score)	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/ Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Roth2004	Men and nonpregnant women 40 to 85 years old, with symptomatic primary OA of the knee and recent (<3 months) x-ray showing osteoarthritis who had flare of pain after washout of stable therapy	Topical diclofenac solution (Pennsaid, 1.5% diclofenac sodium + 45.5% DMSO) qidDMSO solution qid12 weeks	Washout with flare (at least 3 days per week for 1 month) required for enrollment	Aspirin up to 325 mg/day for cardiovascular prophylaxisAcetaminophen up to 4 325 mg tabs/day allowed except for 3 days prior to prior to scheduled final assessment	Patient Global Assessment (0=very good to 4=very poor)Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain, physical function, stiffness subscalesPain on walking (first question of WOMAC pain dimenstion)Timing of outcome assessment not clear
Trnavsky 2004	Men and women 40 to 75 years old with primary knee osteoarthritis, chronic and decompensated accordignt to classification criteria of the American College of Rheumatology	Topical ibuprofen (Dolgit 5% ibuprofen cream) tid Placebo tid 7 days	Washout of 1 to 60 days if patients were on other drugs for OA	Acetaminophen only allowed during washout	Percent responder (reduction of at least 18 mm on 100 point VAS for pain, or at least 23% from baseline) Pain with motion (0 to 100 mm VAS) Pain at rest and overall pain (0 to 100 mm VAS) Lequesne index (measures pain, maximum distance walked, and activities of daily living) (maximum score 24) Patient/investigator global assessment of efficacy (0=bad to 4=very good)

Appendix F. Evidence Table 12[1]. Topical NSAIDs trials

Author Year (Quality Score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Results
Tugwell 2004	Mean age=63.5 57% female 94% white	Mean OA duration not reported Total x-ray score 6.4 vs. 6.2 WOMAC composite indes (pain): 288 vs. 289	1057/NR/622	18 not included in ITT analysis b/c they did not have primary OA or did not take any medication 39% (245) withdrawn/10 lost to follow-up/604 analyzed in ITT analysis and 492 in per-protocol analysis	Topical vs. oral diclofenac (intention-to-treat analyses) Mean changes from baseline WOMAC pain (0-500 mm): -134 vs. -118, NS WOMAC physical function (0-1700 mm): -348. -438p=0.06 WOMAC stiffness (0-200 mm): -45 vs. -52, NS Patient global assessment (0-100 mm): -27 vs. -32, NS Number of responders: 66% vs. 70%, NS
Bookman 2004	Mean age=62 63% female Race not reported	Mean OA duration NR Baseline WOMAC pain score (mean VAS):9.1 vs. 9.3 vs. 9.4	267/262/248	14% (35) withdrawn/lost to f/u not reported/247 analyzed	Topical diclofenac (A) vs. DMSO control (B) vs. placebo control (C) (intention-to-treat analyses) Mean changes from baseline WOMAC pain: -4 vs. -2.5 vs -2.5, p<0.05 for A vs. C WOMAC physical function: -11.6 vs. -5.7 vs. -7.1, p<05 for A vs. C, p<0.01 for A vs. B WOMAC stiffness: -1.5 vs. -0.7 vs. -0.6, p<0.01 for A vs. C, p<0.05 for A vs. B Pain on walking: -0.8 vs. -0.4 vs. -0.6, p<0.05 for A vs. C, p<0.01 for A vs. B Patient global assessment (mean summary score from weeks 1, 2, 3, and 4): 6.7 vs. 7.8 vs. 7.8, p<0.05 for A vs. C and A vs. B Mean acetaminophen use (tablets): 36.2 vs. 49.5 vs. 54.9, NS

Appendix F. Evidence Table 12[1]. Topical NSAIDs trials

Author Year (Quality Score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Results
Roth2004	Mean age=64.168% femaleRace not reported	Mean OA duration NRBaseline WOMAC pain score (mean VAS): 13 vs. 13	568/466/326	30% (98) withdrawn/3 lost to FU/322 analyzed	Topical diclofenac vs. DMSO control (intention-to-treat analyses)Mean changes from baselineWOMAC pain: -5.9 vs. -4.3, p<0.005WOMAC physical function: -15.4 vs. -10.1, p<0.005Patient global assessment: -1.3 vs. -0.9, p<0.005WOMAC stiffness: -1.8 vs. -1.3, p<0.01
Trnavsky 2004	Mean age=67 78% female Race not reported	Mean OA duration NR Baseline pain (0 to 100 mm VAS) score: 63 vs. 59	Not clear/not clear/50	None withdrawn/lost to follow-up/50 analyzed in intention-to-treat analysis	Topical ibuprofen vs. placebo (intention-to-treat analysis) Proportion of responders: 21/25 (84%) vs. 10/25 (40%), p<0.0001 Patient global assessment (good or very good): 17/25 (68%) vs. 4/26 (16%), p not reported Mean changes from baseline (100 mm VAS) Pain on motion: -31.4 vs. -6.9 Pain on rest: -23.5 vs. -10.3 Overall pain: --22.6 vs. -12.3 Mean change from baseline (24 point scale) Lequesne index: -2.9 vs. -0.9

Appendix F. Evidence Table 12[1]. Topical NSAIDs trials

Author Year (Quality Score)	Method of adverse effects assessment?	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Tugwell 2004	Not clear how adverse events identified; categorized according to COSTART, severe AE pre-defined as one causing significant impairment of function or incapaciation and definite hazard to patient's health; adverse events defined according to Compendium of Pharmaceuticals and Specialties	Topical (n=311) vs. oral (n=311) diclofenac All 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	30% vs. 30% withdrawals due to AE or lack of effect 21% vs. 26% withdrawal due to adverse events
Bookman 2004	Patient-recorded, GI complaints assessed by investigators weekly using checklist and dermatological exam performed	Topical diclofenac (n=84) vs. DMSO control (n=80) vs. placebo control (n=80) Minor skin dryness or flakiness: 36% vs. 14% vs. 1% Rash: 13% vs. 8% vs. 4% Paresthesia: 14% vs. 22% vs. 6% GI side effects: No differences	12% vs. 18% vs. 18% withdrawals 6% vs. 4% vs. 0% withdrawal due to adverse events
Roth2004	Open-ended questions and checklist questionnaire used at each clinic visit and with telephone visits. Dermatological assessment at clinic visits.	Topical diclofenac (n=164) vs. DMSO control (n=162)GI side effects: No differencesDry skin: 37% vs. 25%, p<0.05Rash: 11% vs. 5%, p<0.05	27% vs. 33% withdrawals4.8% vs. 2.5% withdrawal due to adverse events
Trnavsky 2004	Not reported	No adverse events recorded	4% vs. 0% withdrawals No withdrawals due to adverse events

Appendix F. Evidence Table 12[1]. Topical NSAIDs trials

Internal Validity						
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Tugwell 2004	yes	yes	yes	yes	yes	yes
Bookman 2004	yes	yes	yes	yes	yes	yes
Roth 2004	yes	yes	yes	yes	yes	unclear
Trnavsky2004	yes	yes	yes	yes	yes	yes

Appendix F. Evidence Table 12[1]. Topical NSAIDs trials

External Validity							
Author Year	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/ eligible/ enrolled**
Tugwell 2004	yes	no/no/no/no	no	yes	no	good	1057/NR/622
Bookman 2004	yes	no/no/no/no	no	yes	no	good	267/262/248
Roth 2004	yes	no/no/no/no	no	yes	no	good	568/428/326
Trnavsky2004	yes	no/no/no/no	no	yes	no	good	50/NR/50

Appendix F. Evidence Table 12[1]. Topical NSAIDs trials

External Validity	
Author Year	**Exclusion criteria**
Tugwell 2004	Secondary arthritis related to syphilitic neuropathy; ochronosis; psoriasis; metabolic bone disease; acute trauma; chondrocalcinosis with a history of pseudogout; fibromyalgia; previous major surgery to the knee or recommendation for knee replacement/reconstruction; recent intra-articular viscosupplementation; current or recent corticosteroid use; topical product use at the application site; history of sensitivity to any of the study drugs, acetylsalicylic acid or other NSAID; severe, uncontrolled cardia, renal hepatic or other systemic disease; documented recent gastroduodenal ulcer or GI bleedind; history of alcohol of other drug abuse; lactationl concomitant skin diseases at the application site; clinically significant elevation of serum creatinine or of AST or ALT; previous participation in a clinical trial within 30 days.
Bookman 2004	Secondary arthritis related to syphilitic neuropathy; ochronosis; psoriasis; metabolic bone disease; acute trauma; sensitivity to diclofenac, ASA or other NSAID, DMSO, propylene glycol, glycerin or ethanol; clinically active renal, hepatic or peptic ulcer disease; history of alcohol or drug abuse; lactation; concomitant skin disease at application site; corticosteroid use; use of another topical product at the application site; oral use of analgesic or glucosamine.
Roth 2004	Secondary arthritis related to systemic inflammatory arthritis; sensitivity to diclofenac, aspirin or any other NSAID, dimethyl sulfoxide, propylene glycol, glycerin, or ethanol; clinically active renal, hepatic, or peptic ulcer disease; a history of alcohol or other drug abuse; lactation; concomitant skin disease at the application site; corticosteroid use, including oral corticosteroid within 14 days, intramuscular corticosteroid within 30 days, intra-articular corticosteroid into the study knee within 90 days, intra-articular corticosteroid into any other joint within 30 days of study entry, or ongoing use of topical corticosteroid at the site of application; use of a topical product, treatment, or device at the application site for the relief of OA; ongoing use of prohibited medication, including NSAIDs, oral analgesic, muscle relaxant, or low-dose antidepressant; ongoing use of glucosamine or chondroitin sulfate sodium (unless used continuously for 90 days before study entry); intra-articular viscosupplementation (eg, hyaluronate sodium derivative) into the study knee in the preceding 90 days; current application for disability benefits on the basis of OA of the knee; fibromyalgia; and other painful or disabling condition affecting the knee.
Trnavsky2004	Secondary OA; obesity (body mass index ≥ 30 kg/m2); chronic painful disease of the hip or the ankle joint; allergic diathesis, bronchial asthma, or known hypersensitivity to NSAID; eczematous skin eruption; any physiotherapy.

Appendix F. Evidence Table 12[1]. Topical NSAIDs trials

External Validity				
Author Year	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**
Tugwell 2004	run-in NR/washout 3-10 days	no	NA	Dimethaid Healthcare Ltd.
Bookman 2004	run-in NR/ washout 7 days (NSAIDs)	no	yes	Dimethaid Healthcare Ltd.
Roth 2004	run-in NR/washout 3 days	no	yes	Dimethaid Healthcare Ltd.
Trnavsky2004	run-in NR/ no washout (exception: 1-60 day washout for pts with previous treatment with drugs having a therapeutic effecton the knee joint)	no	yes	Dolorgiet Pharmaceuticals (Germany