National Institute for Health and Care Excellence

Draft for consultation

Osteoarthritis: assessment and management (update)

[I3] Evidence reviews for the clinical and cost-effectiveness of oral, topical and transdermal medicines for the management of osteoarthritis

NICE guideline

Evidence reviews underpinning recommendations 1.4.1 to 1.4.9 and research recommendations in the NICE guideline

April 2022

Draft for Consultation

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Appendices

Appendix E – Forest plots

E.1 Oral

E.1.1 Paracetamol compared to placebo

Figure 1: Quality of life (Nottingham health profile energy subscale, 0-100, high is good, change score) at ≤3 months

Study or Subgroup	Paracetamol Mean	Paracetamol SD	Paracetamol Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
Prior 2014	2	1.27	267	1.72	1.28	275	0.28 [0.07, 0.49]

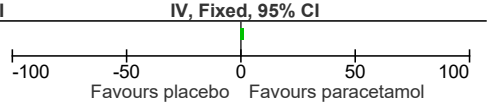


Figure 2: Pain (WOMAC, VAS, Multidimensional Health Assessment Questionnaire [different scale ranges], high is poor, change scores) at ≤3 months

Study or Subgroup	Std. Mean Difference	SE	Paracetamol Total	Placebo Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Altman 2007	-0.2186	0.0962	318	165	12.3%	-0.22 [-0.41, -0.03]
Case 2003	-0.092	0.2651	29	28	1.6%	-0.09 [-0.61, 0.43]
Miceli-richard 2004	0	0.0717	405	374	22.1%	0.00 [-0.14, 0.14]
Pincus 2004 (PACES)	0.0456	0.0599	603	519	31.6%	0.05 [-0.07, 0.16]
Prior 2014	-0.1636	0.0861	267	275	15.3%	-0.16 [-0.33, 0.01]
Reed 2018	-0.0529	0.0815	449	227	17.1%	-0.05 [-0.21, 0.11]
Total (95% CI)			**2071**	**1588**	**100.0%**	**-0.05 [-0.11, 0.02]**

Heterogeneity: Chi² = 7.87, df = 5 (P = 0.16); I² = 36%

Test for overall effect: Z = 1.42 (P = 0.15)

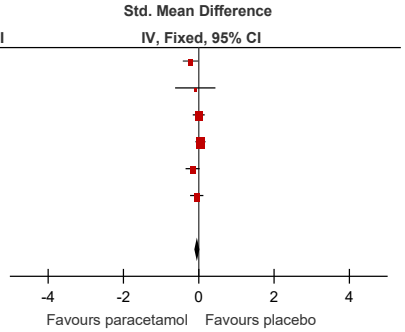


Figure 3: Pain (WOMAC, 0-20, high is poor, change score) at >3 months

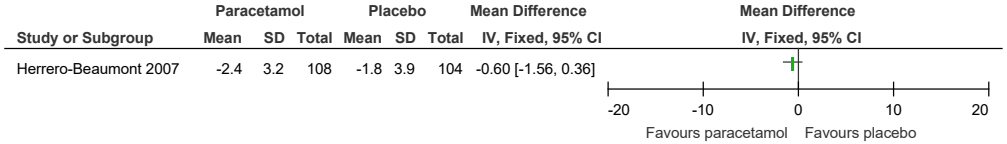


Figure 4: Physical function (WOMAC [different scale ranges], high is poor, change scores) at ≤3 months

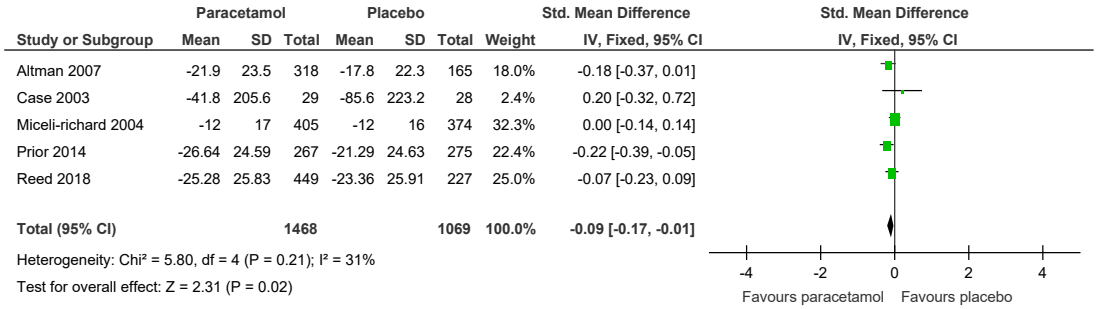


Figure 5: Physical function (WOMAC [different scale ranges], high is poor, change scores) at >3 months

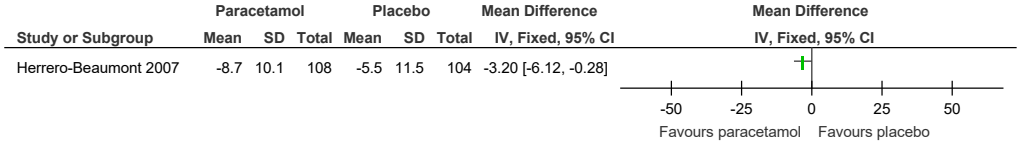


Figure 6: Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months

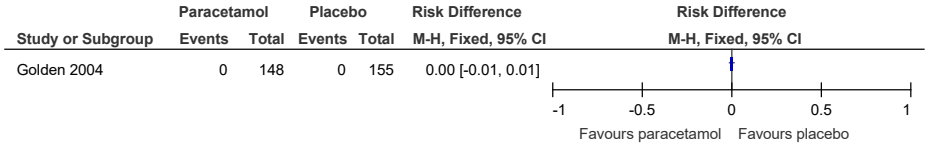


Figure 7: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months

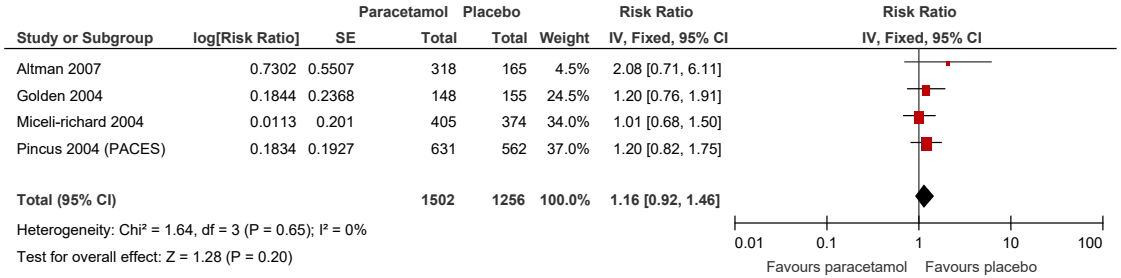


Figure 8: Serious adverse events 2: Cardiovascular adverse events at ≤3 months

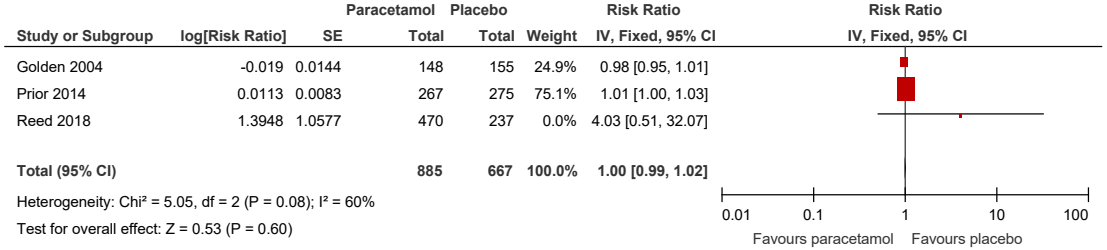


Figure 9: Serious adverse events 2: Cardiovascular adverse events at >3 months

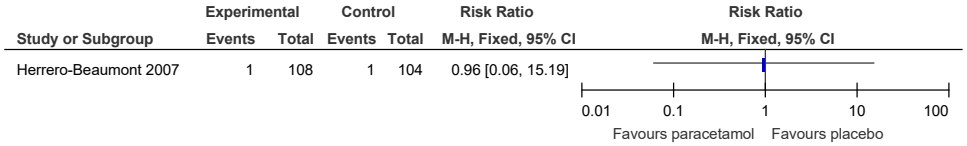


Figure 10: Serious adverse events 3: Hepatorenal adverse events at ≤3 months

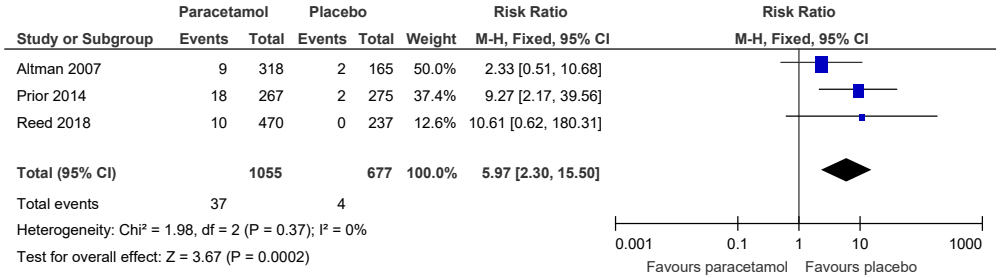


Figure 11: Serious adverse events 3: Hepatorenal adverse events at >3 months

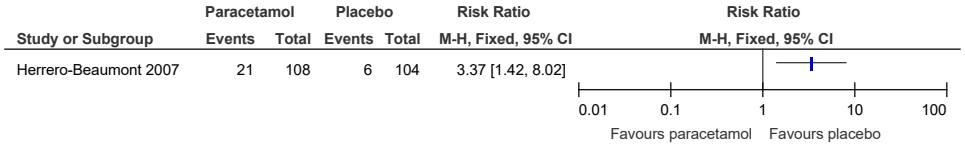
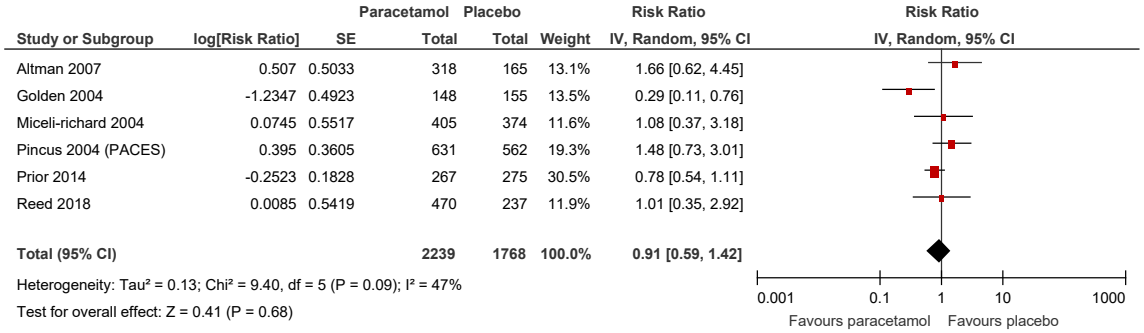


Figure 12: Serious adverse events 4: Central nervous system adverse events at ≤3 months



E.1.2 Oral non-steroidal anti-inflammatory drugs compared to paracetamol

Figure 13: Quality of life (EQ-5D, 0-1, high is good, final value) at ≤3 months

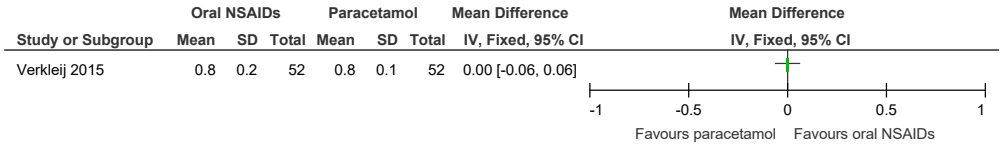


Figure 14: Pain (WOMAC, VAS, Hospital assessment questionnaire pain score [different scale ranges], high is poor, change scores) at ≤3 months

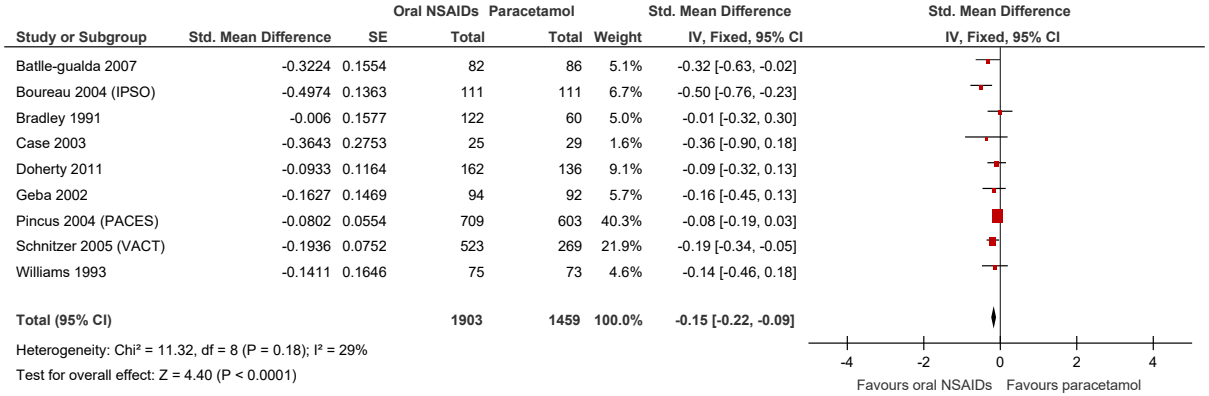


Figure 15: Pain (KOOS, VAS, 0-100, high is poor, final values) at ≤3 months

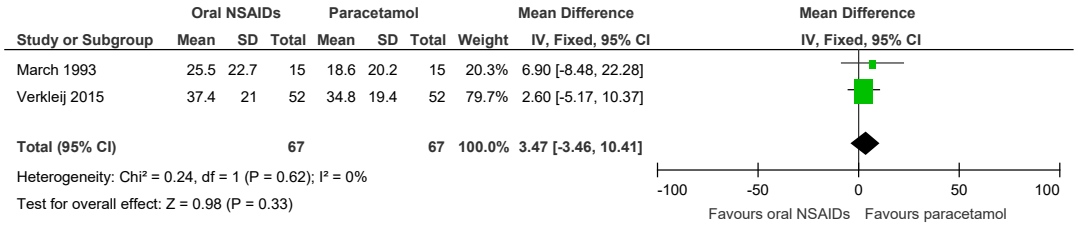


Figure 16: Pain (VAS, 0-10, high is poor, change score) at >3 months

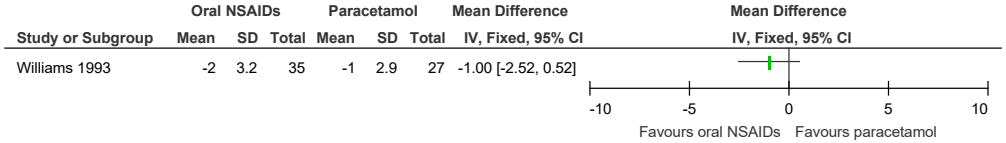


Figure 17: Physical function (WOMAC, Hospital assessment questionnaire disability score [different scale ranges], high is poor, change scores) at ≤3 months

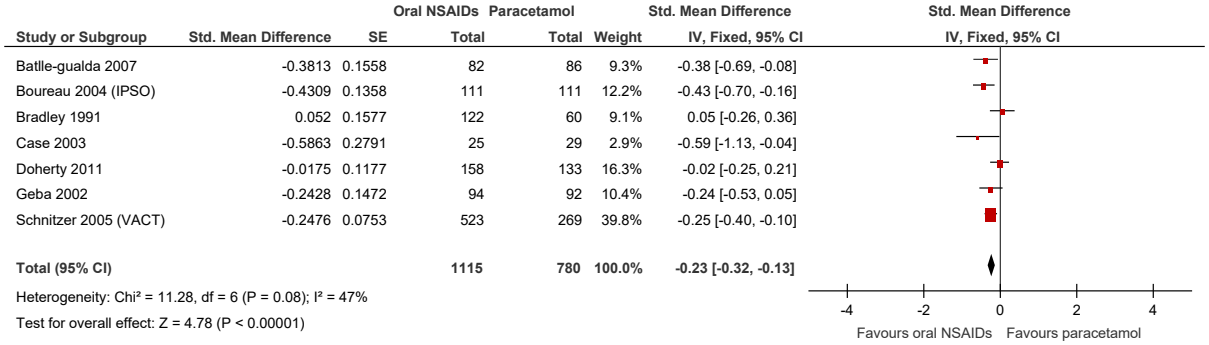


Figure 18: Physical function (KOOS, 0-100, high is poor, final value) at ≤3 months

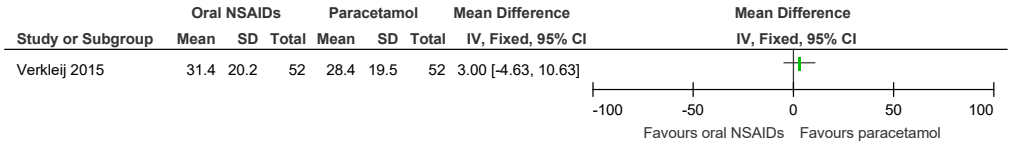


Figure 19: Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months

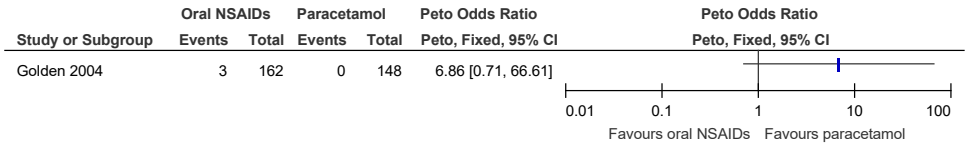


Figure 20: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months

Study or Subgroup	log[Risk Ratio]	SE	Oral NSAIDs Total	Paracetamol Total	Weight	Risk Ratio IV, Fixed, 95% CI
Batlle-gualda 2007	0.6538	0.324	82	86	10.8%	1.92 [1.02, 3.63]
Boureau 2004 (IPSO)	0.3365	0.3917	111	111	7.4%	1.40 [0.65, 3.02]
Bradley 1991	0.0406	0.3508	123	61	9.2%	1.04 [0.52, 2.07]
Golden 2004	0.0653	0.217	161	148	24.0%	1.07 [0.70, 1.63]
Pincus 2004 (PACES)	0.1473	0.1651	723	631	41.5%	1.16 [0.84, 1.60]
Verkleij 2015	0.9985	0.3963	52	52	7.2%	2.71 [1.25, 5.90]
Total (95% CI)			**1252**	**1089**	**100.0%**	**1.28 [1.04, 1.58]**

Heterogeneity: Chi² = 6.64, df = 5 (P = 0.25); I² = 25%

Test for overall effect: Z = 2.33 (P = 0.02)

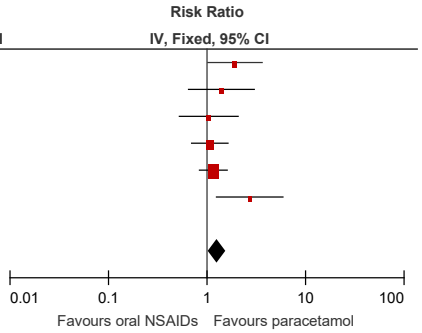


Figure 21: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at >3 months

Study or Subgroup	Oral NSAIDs Events	Oral NSAIDs Total	Paracetamol Events	Paracetamol Total	Risk Ratio M-H, Fixed, 95% CI
Williams 1993	17	90	6	88	2.77 [1.15, 6.70]

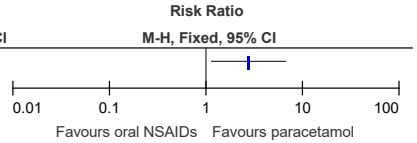


Figure 22: Serious adverse events 2: Cardiovascular adverse events at ≤3 months

Study or Subgroup	Oral NSAIDs Events	Oral NSAIDs Total	Paracetamol Events	Paracetamol Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Boureau 2004 (IPSO)	2	111	2	111	14.4%	1.00 [0.14, 6.97]
Bradley 1991	5	123	1	61	9.6%	2.48 [0.30, 20.76]
Golden 2004	0	161	1	148	11.3%	0.31 [0.01, 7.47]
Schnitzer 2005 (VACT)	9	523	3	269	28.6%	1.54 [0.42, 5.65]
Verkleij 2015	8	52	5	52	36.1%	1.60 [0.56, 4.57]
Total (95% CI)		**970**		**641**	**100.0%**	**1.44 [0.73, 2.83]**
Total events	24		12			

Heterogeneity: Chi² = 1.34, df = 4 (P = 0.85); I² = 0%

Test for overall effect: Z = 1.04 (P = 0.30)

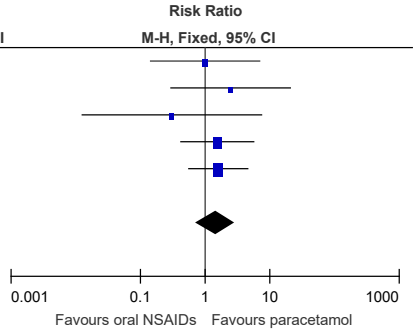


Figure 23: Serious adverse events 2: Cardiovascular adverse events at >3 months

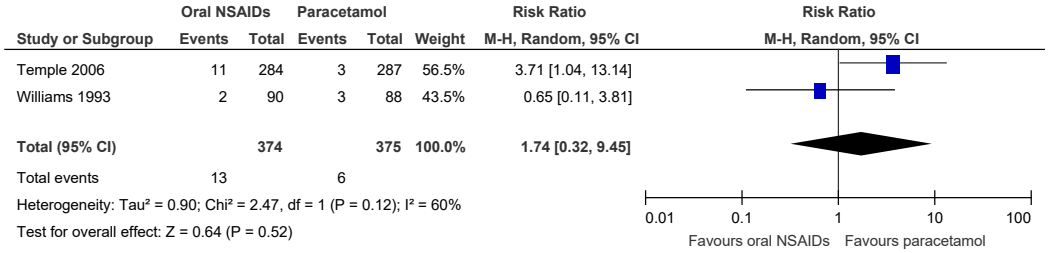


Figure 24: Serious adverse events 3: Hepatorenal adverse events at ≤3 months

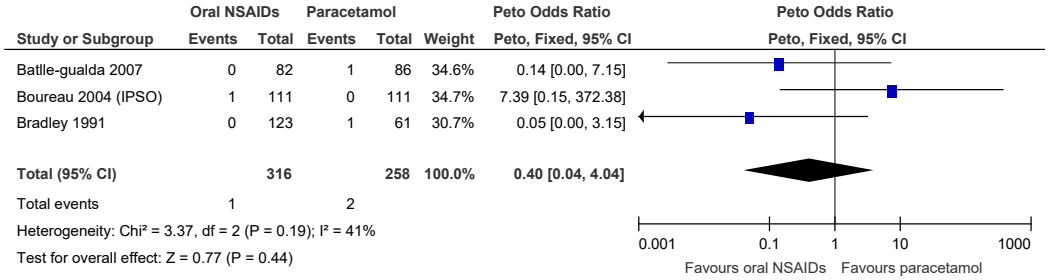


Figure 25: Serious adverse events 3: Hepatorenal adverse events at >3 months

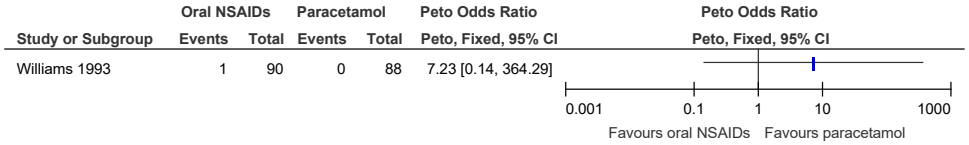


Figure 26: Serious adverse events 4: Central nervous system adverse events at ≤3 months

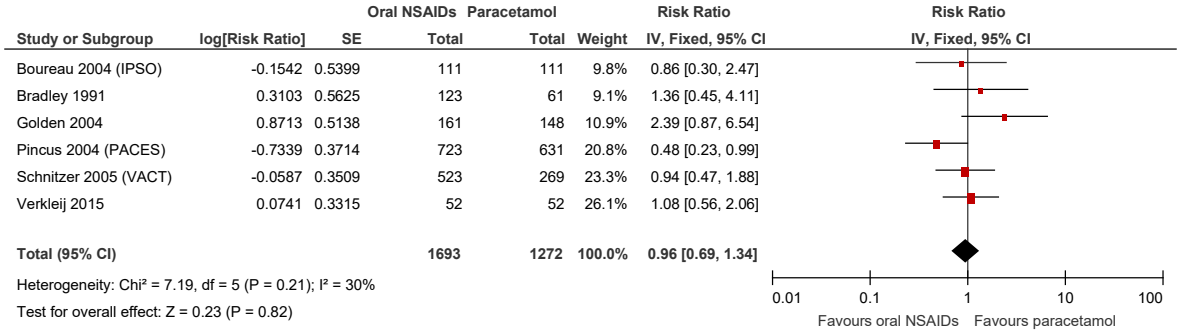
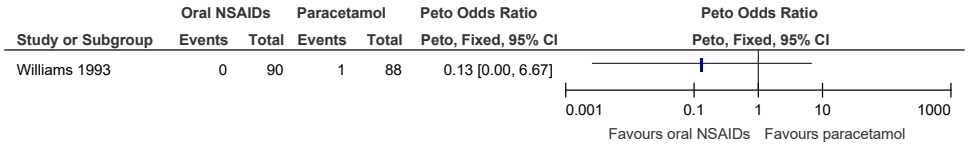


Figure 27: Serious adverse events 4: Central nervous system adverse events at >3 months



E.1.3 Oral non-steroidal anti-inflammatory drugs compared to placebo

Figure 28: Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at ≤3 months

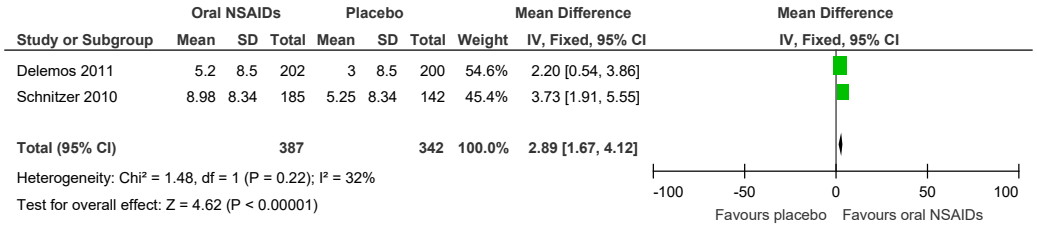


Figure 29: Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at ≤3 months

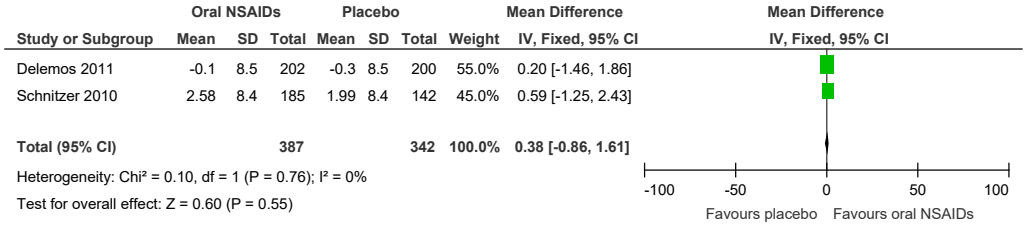


Figure 30: Quality of life (SF-36 bodily pain subscale, 0-100, high is good, change score) at ≤3 months

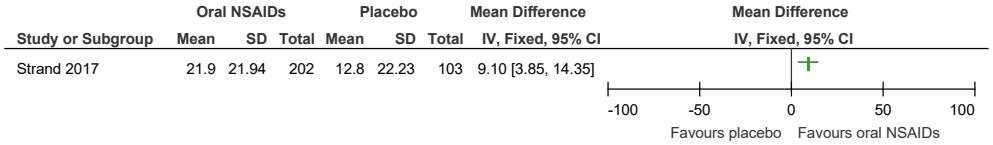


Figure 31: Quality of life (SF-36 physical functioning subscale, 0-100, high is good, change score) at ≤3 months

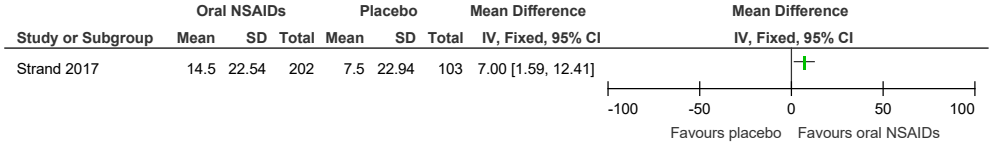


Figure 32: Quality of life (SF-36 role physical subscale, 0-100, high is good, change score) at ≤3 months

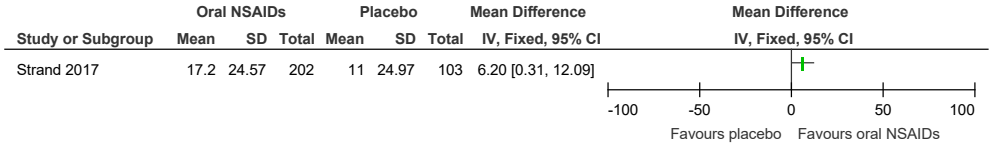


Figure 33: Quality of life (SF-36 vitality subscale, 0-100, high is good, change score) at ≤3 months

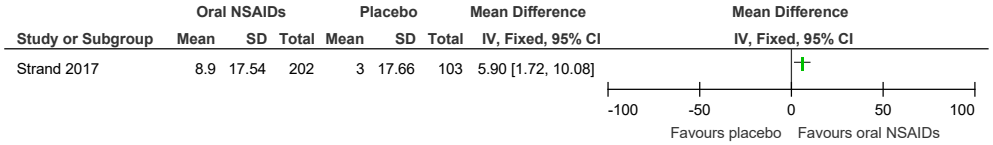


Figure 34: Quality of life (SF-36 general health subscale, 0-100, high is good, change score) at ≤3 months

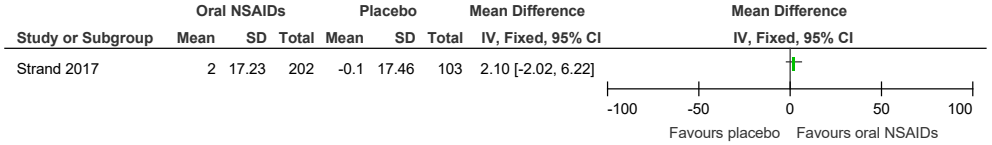


Figure 35: Quality of life (SF-36 mental health subscale, 0-100, high is good, change score) at ≤3 months

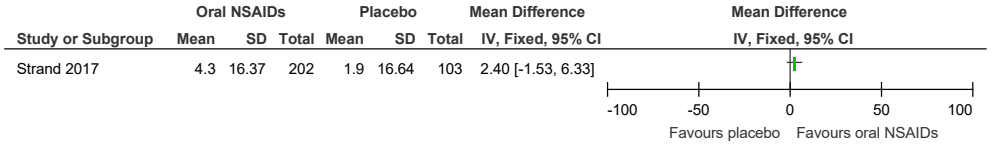


Figure 36: Quality of life (SF-36 role emotional subscale, 0-100, high is good, change score) at ≤3 months

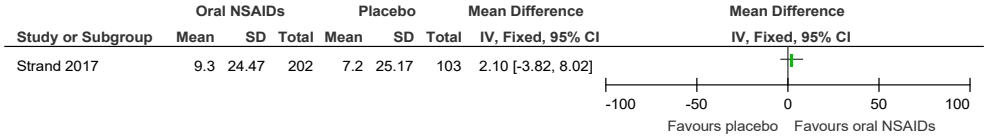


Figure 37: Quality of life (SF-36 social functioning subscale, 0-100, high is good, change score) at ≤3 months

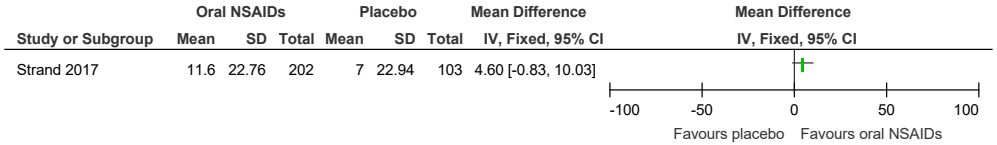


Figure 38: Pain (WOMAC, VAS [different scale ranges], high is poor, change scores) at ≤3 months

Study or Subgroup	Std. Mean Difference	SE	Oral NSAIDs Total	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Asmus 2014 (study 1)	-0.3898	0.105	186	184	2.3%	-0.39 [-0.60, -0.18]
Asmus 2014 (study 2)	-0.2294	0.103	194	186	2.3%	-0.23 [-0.43, -0.03]
Baerwald 2010	-0.2127	0.0974	156	331	2.3%	-0.21 [-0.40, -0.02]
Bensen 1999	-0.3746	0.0932	574	146	2.4%	-0.37 [-0.56, -0.19]
Birbara 2006	-0.33	0.0976	320	159	2.3%	-0.33 [-0.52, -0.14]
Bocanegra 1998	-0.5106	0.1343	154	91	2.1%	-0.51 [-0.77, -0.25]
Case 2003	-0.4221	0.2784	25	28	1.3%	-0.42 [-0.97, 0.12]
Conaghan 2013	-0.2958	0.0938	233	227	2.4%	-0.30 [-0.48, -0.11]
Delemos 2011	-0.2761	0.1002	202	200	2.3%	-0.28 [-0.47, -0.08]
Essex 2012	-0.1312	0.1394	249	65	2.1%	-0.13 [-0.40, 0.14]
Essex 2014	-0.1319	0.1427	254	61	2.1%	-0.13 [-0.41, 0.15]
Essex 2016	-0.1755	0.1457	254	58	2.0%	-0.18 [-0.46, 0.11]
Fleischmann 2006	-0.2967	0.0815	444	231	2.4%	-0.30 [-0.46, -0.14]
Ghosh 2007	-1.6838	0.1215	304	123	2.2%	-1.68 [-1.92, -1.45]
Gibofsky 2003	-0.5192	0.1272	189	96	2.2%	-0.52 [-0.77, -0.27]
Gibofsky 2014	-0.2986	0.1217	202	103	2.2%	-0.30 [-0.54, -0.06]
Gordo 2017	-0.2107	0.1484	245	56	2.0%	-0.21 [-0.50, 0.08]
Kivitz 2002	-0.1974	0.0991	204	205	2.3%	-0.20 [-0.39, -0.00]
Kivitz 2004	-0.4634	0.0861	410	208	2.4%	-0.46 [-0.63, -0.29]
Lee 2017	-0.3792	0.146	145	71	2.0%	-0.38 [-0.67, -0.09]
Lehmann 2005	-0.2304	0.0691	420	424	2.5%	-0.23 [-0.37, -0.09]
Leung 2002	-0.4778	0.1426	445	56	2.1%	-0.48 [-0.76, -0.20]
Lund 1998	-0.263	0.105	274	137	2.3%	-0.26 [-0.47, -0.06]
Makarowski 2002	-0.3376	0.1314	118	117	2.1%	-0.34 [-0.60, -0.08]
McKenna 2001A	-0.3691	0.182	63	60	1.8%	-0.37 [-0.73, -0.01]
McKenna 2001B	-0.4188	0.0875	398	200	2.4%	-0.42 [-0.59, -0.25]
Paul 2009	-1.803	0.1445	226	89	2.0%	-1.80 [-2.09, -1.52]
Pincus 2004 (PACES)	-0.0398	0.0578	709	519	2.5%	-0.04 [-0.15, 0.07]
Puopolo 2007	-0.4203	0.108	431	109	2.3%	-0.42 [-0.63, -0.21]
Rother 2007	-0.3798	0.1254	132	127	2.2%	-0.38 [-0.63, -0.13]
Schnitzer 2010	-0.4546	0.0958	226	221	2.3%	-0.45 [-0.64, -0.27]
Schnitzer 2011A	-0.3128	0.0696	419	416	2.5%	-0.31 [-0.45, -0.18]
Schnitzer 2011B	-0.3508	0.0892	254	257	2.4%	-0.35 [-0.53, -0.18]
Schubiger 1980	-0.1895	0.1957	114	34	1.7%	-0.19 [-0.57, 0.19]
Sheldon 2005	-0.2726	0.0722	393	382	2.5%	-0.27 [-0.41, -0.13]
Simon 2009	-0.3942	0.0997	151	318	2.3%	-0.39 [-0.59, -0.20]
Smugar 2006	-0.5803	0.0675	916	301	2.5%	-0.58 [-0.71, -0.45]
Strand 2017	-0.2886	0.1216	202	103	2.2%	-0.29 [-0.53, -0.05]
Tannenbaum 2004	-0.184	0.0789	481	243	2.4%	-0.18 [-0.34, -0.03]
Truitt 2001	-0.2902	0.1679	115	52	1.9%	-0.29 [-0.62, 0.04]
Wiesenhutter 2005	-0.4206	0.1102	424	104	2.3%	-0.42 [-0.64, -0.20]
Williams 2001	0.2407	0.0792	472	243	2.4%	0.24 [0.09, 0.40]
Wittenberg 2006	-0.3966	0.1435	145	75	2.0%	-0.40 [-0.68, -0.12]
Yocum 2000	-0.3712	0.0899	617	157	2.4%	-0.37 [-0.55, -0.19]
Zhao 1999	-0.2976	0.0758	873	219	2.5%	-0.30 [-0.45, -0.15]
Total (95% CI)			**13962**	**7792**	**100.0%**	**-0.37 [-0.45, -0.28]**

Figure 39: Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months

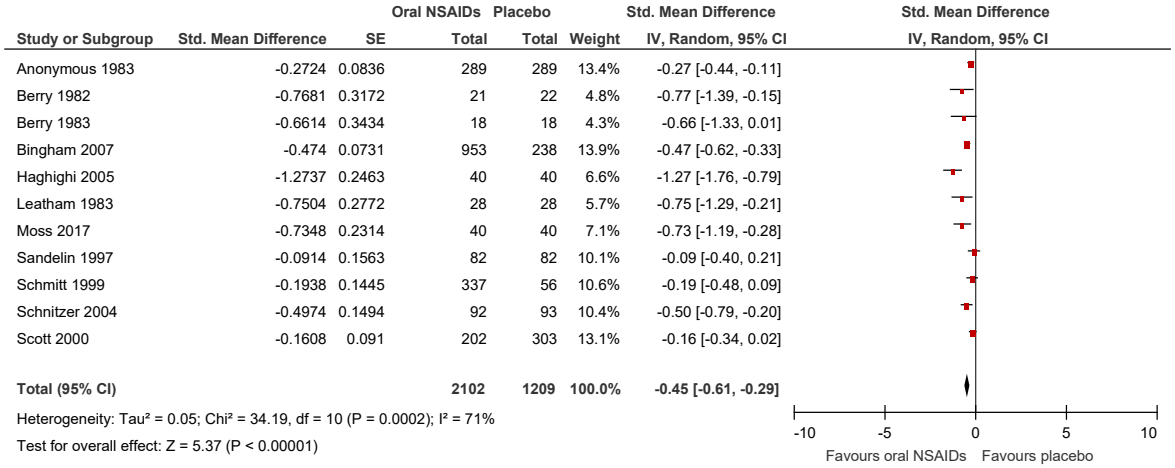


Figure 40: Pain (WOMAC, 0-500, high is poor, change score) at >3 months

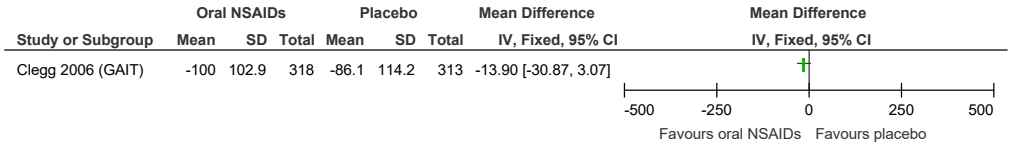


Figure 41: Physical function (WOMAC [different scale ranges], high is poor, change scores) at ≤3 months

Study or Subgroup	Std. Mean Difference	SE	Oral NSAIDs Total	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Asmus 2014 (study 1)	-0.5448	0.1059	186	184	3.4%	-0.54 [-0.75, -0.34]
Asmus 2014 (study 2)	-0.1927	0.1029	194	186	3.5%	-0.19 [-0.39, 0.01]
Baerwald 2010	-0.2818	0.0975	156	331	3.7%	-0.28 [-0.47, -0.09]
Birbara 2006	-0.325	0.0975	321	159	3.7%	-0.33 [-0.52, -0.13]
Case 2003	-0.3576	0.2775	25	28	0.8%	-0.36 [-0.90, 0.19]
Delemos 2011	-0.3354	0.1005	202	200	3.6%	-0.34 [-0.53, -0.14]
Essex 2012	-0.1937	0.1395	249	65	2.4%	-0.19 [-0.47, 0.08]
Essex 2014	-0.3227	0.1432	254	61	2.3%	-0.32 [-0.60, -0.04]
Fleischmann 2006	-0.388	0.0818	444	231	4.4%	-0.39 [-0.55, -0.23]
Gibofsky 2003	-0.4848	0.127	189	96	2.7%	-0.48 [-0.73, -0.24]
Gibofsky 2014	-0.3585	0.122	202	103	2.9%	-0.36 [-0.60, -0.12]
Lee 2017	-0.2731	0.1455	145	71	2.3%	-0.27 [-0.56, 0.01]
Lehmann 2005	-0.1831	0.069	420	424	5.0%	-0.18 [-0.32, -0.05]
Leung 2002	-0.3927	0.1423	445	56	2.3%	-0.39 [-0.67, -0.11]
Makarowski 2002	-0.4344	0.132	118	117	2.6%	-0.43 [-0.69, -0.18]
McKenna 2001B	-0.1509	0.0868	398	200	4.2%	-0.15 [-0.32, 0.02]
Puopolo 2007	-0.3635	0.1079	428	109	3.3%	-0.36 [-0.57, -0.15]
Rother 2007	-0.2761	0.1249	132	127	2.8%	-0.28 [-0.52, -0.03]
Schnitzer 2010	-0.517	0.0962	226	221	3.8%	-0.52 [-0.71, -0.33]
Schnitzer 2011A	-0.3181	0.0697	419	416	5.0%	-0.32 [-0.45, -0.18]
Schnitzer 2011B	-0.4513	0.0896	254	257	4.0%	-0.45 [-0.63, -0.28]
Sheldon 2005	-0.3608	0.0724	393	382	4.8%	-0.36 [-0.50, -0.22]
Simon 2009	-0.0068	0.0988	151	318	3.7%	-0.01 [-0.20, 0.19]
Smugar 2006	-0.5711	0.0674	916	301	5.1%	-0.57 [-0.70, -0.44]
Strand 2017	-0.1854	0.1213	202	103	2.9%	-0.19 [-0.42, 0.05]
Tannenbaum 2004	-0.2569	0.079	481	243	4.5%	-0.26 [-0.41, -0.10]
Trudeau 2015	-0.0426	0.1782	63	63	1.7%	-0.04 [-0.39, 0.31]
Truitt 2001	-0.3303	0.1681	115	52	1.8%	-0.33 [-0.66, -0.00]
Wittenberg 2006	-0.3203	0.1431	145	75	2.3%	-0.32 [-0.60, -0.04]
Zhao 1999	-0.2629	0.0758	873	219	4.7%	-0.26 [-0.41, -0.11]
Total (95% CI)			**8746**	**5398**	**100.0%**	**-0.32 [-0.37, -0.27]**

Heterogeneity: Tau² = 0.01; Chi² = 54.07, df = 29 (P = 0.003); I² = 46%

Test for overall effect: Z = 12.32 (P < 0.00001)

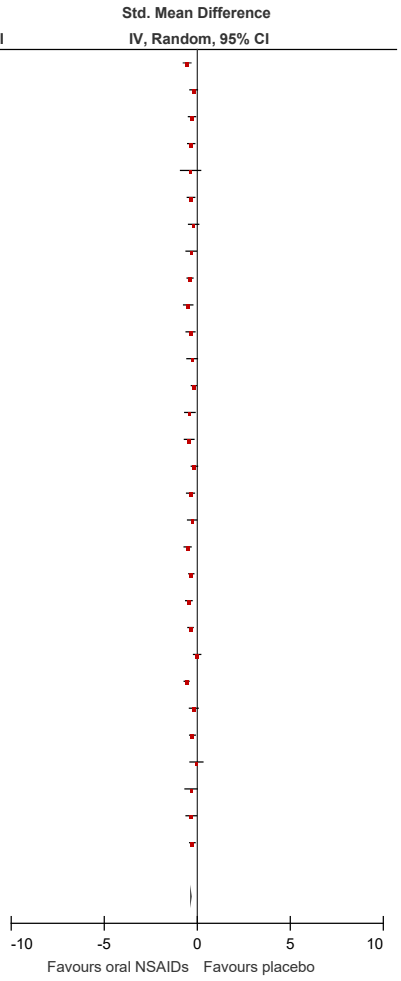


Figure 42: Physical function (WOMAC, 0-68, high is poor, final value) at ≤3 months

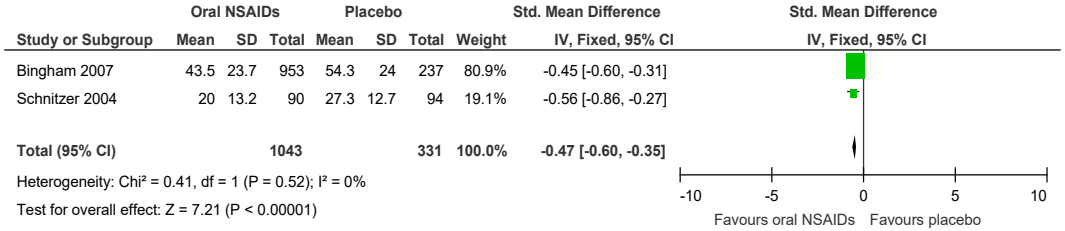


Figure 43: Physical function (WOMAC, 0-1700, high is poor, change score) at >3 months

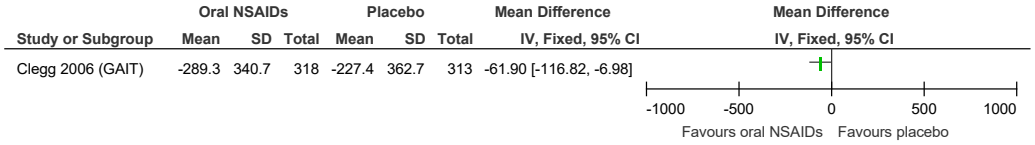


Figure 44: Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months

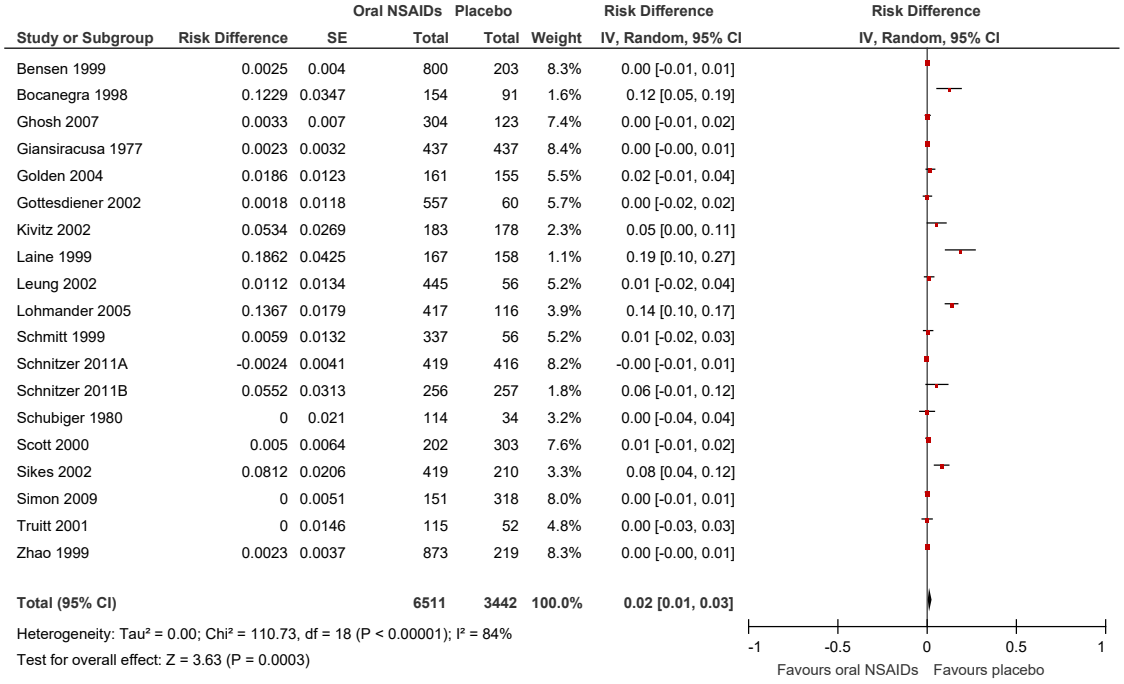


Figure 45: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months

Study or Subgroup	Risk Difference	SE	Oral NSAIDs Total	Placebo Total	Weight	Risk Difference IV, Fixed, 95% CI
Amundsen 1983	-0.0481	0.0507	104	52	0.5%	-0.05 [-0.15, 0.05]
Andelman 1983	0.35	0.1462	20	10	0.1%	0.35 [0.06, 0.64]
Anonymous 1983	-0.0067	0.0238	299	299	2.2%	-0.01 [-0.05, 0.04]
Baerwald 2010	0.0378	0.0373	156	330	0.9%	0.04 [-0.04, 0.11]
Bakshi 1991	-0.0258	0.0428	208	106	0.7%	-0.03 [-0.11, 0.06]
Bensen 1999	0.0558	0.0332	800	203	1.1%	0.06 [-0.01, 0.12]
Bingham 2007	-0.0101	0.0096	962	244	13.5%	-0.01 [-0.03, 0.01]
Birbara 2006	0.0027	0.0243	326	162	2.1%	0.00 [-0.04, 0.05]
Conaghan 2013	0.0134	0.0335	233	227	1.1%	0.01 [-0.05, 0.08]
Couto 2018	0.0244	0.0233	409	409	2.3%	0.02 [-0.02, 0.07]
Cryer 2011	-0.0066	0.0311	488	246	1.3%	-0.01 [-0.07, 0.05]
Dore 1995	0.1172	0.0539	168	86	0.4%	0.12 [0.01, 0.22]
Essex 2012	-0.0362	0.0305	255	67	1.3%	-0.04 [-0.10, 0.02]
Essex 2014	0.0112	0.019	256	62	3.4%	0.01 [-0.03, 0.05]
Famaey 1976	0.25	0.126	20	20	0.1%	0.25 [0.00, 0.50]
Fleischmann 1997	-0.0077	0.0496	185	94	0.5%	-0.01 [-0.10, 0.09]
Fleischmann 2006	0.0171	0.0327	444	231	1.2%	0.02 [-0.05, 0.08]
Ghosh 2007	0.076	0.024	304	123	2.2%	0.08 [0.03, 0.12]
Golden 2004	0.0494	0.0448	161	155	0.6%	0.05 [-0.04, 0.14]
Gordo 2017	0.007	0.0203	309	79	3.0%	0.01 [-0.03, 0.05]
Hubault 1976	0	0.196	9	9	0.0%	0.00 [-0.38, 0.38]
Kageyama 1973	-0.0487	0.0569	74	43	0.4%	-0.05 [-0.16, 0.06]
Karakaya 1977	-0.0571	0.2019	14	5	0.0%	-0.06 [-0.45, 0.34]
Kivitz 2001B	0.0951	0.0302	843	218	1.4%	0.10 [0.04, 0.15]
Kivitz 2004	-0.0161	0.0205	410	208	3.0%	-0.02 [-0.06, 0.02]
Leung 2002	0.0112	0.0134	445	56	6.9%	0.01 [-0.02, 0.04]
Lopez sanchez 1983	0.3	0.1538	10	10	0.1%	0.30 [-0.00, 0.60]
Lund 1998	0.0036	0.0346	274	137	1.0%	0.00 [-0.06, 0.07]
Makarowski 2002	0.0931	0.0312	118	117	1.3%	0.09 [0.03, 0.15]
McKenna 2001A	0.0111	0.0554	63	60	0.4%	0.01 [-0.10, 0.12]
Paul 2009	0.0426	0.019	282	141	3.4%	0.04 [0.01, 0.08]
Pincus 2004 (PACES)	0.03	0.016	723	562	4.8%	0.03 [-0.00, 0.06]
Puopolo 2007	-0.004	0.0196	437	111	3.2%	-0.00 [-0.04, 0.03]
Sandelin 1997	0.061	0.0474	82	82	0.6%	0.06 [-0.03, 0.15]
Schmitt 1999	0.0059	0.0132	337	56	7.1%	0.01 [-0.02, 0.03]
Schnitzer 2011A	0.0016	0.0214	419	416	2.7%	0.00 [-0.04, 0.04]
Schnitzer 2011B	0.0552	0.0313	256	257	1.3%	0.06 [-0.01, 0.12]
Schubiger 1980	-0.0005	0.0554	114	34	0.4%	-0.00 [-0.11, 0.11]
Scott 2000	0.1419	0.0442	202	303	0.6%	0.14 [0.06, 0.23]
Sheldon 2005	0.0041	0.0134	393	382	6.9%	0.00 [-0.02, 0.03]
Smugar 2006	0.0206	0.0195	916	301	3.3%	0.02 [-0.02, 0.06]
Tannenbaum 2004	0.0468	0.0254	481	243	1.9%	0.05 [-0.00, 0.10]
Wasserman 1984	0	0.0655	14	14	0.3%	0.00 [-0.13, 0.13]
Wiesenhutter 2005	0.0138	0.016	424	104	4.8%	0.01 [-0.02, 0.05]
Williams 2000	0.0144	0.02	453	231	3.1%	0.01 [-0.02, 0.05]
Williams 2001	0.0359	0.0283	472	243	1.5%	0.04 [-0.02, 0.09]
Yocum 2000	0.0403	0.0343	617	157	1.1%	0.04 [-0.03, 0.11]

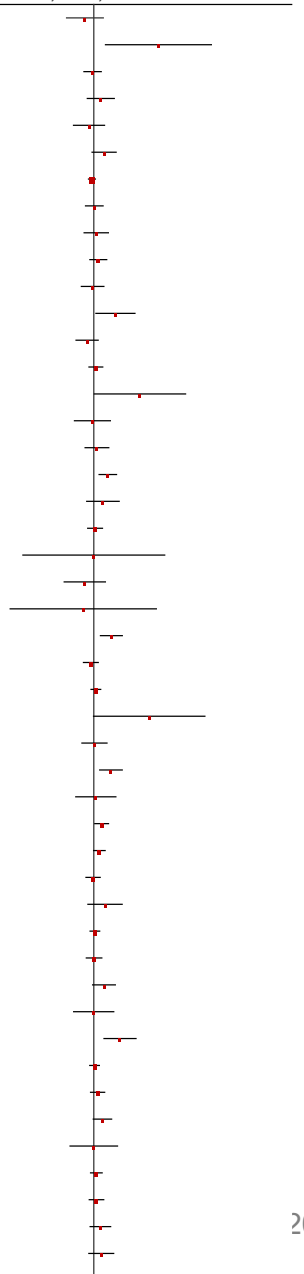


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Figure 46: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at >3 months

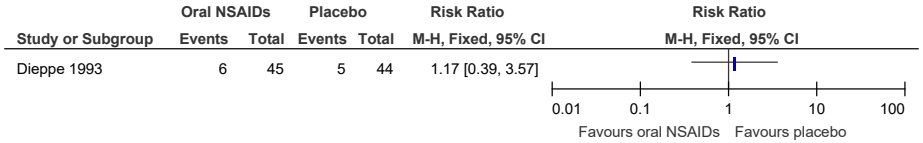


Figure 47: Serious adverse events 2: Cardiovascular adverse events at ≤3 months

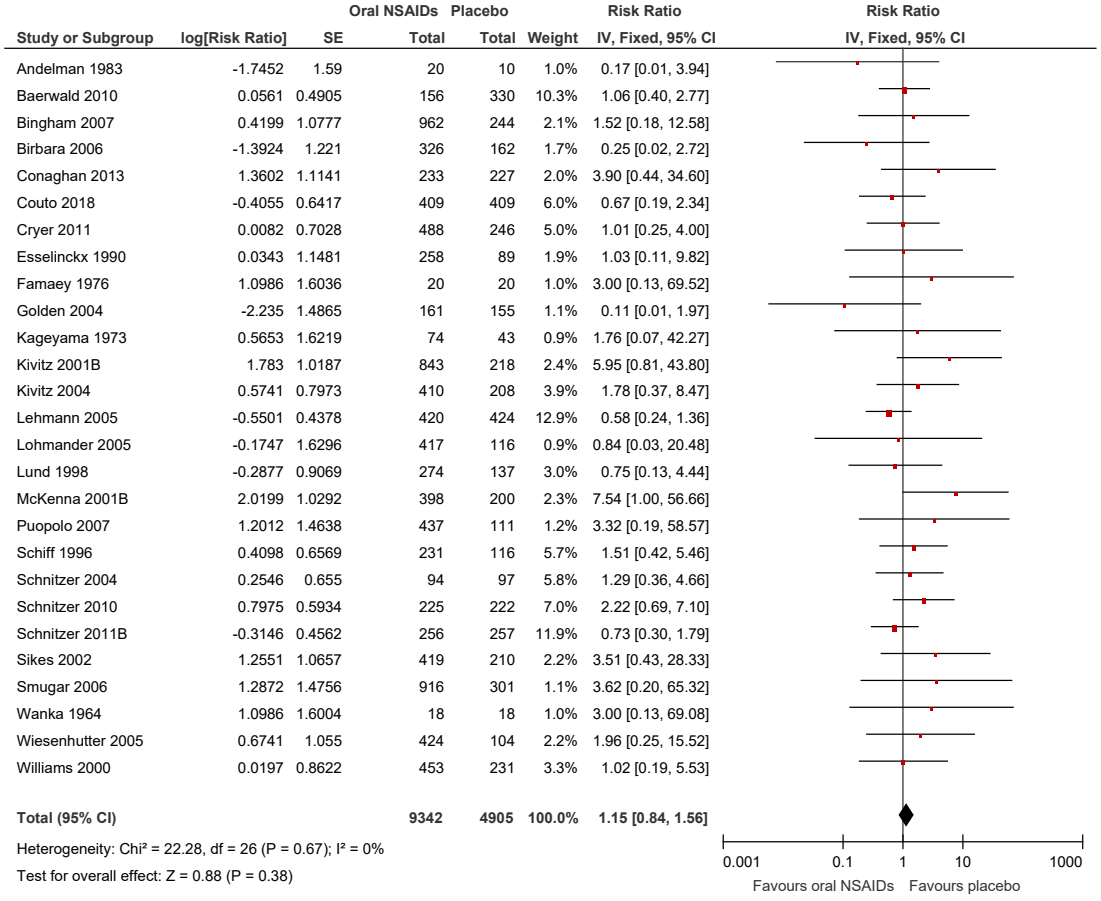


Figure 48: Serious adverse events 2: Cardiovascular adverse events at >3 months

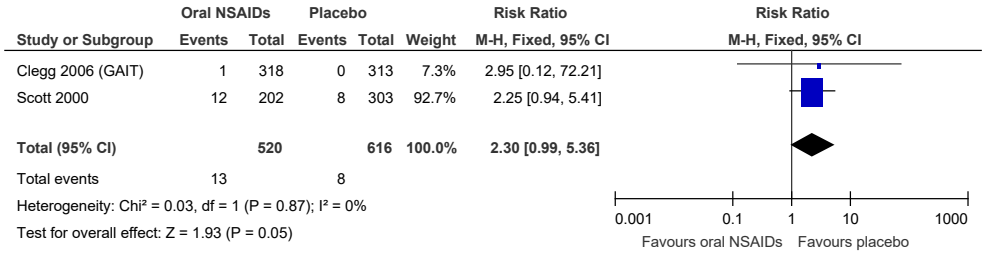


Figure 49: Serious adverse events 3: Hepatorenal adverse events at ≤3 months

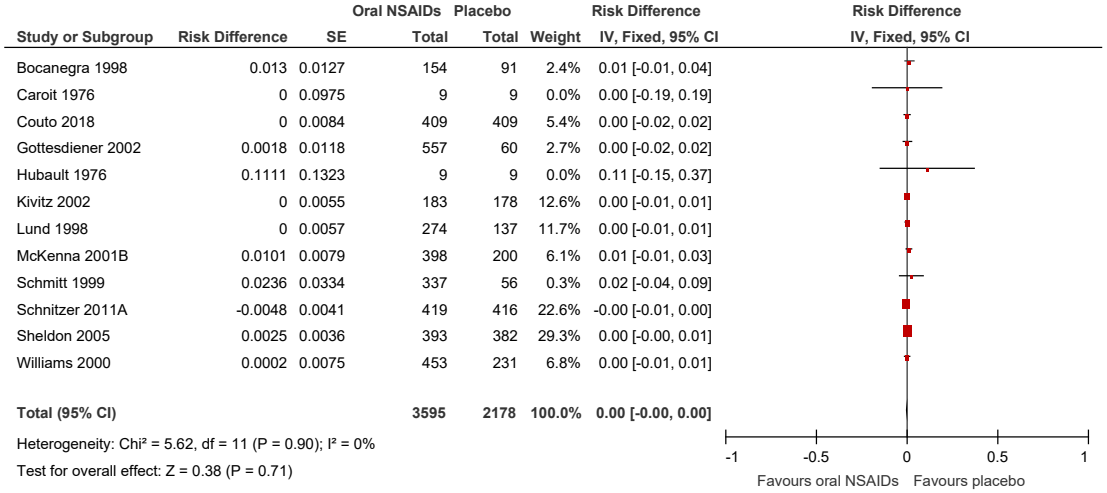


Figure 50: Serious adverse events 3: Hepatorenal adverse events at >3 months

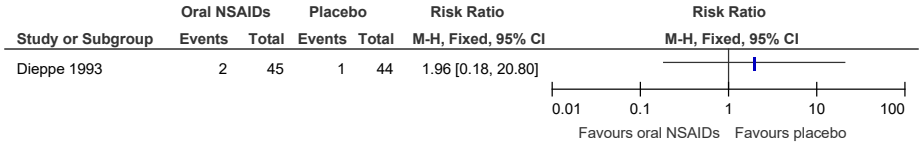
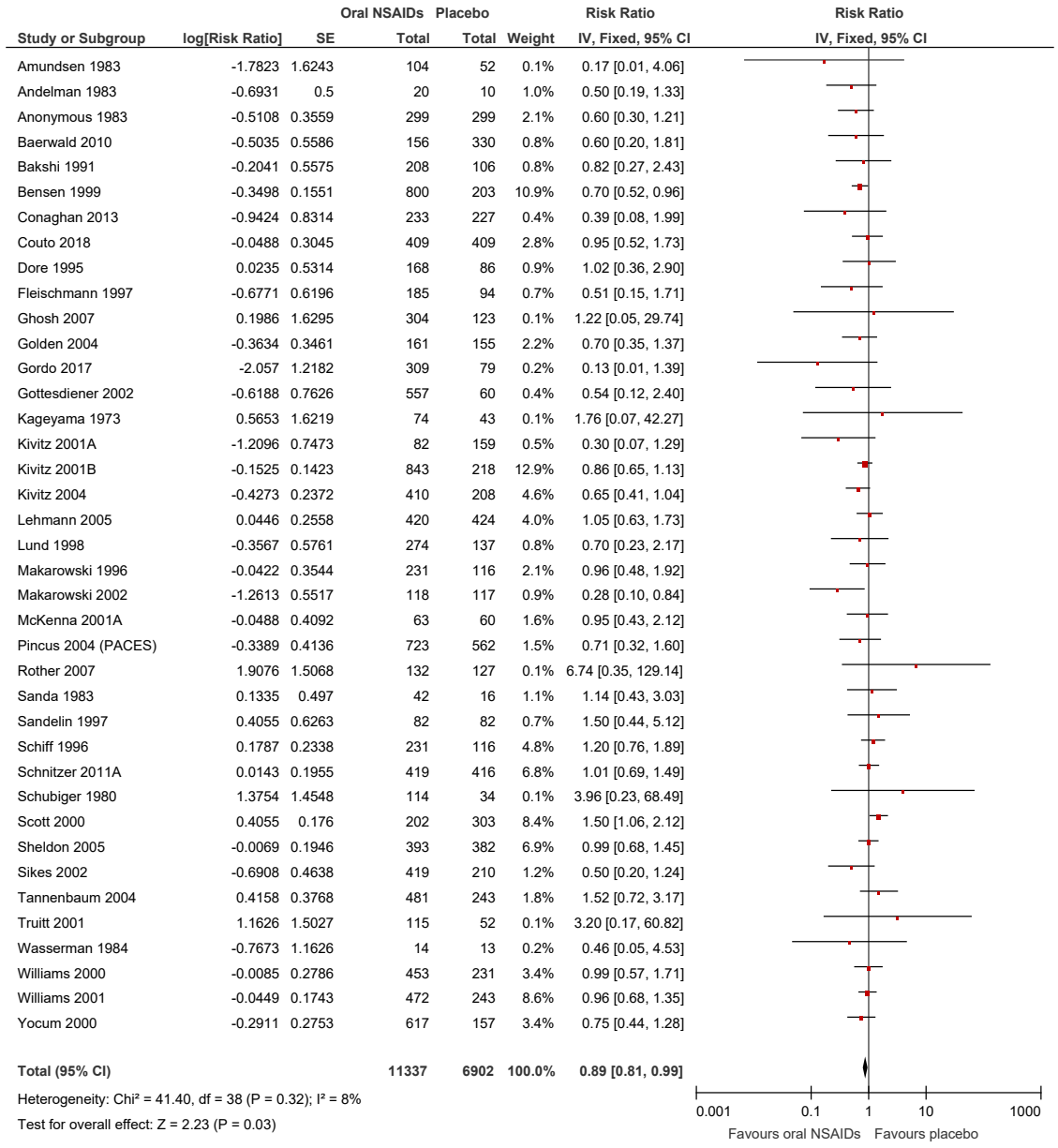


Figure 51: Serious adverse events 4: Central nervous system adverse events at ≤3 months


Oral NSAIDs Placebo Risk Ratio Risk Ratio
Study or Subgroup log[Risk Ratio] SE Total Total Weight IV, Fixed, 95% CI IV, Fixed, 95% CI
Amundsen 1983 -1.7823 1.6243 104 52 0.1% 0.17 [0.01, 4.06]
Andelman 1983 -0.6931 0.5 20 10 1.0% 0.50 [0.19, 1.33]
Anonymous 1983 -0.5108 0.3559 299 299 2.1% 0.60 [0.30, 1.21]
Baerwald 2010 -0.5035 0.5586 156 330 0.8% 0.60 [0.20, 1.81]
Bakshi 1991 -0.2041 0.5575 208 106 0.8% 0.82 [0.27, 2.43]
Bensen 1999 -0.3498 0.1551 800 203 10.9% 0.70 [0.52, 0.96]
Conaghan 2013 -0.9424 0.8314 233 227 0.4% 0.39 [0.08, 1.99]
Couto 2018 -0.0488 0.3045 409 409 2.8% 0.95 [0.52, 1.73]
Dore 1995 0.0235 0.5314 168 86 0.9% 1.02 [0.36, 2.90]
Fleischmann 1997 -0.6771 0.6196 185 94 0.7% 0.51 [0.15, 1.71]
Ghosh 2007 0.1986 1.6295 304 123 0.1% 1.22 [0.05, 29.74]
Golden 2004 -0.3634 0.3461 161 155 2.2% 0.70 [0.35, 1.37]
Gordo 2017 -2.057 1.2182 309 79 0.2% 0.13 [0.01, 1.39]
Gottesdiener 2002 -0.6188 0.7626 557 60 0.4% 0.54 [0.12, 2.40]
Kageyama 1973 0.5653 1.6219 74 43 0.1% 1.76 [0.07, 42.27]
Kivitz 2001A -1.2096 0.7473 82 159 0.5% 0.30 [0.07, 1.29]
Kivitz 2001B -0.1525 0.1423 843 218 12.9% 0.86 [0.65, 1.13]
Kivitz 2004 -0.4273 0.2372 410 208 4.6% 0.65 [0.41, 1.04]
Lehmann 2005 0.0446 0.2558 420 424 4.0% 1.05 [0.63, 1.73]
Lund 1998 -0.3567 0.5761 274 137 0.8% 0.70 [0.23, 2.17]
Makarowski 1996 -0.0422 0.3544 231 116 2.1% 0.96 [0.48, 1.92]
Makarowski 2002 -1.2613 0.5517 118 117 0.9% 0.28 [0.10, 0.84]
McKenna 2001A -0.0488 0.4092 63 60 1.6% 0.95 [0.43, 2.12]
Pincus 2004 (PACES) -0.3389 0.4136 723 562 1.5% 0.71 [0.32, 1.60]
Rother 2007 1.9076 1.5068 132 127 0.1% 6.74 [0.35, 129.14]
Sanda 1983 0.1335 0.497 42 16 1.1% 1.14 [0.43, 3.03]
Sandelin 1997 0.4055 0.6263 82 82 0.7% 1.50 [0.44, 5.12]
Schiff 1996 0.1787 0.2338 231 116 4.8% 1.20 [0.76, 1.89]
Schnitzer 2011A 0.0143 0.1955 419 416 6.8% 1.01 [0.69, 1.49]
Schubiger 1980 1.3754 1.4548 114 34 0.1% 3.96 [0.23, 68.49]
Scott 2000 0.4055 0.176 202 303 8.4% 1.50 [1.06, 2.12]
Sheldon 2005 -0.0069 0.1946 393 382 6.9% 0.99 [0.68, 1.45]
Sikes 2002 -0.6908 0.4638 419 210 1.2% 0.50 [0.20, 1.24]
Tannenbaum 2004 0.4158 0.3768 481 243 1.8% 1.52 [0.72, 3.17]
Truitt 2001 1.1626 1.5027 115 52 0.1% 3.20 [0.17, 60.82]
Wasserman 1984 -0.7673 1.1626 14 13 0.2% 0.46 [0.05, 4.53]
Williams 2000 -0.0085 0.2786 453 231 3.4% 0.99 [0.57, 1.71]
Williams 2001 -0.0449 0.1743 472 243 8.6% 0.96 [0.68, 1.35]
Yocum 2000 -0.2911 0.2753 617 157 3.4% 0.75 [0.44, 1.28]
Total (95% CI) 11337 6902 100.0% 0.89 [0.81, 0.99]
Heterogeneity: Chi² = 41.40, df = 38 (P = 0.32); I² = 8%
Test for overall effect: Z = 2.23 (P = 0.03)
0.001 0.1 1 10 1000
Favours oral NSAIDs Favours placebo

E.1.4 Non-steroidal anti-inflammatory drugs and gastroprotection compared to paracetamol

Figure 52: Quality of life (SF-36 bodily pain subscale, 0-100, high is good, change score) at ≤3 months

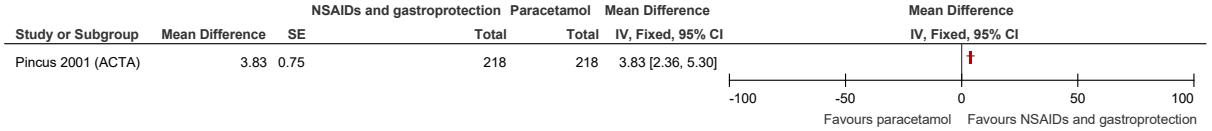


Figure 53: Pain (MDHAQ VAS, 0-100, high is poor, change score) at ≤3 months

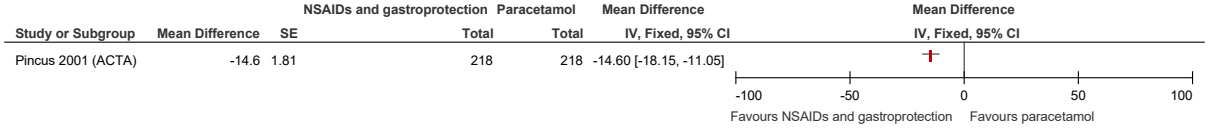


Figure 54: Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months

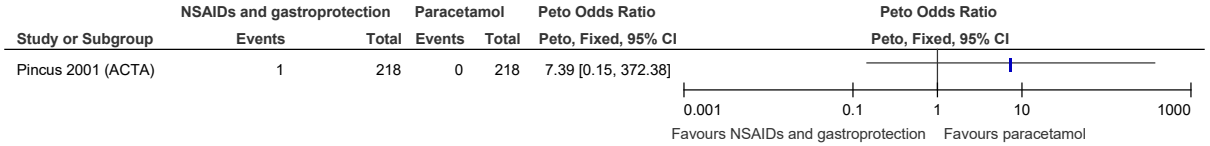


Figure 55: Serious adverse events 2: Cardiovascular adverse events at ≤3 months

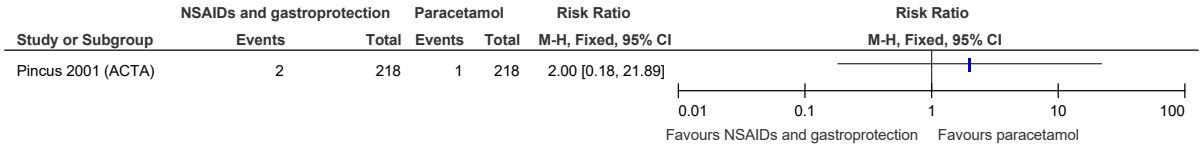


Figure 56: Serious adverse events 3: Hepatorenal adverse events at ≤3 months

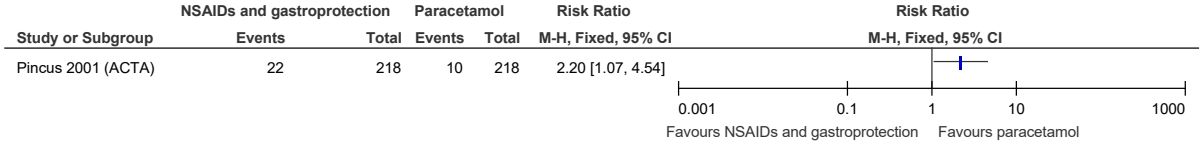
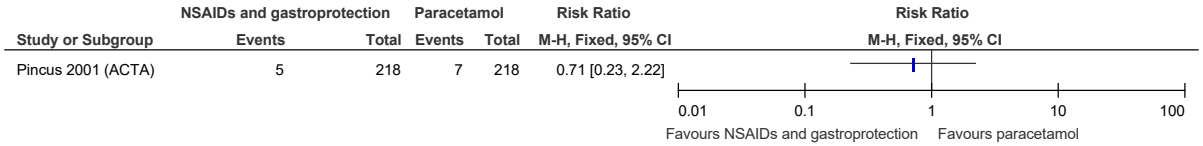


Figure 57: Serious adverse events 4: Central nervous system adverse events at ≤3 months



E.1.5 Non-steroidal anti-inflammatory drugs and gastroprotection compared to oral non-steroidal anti-inflammatory drugs

Figure 58: Pain (VAS, 0-10, high is poor, change score) at ≤3 months

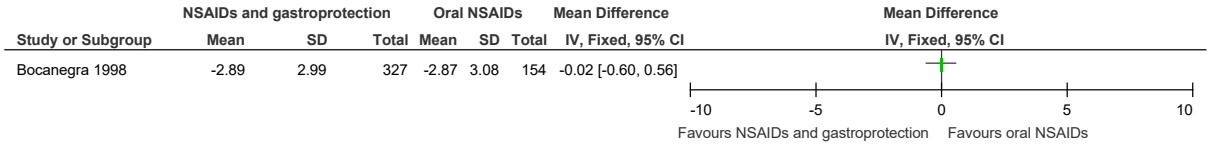


Figure 59: Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months

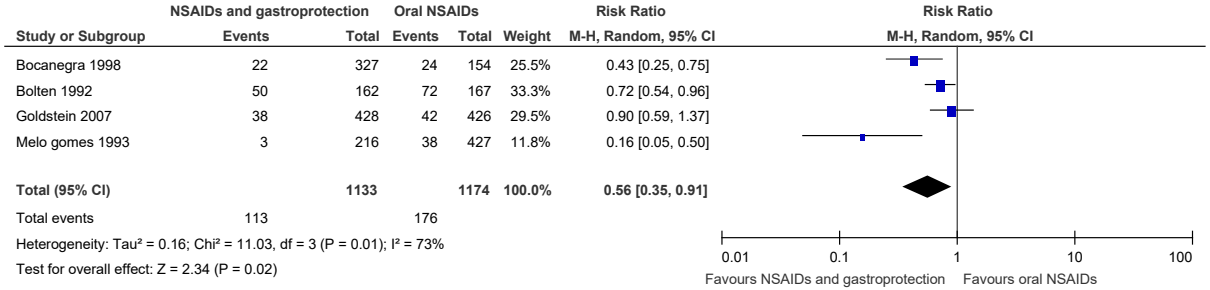


Figure 60: Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at >3 months

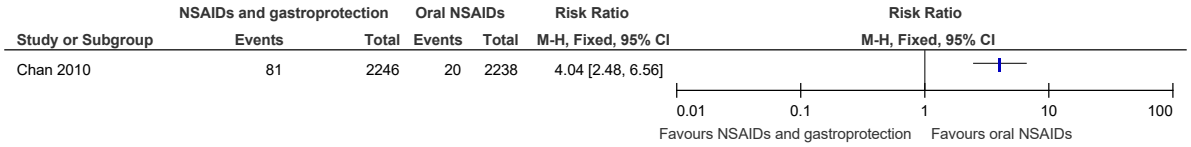


Figure 61: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months

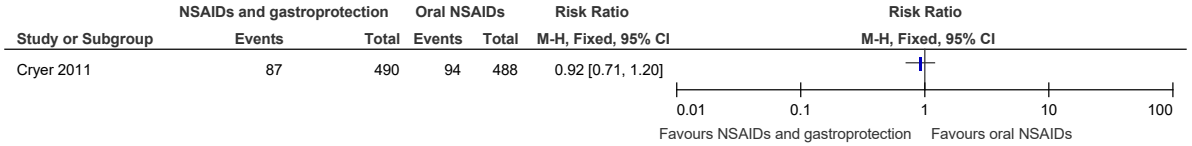


Figure 62: Serious adverse events 2: Cardiovascular adverse events at ≤3 months

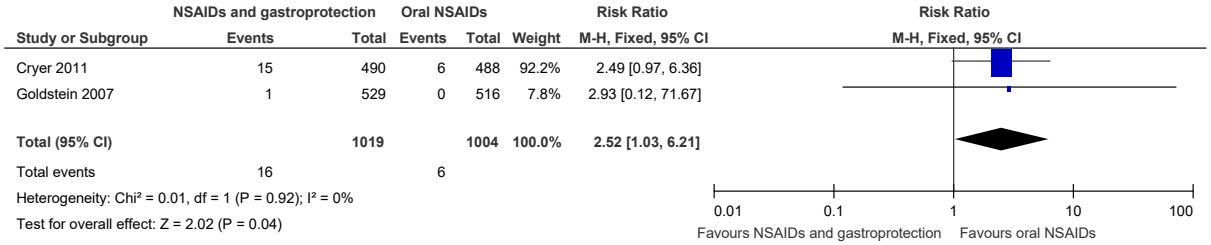


Figure 63: Serious adverse events 3: Hepatorenal adverse events at ≤3 months

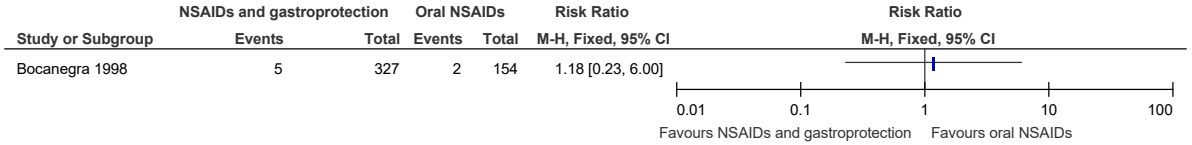
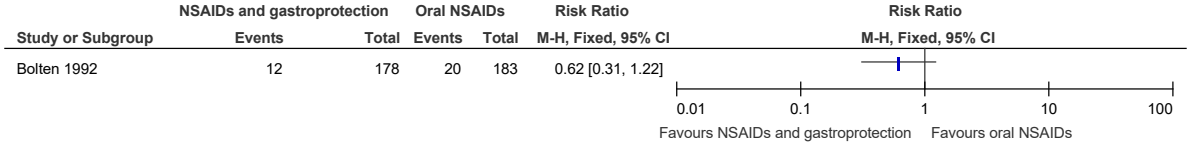


Figure 64: Serious adverse events 4: Central nervous system adverse events at ≤3 months



E.1.6 Non-steroidal anti-inflammatory drugs and gastroprotection compared to placebo

Figure 65: Pain (VAS, 0-10, high is poor, change score) at ≤3 months

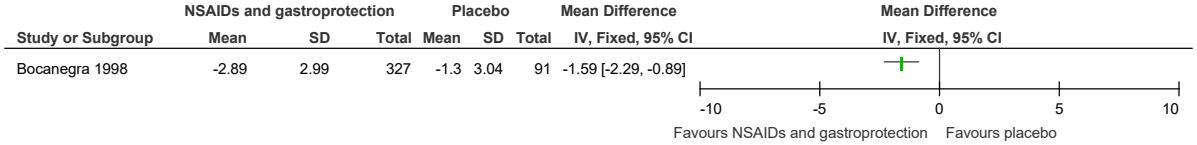


Figure 66: Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months

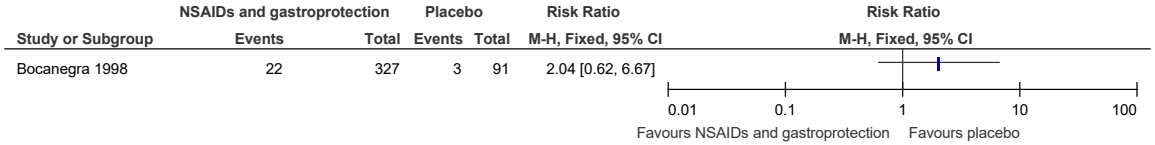


Figure 67: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months

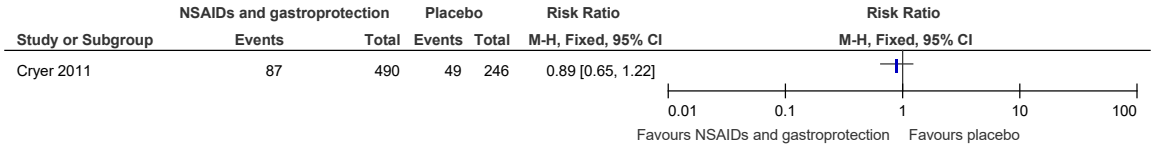


Figure 68: Serious adverse events 2: Cardiovascular adverse events at ≤3 months

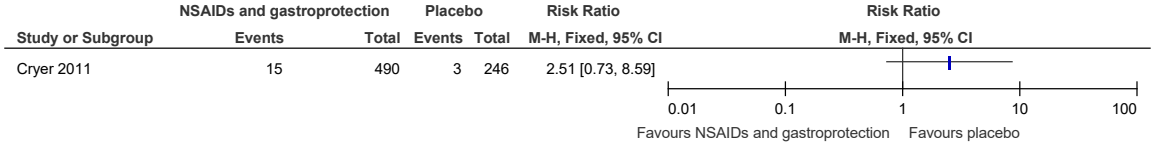
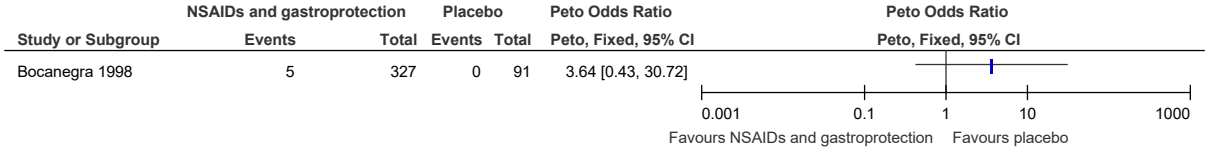


Figure 69: Serious adverse events 3: Hepatorenal adverse events at ≤3 months



E.1.7 Weak opioids compared to placebo

Figure 70: Pain (WOMAC, 0-500, high is poor, change score) at ≤3 months)

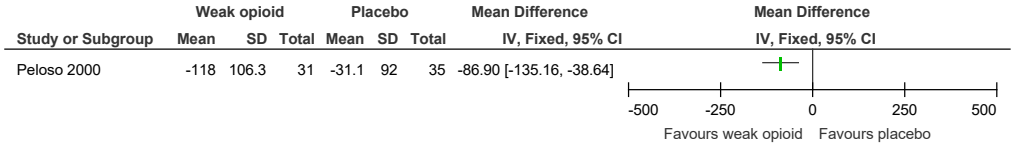
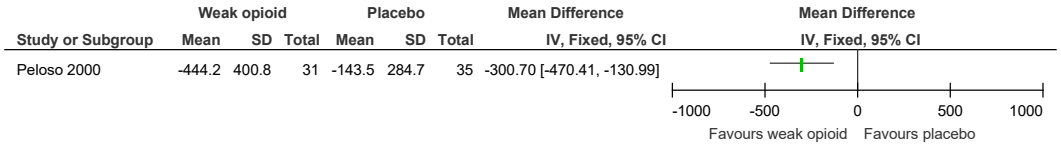


Figure 71: Physical function (WOMAC, 0-1700, high is poor, change score) at ≤3 months)



E.1.8 Strong opioids compared to oral non-steroidal anti-inflammatory drugs

Figure 72: Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at ≤3 months

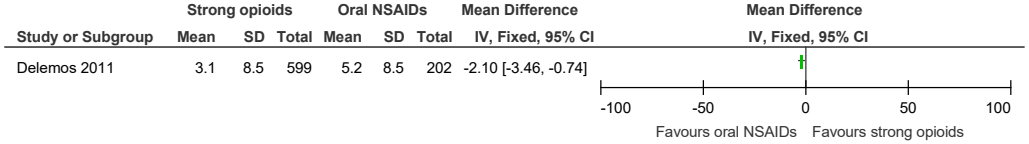


Figure 73: Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at ≤3 months

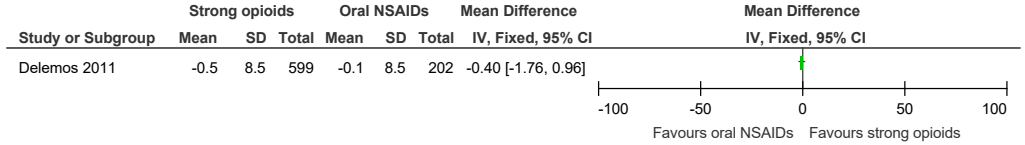


Figure 74: Pain (WOMAC, 0-500, high is poor, change scores) at ≤3 months

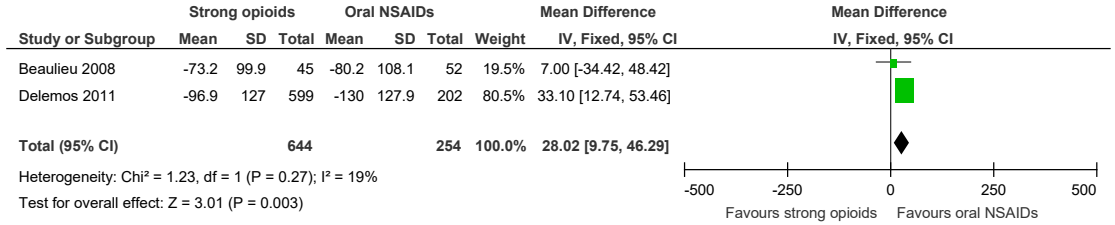


Figure 75: Pain (VAS, 0-100, high is poor, final value) at ≤3 months

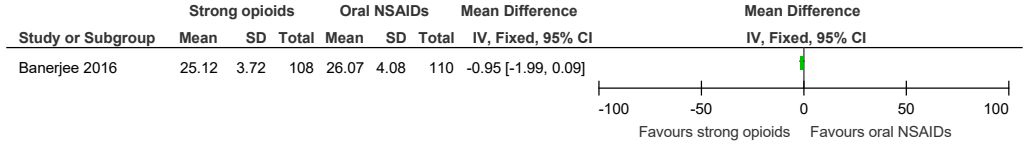


Figure 76: Physical function (WOMAC, 0-1700, high is poor, change scores) at ≤3 months

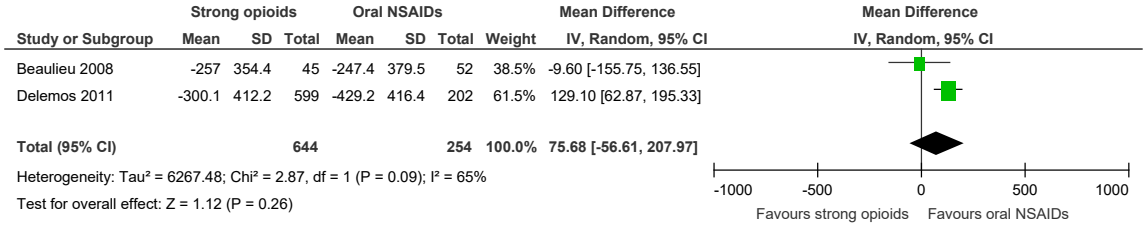


Figure 77: Serious adverse events 3: Hepatorenal adverse events at ≤3 months

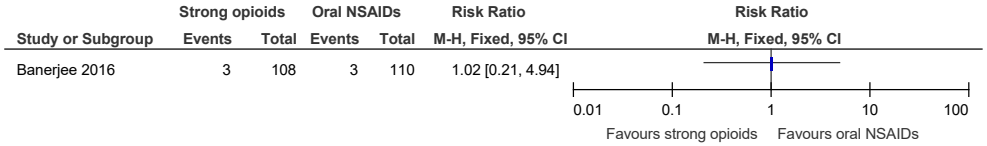
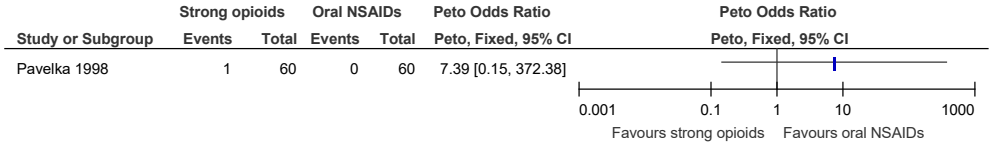


Figure 78: Serious adverse events 4: Central nervous system adverse events at ≤3 months



E.1.9 Strong opioids compared to placebo

Figure 79: Quality of life (EQ-5D, 0-1, high is good, change scores) at ≤3 months

	Strong opioids			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Afilalo 2010	0.16	0.37	686	0.1	0.37	337	47.5%	0.06 [0.01, 0.11]
Serrie 2017	0.15	0.05	650	0.2	0.02	337	52.5%	-0.05 [-0.05, -0.05]
Total (95% CI)			**1336**			**674**	**100.0%**	**0.00 [-0.11, 0.11]**

Heterogeneity: Tau² = 0.01; Chi² = 19.81, df = 1 (P < 0.00001); I² = 95%

Test for overall effect: Z = 0.04 (P = 0.97)

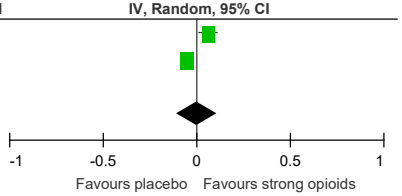


Figure 80: Quality of life (SF-36 physical component summary, 0-100, high is good, change scores) at ≤3 months

	Strong opioids			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Delemos 2011	3.1	8.5	599	3	8.5	200	40.6%	0.10 [-1.26, 1.46]
Gana 2006	3.6	8.5	806	2.4	8.6	205	43.4%	1.20 [-0.12, 2.52]
Matsumoto 2005	4	9.6	125	1.8	7.8	124	15.9%	2.20 [0.03, 4.37]
Total (95% CI)			**1530**			**529**	**100.0%**	**0.91 [0.05, 1.78]**

Heterogeneity: Chi² = 2.90, df = 2 (P = 0.23); I² = 31%

Test for overall effect: Z = 2.06 (P = 0.04)

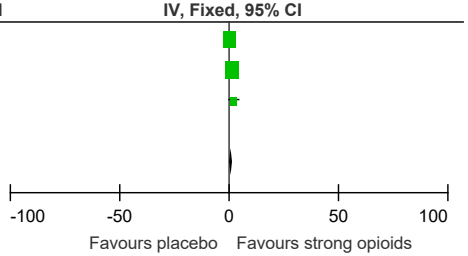


Figure 81: Quality of life (SF-36 mental component summary, 0-100, high is good, change scores) at ≤3 months

	Strong opioids			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Delemos 2011	-0.5	8.5	599	-0.3	8.5	200	38.2%	-0.20 [-1.56, 1.16]
Gana 2006	0.1	8.5	806	-0.3	8.6	205	38.9%	0.40 [-0.92, 1.72]
Matsumoto 2005	-0.8	10.1	125	2.2	10	124	22.9%	-3.00 [-5.50, -0.50]
Total (95% CI)			**1530**			**529**	**100.0%**	**-0.61 [-2.19, 0.97]**

Heterogeneity: Tau² = 1.22; Chi² = 5.60, df = 2 (P = 0.06); I² = 64%

Test for overall effect: Z = 0.75 (P = 0.45)

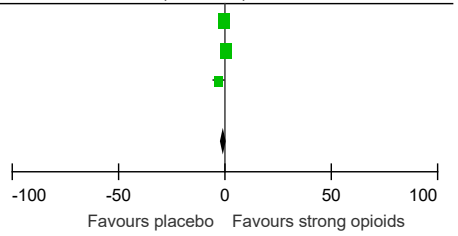


Figure 82: Quality of life (SF-36 pain subscale, 0-100, high is good, final value and change score) at ≤3 months

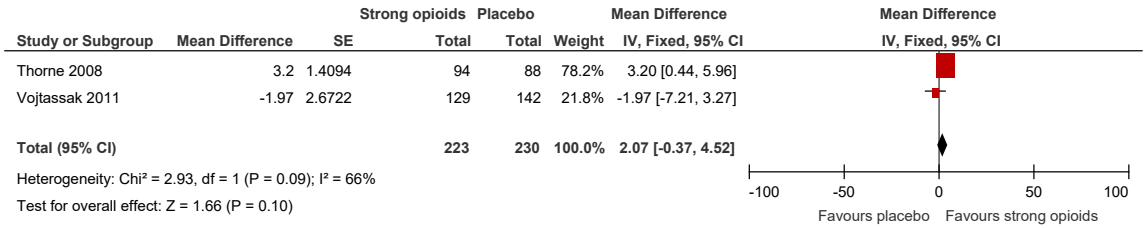


Figure 83: Quality of life (SF-36 physical functioning subscale, 0-100, high is good, final value) at ≤3 months

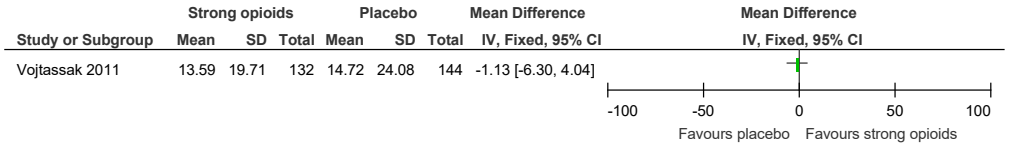


Figure 84: Quality of life (SF-36 vitality subscale, 0-100, high is good, final value) at ≤3 months

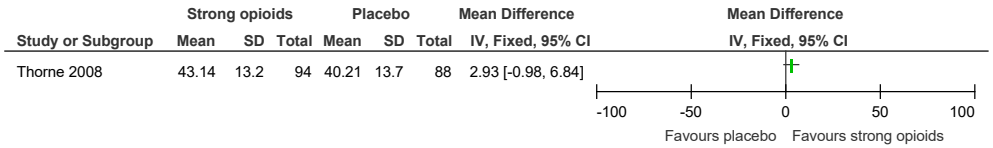


Figure 85: Quality of life (SF-36 general health perception subscale, 0-100, high is good, final value) at ≤3 months

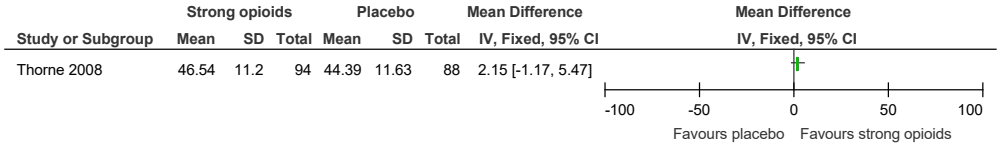


Figure 86: Quality of life (SF-36 social functioning subscale, 0-100, high is good, final value) at ≤3 months

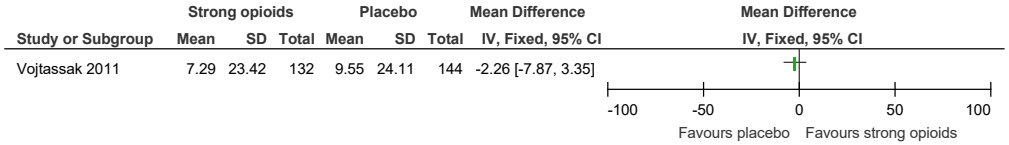


Figure 87: Pain (WOMAC, VAS, NRS [different scale ranges], high is poor, change scores) at ≤3 months

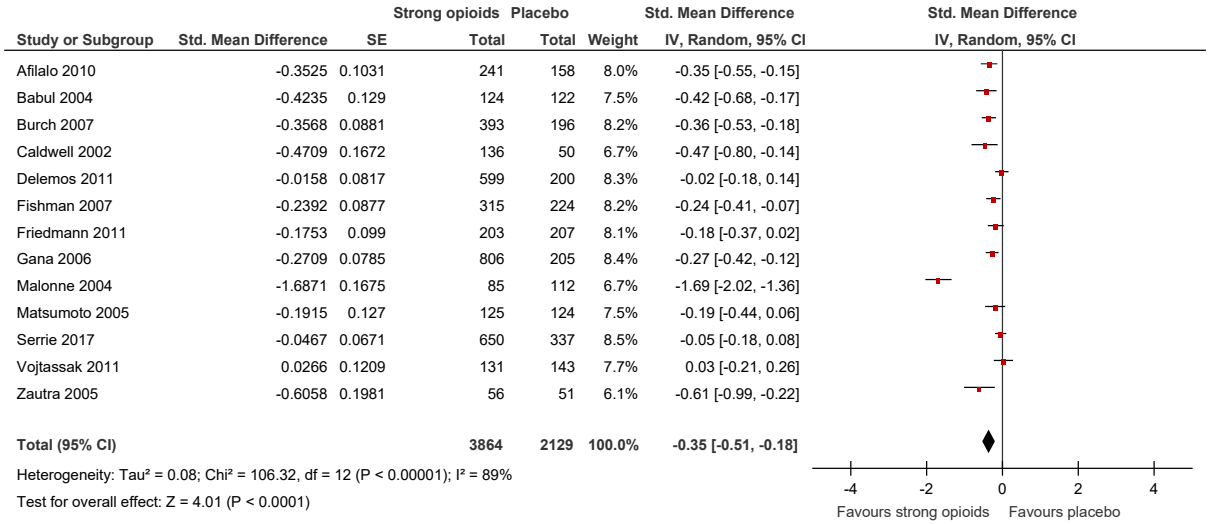


Figure 88: Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months

Study or Subgroup	Std. Mean Difference	SE	Strong opioids Total	Placebo Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Chindalore 2005	-0.2009	0.1719	102	51	30.8%	-0.20 [-0.54, 0.14]
Fleischmann 2001	-0.4314	0.1782	63	66	28.6%	-0.43 [-0.78, -0.08]
Thorne 2008	-0.3707	0.1496	94	88	40.6%	-0.37 [-0.66, -0.08]
Total (95% CI)			**259**	**205**	**100.0%**	**-0.34 [-0.52, -0.15]**

Heterogeneity: Chi² = 0.96, df = 2 (P = 0.62); I² = 0%

Test for overall effect: Z = 3.52 (P = 0.0004)

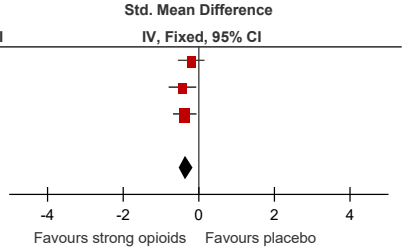


Figure 89: Physical function (WOMAC [different scale ranges], high is poor, change scores) at ≤3 months

Study or Subgroup	Std. Mean Difference	SE	Strong opioids Total	Placebo Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Afilalo 2010	-0.3092	0.103	241	158	16.5%	-0.31 [-0.51, -0.11]
Babul 2004	-0.4234	0.129	124	122	10.5%	-0.42 [-0.68, -0.17]
Caldwell 2002	-0.3577	0.1668	134	50	6.3%	-0.36 [-0.68, -0.03]
Delemos 2011	-0.0242	0.0817	599	200	26.2%	-0.02 [-0.18, 0.14]
Gana 2006	-0.2517	0.0784	806	205	28.5%	-0.25 [-0.41, -0.10]
Vojtassak 2011	-0.0022	0.1205	132	144	12.0%	-0.00 [-0.24, 0.23]
Total (95% CI)			**2036**	**879**	**100.0%**	**-0.20 [-0.28, -0.11]**

Heterogeneity: Chi² = 12.77, df = 5 (P = 0.03); I² = 61%

Test for overall effect: Z = 4.69 (P < 0.00001)

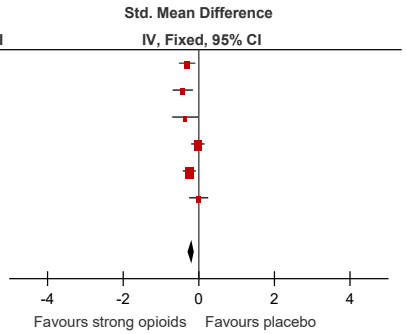


Figure 90: Physical function (WOMAC [different scale ranges], high is poor, final values) at ≤3 months

Study or Subgroup	Std. Mean Difference	SE	Strong opioids Total	Placebo Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Fleischmann 2001	-0.3328	0.1774	63	66	41.3%	-0.33 [-0.68, 0.01]
Thorne 2008	-0.2542	0.1489	94	88	58.7%	-0.25 [-0.55, 0.04]
Total (95% CI)			**157**	**154**	**100.0%**	**-0.29 [-0.51, -0.06]**

Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%

Test for overall effect: Z = 2.51 (P = 0.01)

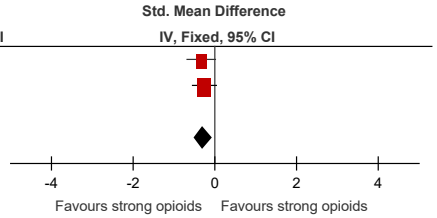


Figure 91: Psychological distress (negative affect scale, 0-10, high is poor, change score) at ≤3 months

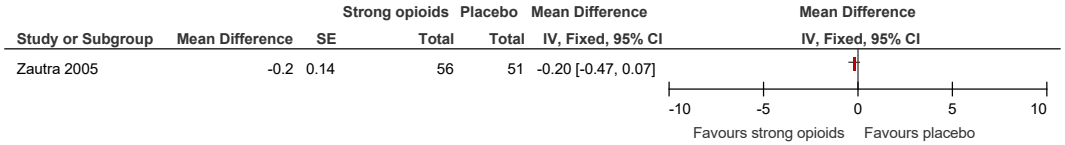


Figure 92: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months

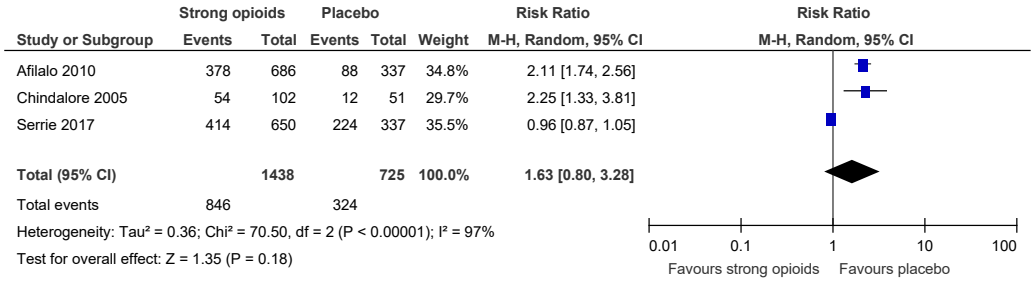


Figure 93: Serious adverse events 2: Cardiovascular adverse events at ≤3 months

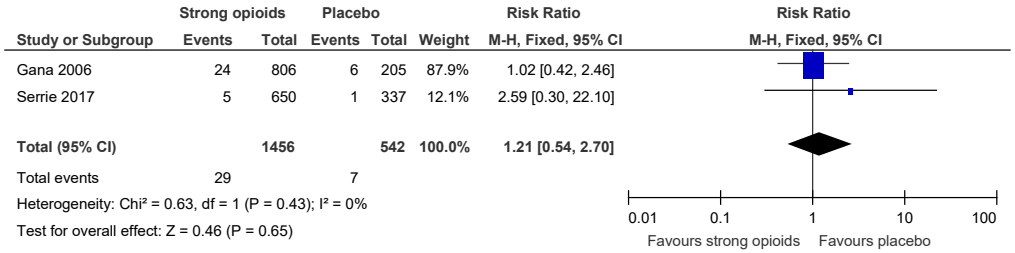
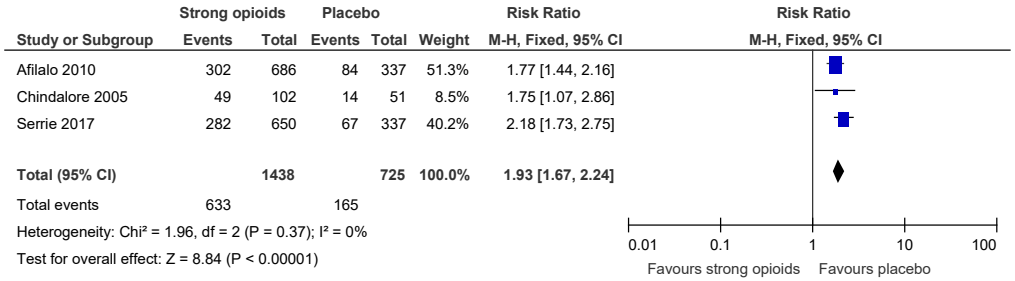


Figure 94: Serious adverse events 4: Central nervous system adverse events at ≤3 months



E.1.10 Anti-epileptic drugs compared to paracetamol

Figure 95: Pain (WOMAC, 0-100, %, high is poor, change score) at ≤3 months

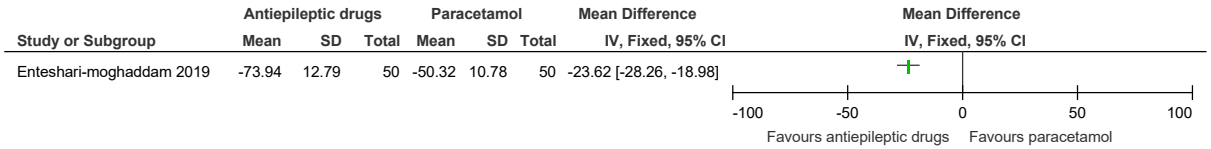


Figure 96: Physical function (WOMAC, 0-100, %, high is poor, change score) at ≤3 months

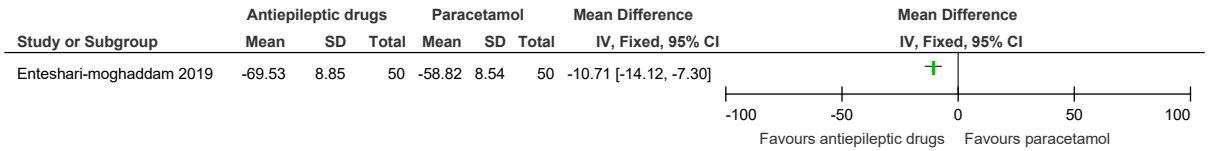
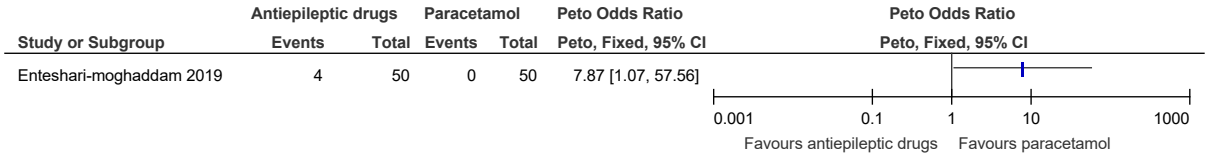


Figure 97: Serious adverse events 4: Central nervous system adverse events at ≤3 months



E.1.11 Anti-epileptic drugs compared to antidepressants

Figure 98: Pain (AUSCAN, 0-500, high is poor, change score) at ≤3 months

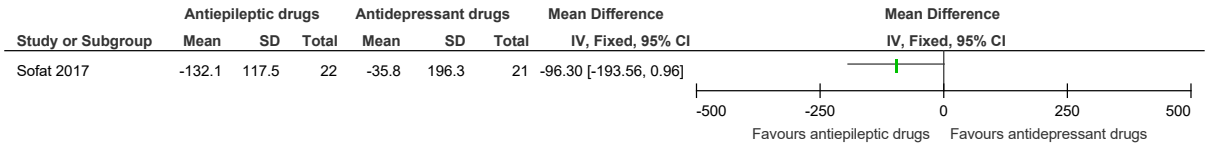


Figure 99: Pain (WOMAC, 0-100, %, high is poor, change score) at ≤3 months

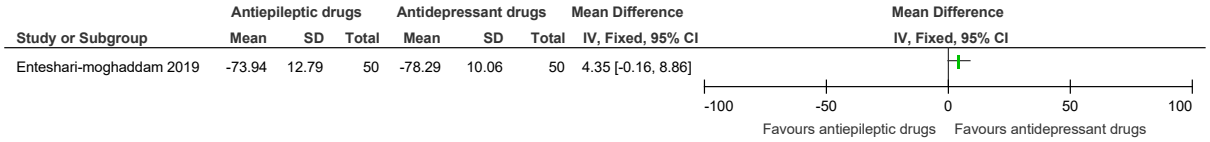


Figure 100: Physical function (AUSCAN, 0-900, high is poor, change scores) at ≤3 months

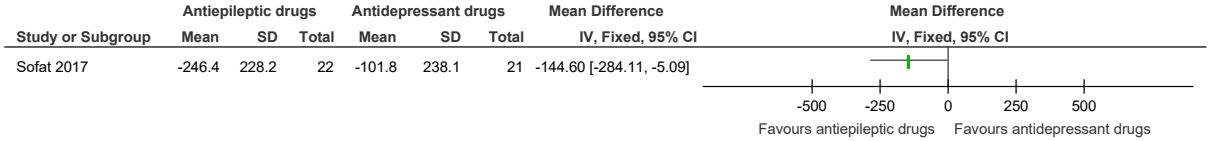


Figure 101: Physical function (WOMAC, 0-100, %, high is poor, change score) at ≤3 months

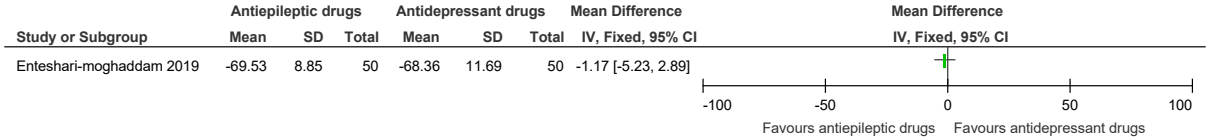


Figure 102: Psychological distress (HADS anxiety score, 0-21, high is poor, change score) at ≤3 months

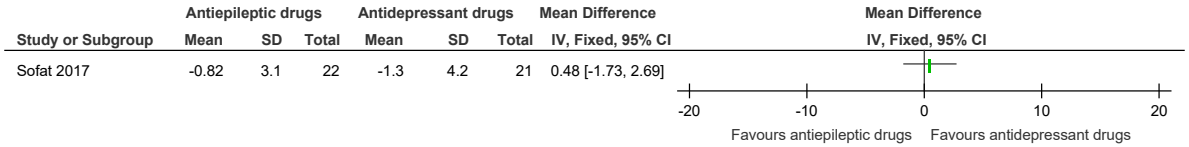


Figure 103: Psychological distress (HADS depression score, 0-21, high is poor, change score) at ≤3 months)

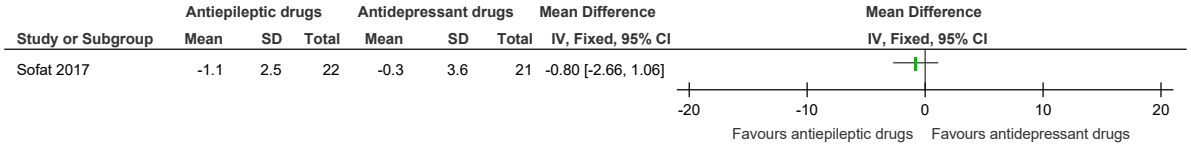


Figure 104: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months

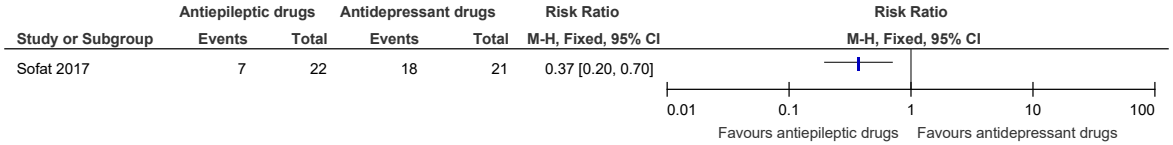


Figure 105: Serious adverse events 2: Cardiovascular adverse events at ≤3 months

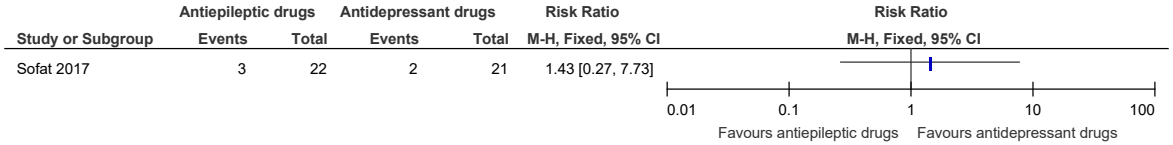
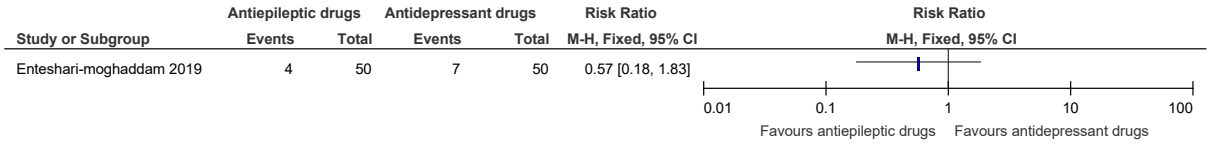


Figure 106: Serious adverse events 4: Central nervous system adverse events at ≤3 months



E.1.12 Anti-epileptic drugs compared to placebo

Figure 107: Pain (AUSCAN, 0-500, high is poor, change score) at ≤3 months

	Antiepileptic drugs			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Sofat 2017	-132.1	117.5	22	-46.61	113.3	22	-85.49 [-153.70, -17.28]	

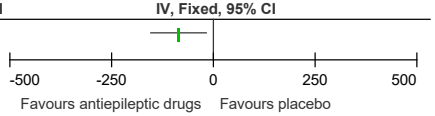


Figure 108: Physical function (AUSCAN, 0-900, high is poor, change score) at ≤3 months

	Antiepileptic drugs			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Sofat 2017	-246.4	228.2	22	-67.3	161.1	22	-179.10 [-295.82, -62.38]	

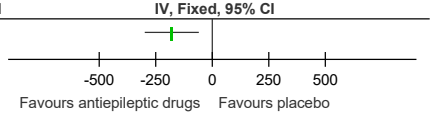


Figure 109: Psychological distress (HADS anxiety score, 0-21, high is poor, change score) at ≤3 months)

	Antiepileptic drugs			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Sofat 2017	-0.82	3.1	22	0.5	2.2	22	-1.32 [-2.91, 0.27]	

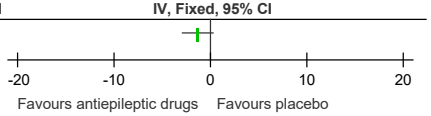


Figure 110: Psychological distress (HADS depression score, 0-21, high is poor, change score) at ≤3 months)

	Antiepileptic drugs			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Sofat 2017	-1.1	2.5	22	0.05	3.2	22	-1.15 [-2.85, 0.55]	

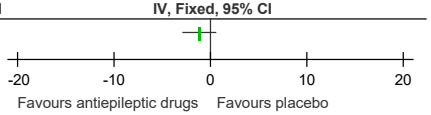


Figure 111: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months

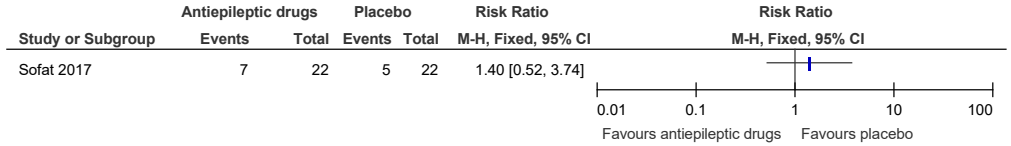
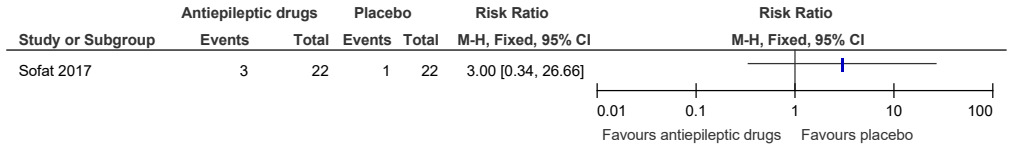


Figure 112: Serious adverse events 2: Cardiovascular adverse events at ≤3 months



E.1.13 Antidepressants compared to paracetamol

Figure 113: Pain (WOMAC, 0-100, %, high is poor, change score) at ≤3 months)

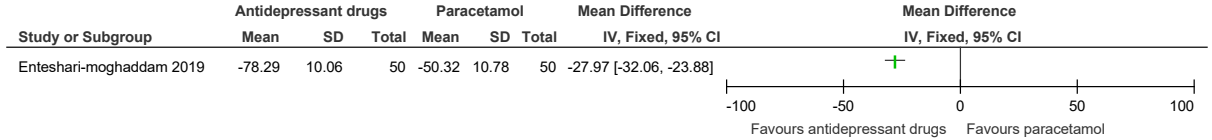


Figure 114: Physical function (WOMAC, 0-100, %, high is poor, change score) at ≤3 months

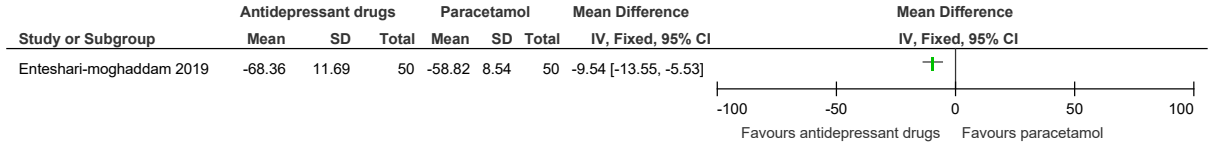
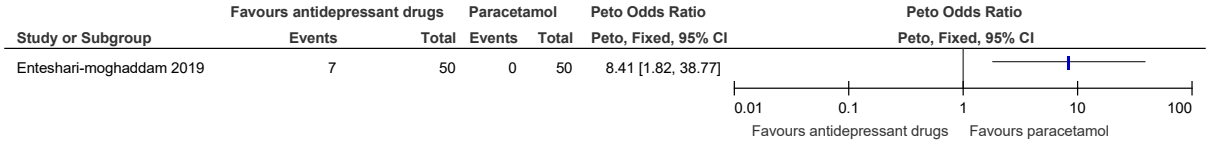


Figure 115: Serious adverse events 4: Central nervous system adverse events at ≤3 months



E.1.14 Antidepressants compared to placebo

Figure 116: Quality of life (EQ-5D, -0.11-1, high is good, change scores) at ≤3 months

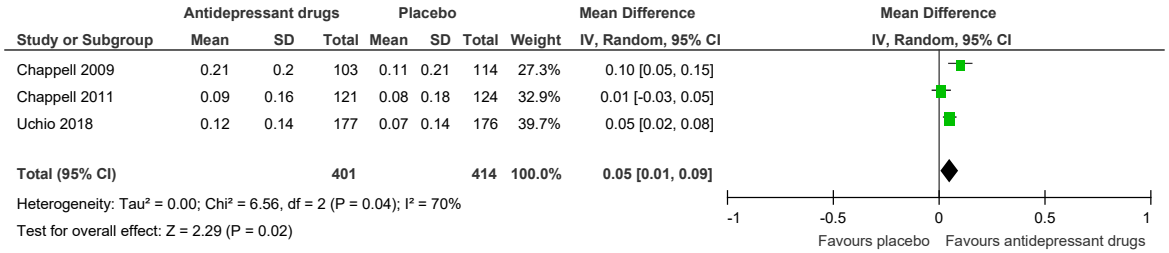


Figure 117: Quality of life (SF-36 physical function, 0-100, high is good, change score) at ≤3 months

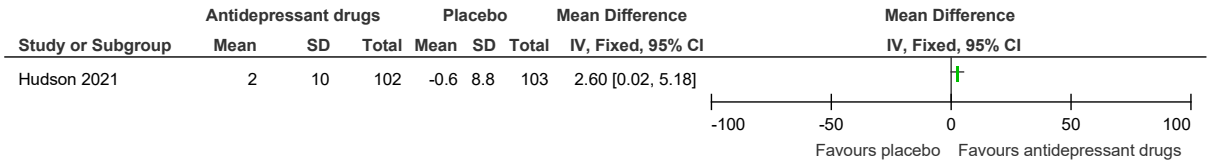


Figure 118: Quality of life (SF-36 bodily pain, 0-100, high is good, change score) at ≤3 months

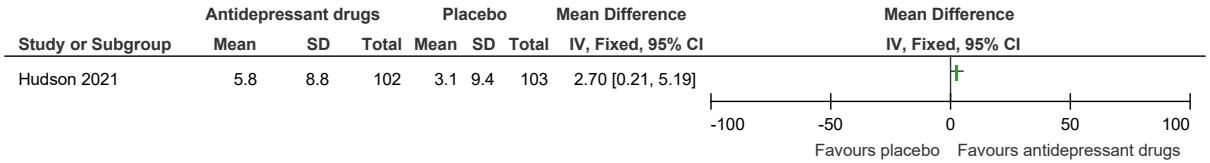


Figure 119: Quality of life (SF-36 role physical, 0-100, high is good, change score) at ≤3 months

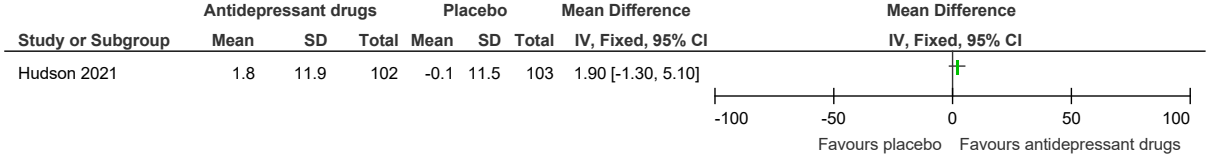


Figure 120: Quality of life (SF-36 vitality, 0-100, high is good, change score) at ≤3 months

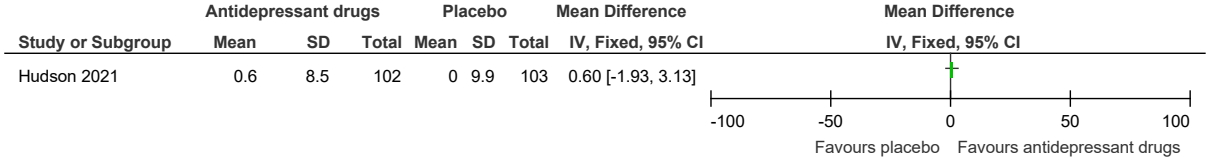


Figure 121: Quality of life (SF-36 general health, 0-100, high is good, change score) at ≤3 months

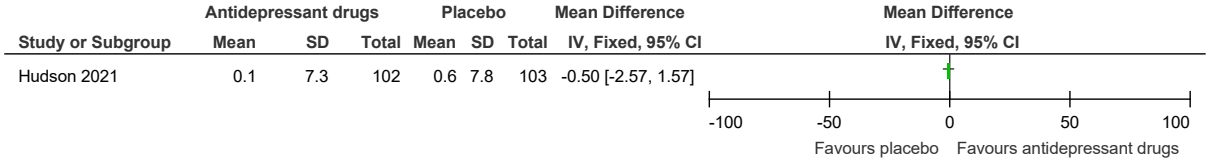


Figure 122: Quality of life (SF-36 role emotional, 0-100, high is good, change score) at ≤3 months

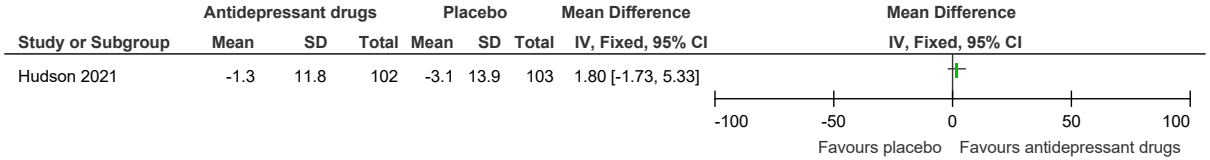


Figure 123: Quality of life (SF-36 mental health, 0-100, high is good, change score) at ≤3 months

Study or Subgroup	Antidepressant drugs Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Hudson 2021	-0.6	9.7	102	-0.4	8.9	103	-0.20 [-2.75, 2.35]

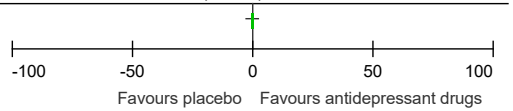


Figure 124: Quality of life (SF-36 social function, 0-100, high is good, change score) at ≤3 months

Study or Subgroup	Antidepressant drugs Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Hudson 2021	0.4	13.2	102	-1.6	12.8	103	2.00 [-1.56, 5.56]

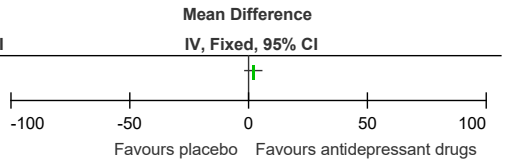


Figure 125: Pain (WOMAC, AUSCAN [different scale ranges], high is poor, change scores) at ≤3 months

Study or Subgroup	Antidepressant drugs Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Chappell 2009	-4.64	3.62	107	-3.24	3.79	117	11.4%	-0.38 [-0.64, -0.11]
Chappell 2011	-4.27	3.3	123	-3.49	3.89	127	12.9%	-0.22 [-0.46, 0.03]
Frakes 2011	-22.05	17.7	258	-15.6	14.4	256	26.2%	-0.40 [-0.57, -0.22]
Hudson 2021	-24.3	22.5	102	-18.7	25.8	103	10.6%	-0.23 [-0.51, 0.04]
Sofat 2017	-35.8	196.3	21	-46.61	113.3	22	2.2%	0.07 [-0.53, 0.66]
Uchio 2018	-3.99	2.79	177	-2.43	2.79	176	17.7%	-0.56 [-0.77, -0.35]
Wang 2017	-3.03	2.84	184	-2.32	2.82	182	18.9%	-0.25 [-0.46, -0.04]
Total (95% CI)			**972**			**983**	**100.0%**	**-0.34 [-0.43, -0.25]**

Heterogeneity: Chi² = 8.62, df = 6 (P = 0.20); I² = 30%

Test for overall effect: Z = 7.55 (P < 0.00001)

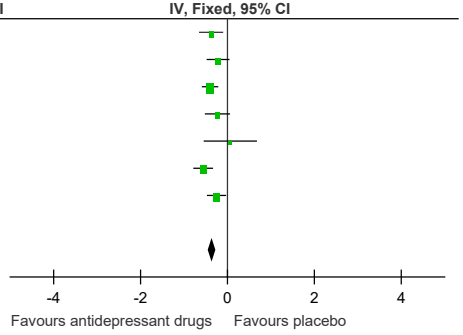


Figure 126: Pain (WOMAC, 0-20, high is poor, final value) at >3 months

Study or Subgroup	Antidepressant drugs Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Abou-Raya 2012	6	4.1	144	8.4	5.4	144	-2.40 [-3.51, -1.29]

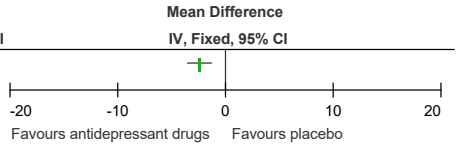


Figure 127: Physical function (WOMAC, AUSCAN [different scale ranges], high is poor, change scores) at ≤3 months

Study or Subgroup	Antidepressant drugs Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Chappell 2011	-13.78	10.78	118	-10.75	10.98	126	14.3%	-0.28 [-0.53, -0.03]
Frakes 2011	-21.1	17.9	251	-13.81	18	253	29.3%	-0.41 [-0.58, -0.23]
Hudson 2021	-23.2	21.5	102	-18	23.2	103	12.1%	-0.23 [-0.51, 0.04]
Sofat 2017	-101.8	238.1	21	-67.3	161.1	22	2.5%	-0.17 [-0.77, 0.43]
Uchio 2018	-11.77	8.91	177	-7.07	8.76	176	20.2%	-0.53 [-0.74, -0.32]
Wang 2017	-9.64	9.2	184	-7.28	9.02	182	21.5%	-0.26 [-0.46, -0.05]
Total (95% CI)			**853**			**862**	**100.0%**	**-0.35 [-0.45, -0.26]**

Heterogeneity: Chi² = 5.31, df = 5 (P = 0.38); I² = 6%

Test for overall effect: Z = 7.26 (P < 0.00001)

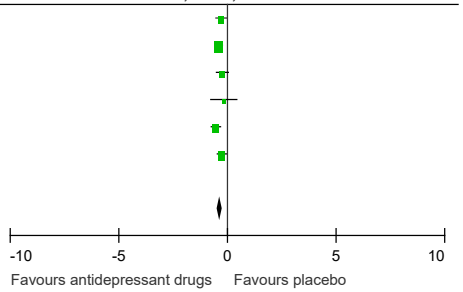


Figure 128: Physical function (WOMAC, 0-68, high is poor, final value) at >3 months

Study or Subgroup	Antidepressant drugs Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Abou-Raya 2012	24.6	8.4	144	30.3	9.8	144	-5.70 [-7.81, -3.59]

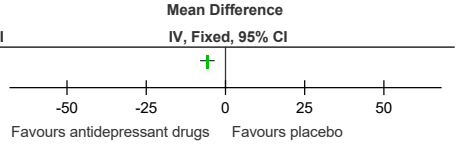


Figure 129: Psychological distress (Beck depression Inventory, HADS depression score [different scale ranges], high is poor, change scores) at ≤3 months

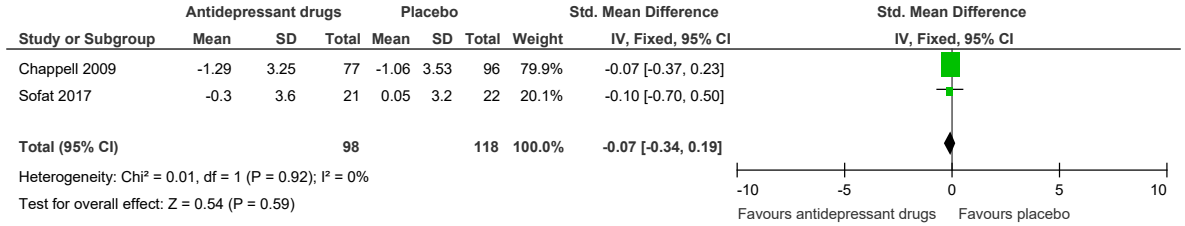


Figure 130: Psychological distress (HADS anxiety scale, 0-21, high is poor, change scores) at ≤3 months)

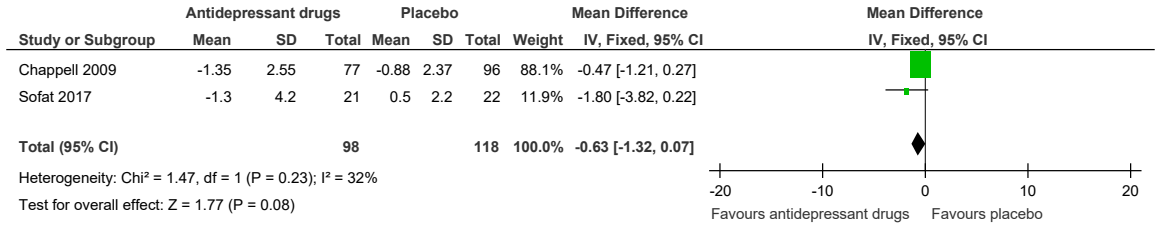


Figure 131: Psychological distress (Geriatric depression scale, 0-15, high is poor, final value) at >3 months

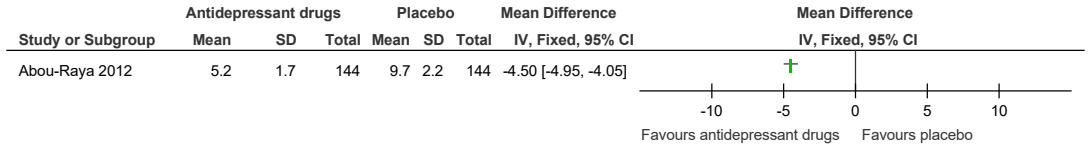


Figure 132: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months

Study or Subgroup	Antidepressant drugs Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chappell 2011	9	128	2	128	23.8%	4.50 [0.99, 20.42]
Frakes 2011	0	264	1	260	18.0%	0.33 [0.01, 8.02]
Sofat 2017	18	21	5	22	58.2%	3.77 [1.71, 8.31]
Total (95% CI)		**413**		**410**	**100.0%**	**3.33 [1.70, 6.49]**
Total events	27		8			

Heterogeneity: Chi² = 2.27, df = 2 (P = 0.32); I² = 12%

Test for overall effect: Z = 3.52 (P = 0.0004)

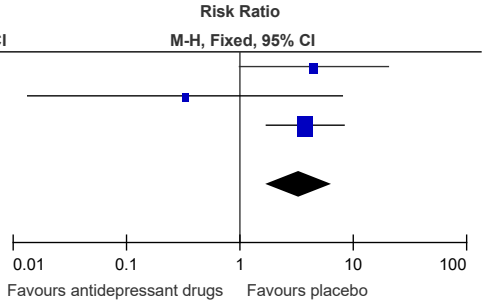


Figure 133: Serious adverse events 2: Cardiovascular adverse events at ≤3 months

Study or Subgroup	Antidepressant drugs Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chappell 2011	2	128	1	128	28.8%	2.00 [0.18, 21.78]
Frakes 2011	2	264	0	260	14.5%	4.92 [0.24, 102.08]
Hudson 2021	2	99	0	102	14.2%	5.15 [0.25, 105.94]
Sofat 2017	2	21	1	22	28.1%	2.10 [0.20, 21.42]
Uchio 2018	1	178	0	176	14.5%	2.97 [0.12, 72.33]
Total (95% CI)		**690**		**688**	**100.0%**	**3.04 [0.92, 10.08]**
Total events	9		2			

Heterogeneity: Chi² = 0.43, df = 4 (P = 0.98); I² = 0%

Test for overall effect: Z = 1.82 (P = 0.07)

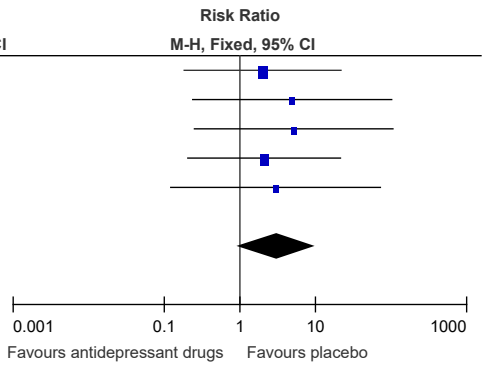


Figure 134: Serious adverse events 3: Hepatic and renal adverse events at ≤3 months

Study or Subgroup	Favours antidepressant drugs Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Chappell 2011	0	128	1	128	33.3%	0.14 [0.00, 6.82]
Frakes 2011	1	264	0	260	33.3%	7.28 [0.14, 366.83]
Hudson 2021	0	99	1	102	33.3%	0.14 [0.00, 7.03]
Total (95% CI)		**491**		**490**	**100.0%**	**0.52 [0.05, 4.96]**
Total events	1		2			

Heterogeneity: Chi² = 2.63, df = 2 (P = 0.27); I² = 24%

Test for overall effect: Z = 0.57 (P = 0.57)

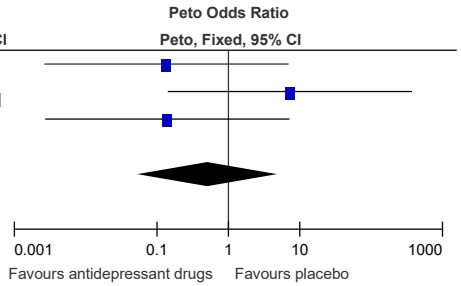
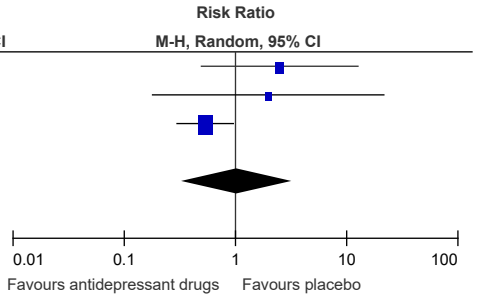


Figure 135: Serious adverse events 4: Central nervous system adverse events at ≤3 months

Study or Subgroup	Antidepressant drugs Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chappell 2011	5	128	2	128	27.9%	2.50 [0.49, 12.65]
Frakes 2011	2	264	1	260	16.7%	1.97 [0.18, 21.59]
Hudson 2021	14	99	27	102	55.3%	0.53 [0.30, 0.96]
Total (95% CI)		**491**		**490**	**100.0%**	**1.02 [0.33, 3.19]**
Total events	21		30			

Heterogeneity: Tau² = 0.52; Chi² = 3.94, df = 2 (P = 0.14); I² = 49%

Test for overall effect: Z = 0.04 (P = 0.97)



E.1.15 Glucosamine compared to paracetamol

Figure 136: Pain (WOMAC, 0-20, high is poor, change score) at >3 months

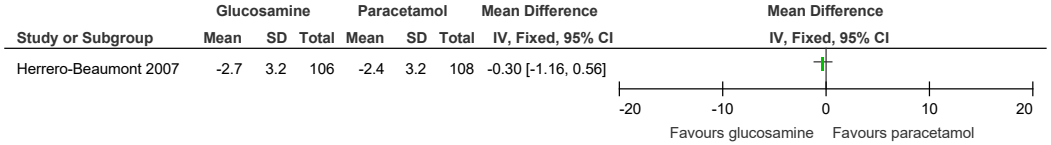


Figure 137: Physical function (WOMAC, 0-68, high is poor, change score) at >3 months

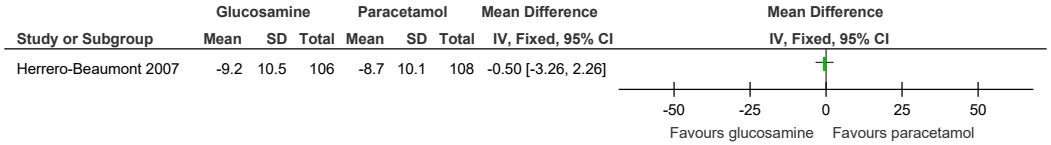


Figure 138: Serious adverse events 2: Cardiovascular adverse events at >3 months

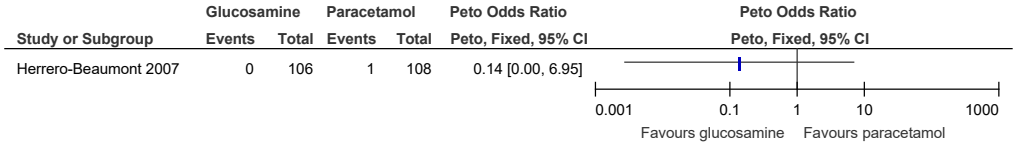
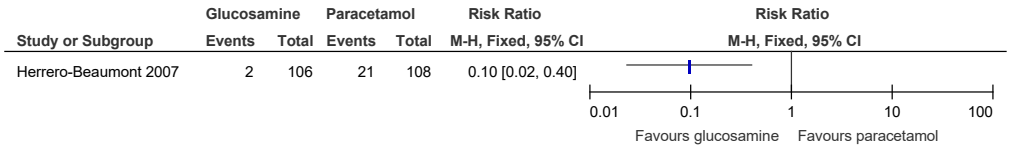


Figure 139: Serious adverse events 3: Hepatorenal adverse events at >3 months



E.1.16 Glucosamine compared to oral non-steroidal anti-inflammatory drugs

Figure 140: Pain (WOMAC [different scale ranges], high is poor, change scores) at >3 months

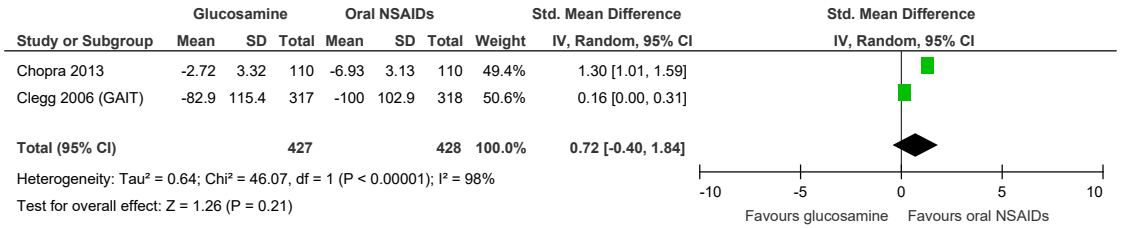


Figure 141: Physical function (WOMAC [different scale ranges], high is poor, change scores) at >3 months

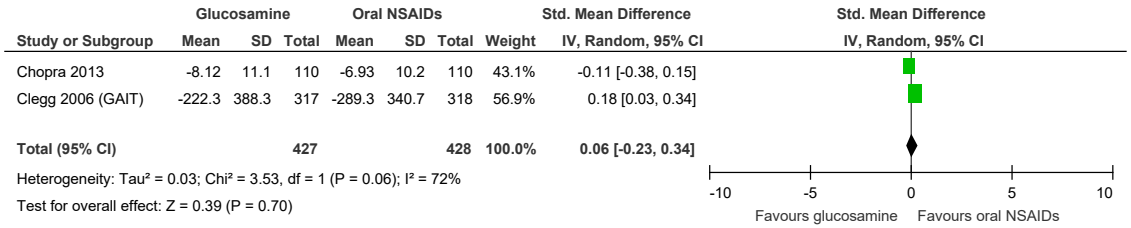


Figure 142: Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months

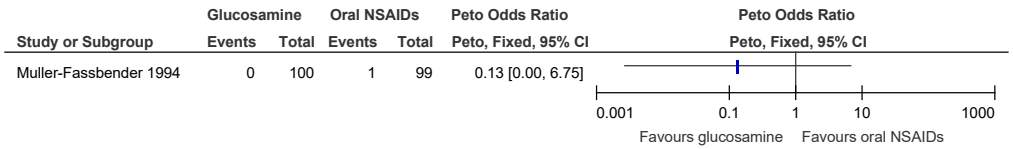


Figure 143: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months

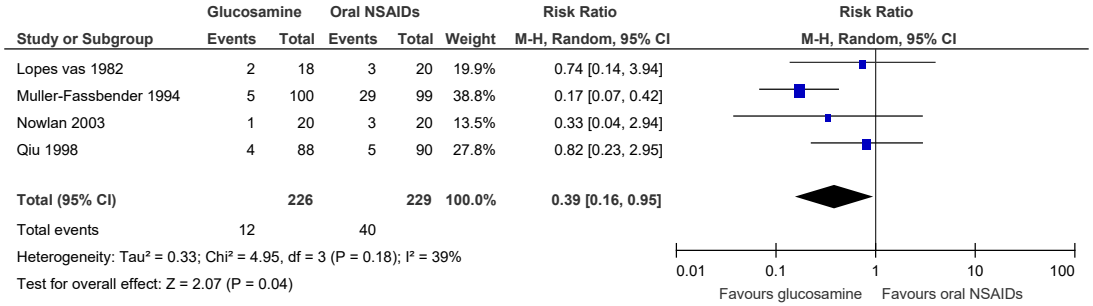


Figure 144: Serious adverse events 2: Cardiovascular adverse events at ≤3 months

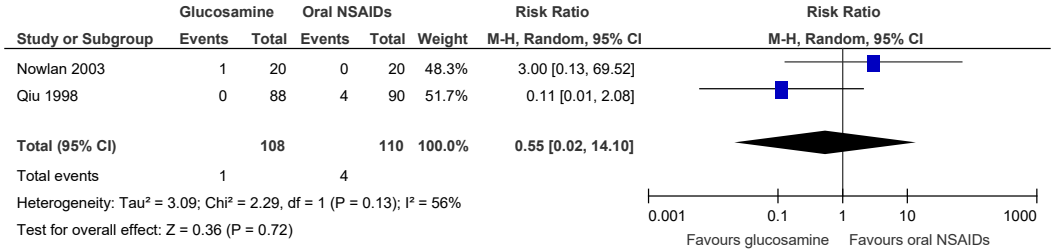


Figure 145: Serious adverse events 2: Cardiovascular adverse events at >3 months

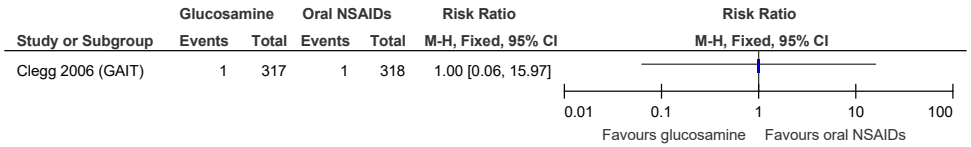


Figure 146: Serious adverse events 3: Hepatorenal adverse events at ≤3 months

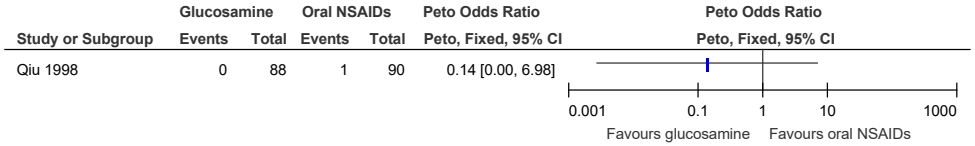


Figure 147: Serious adverse events 3: Hepatorenal adverse events at >3 months

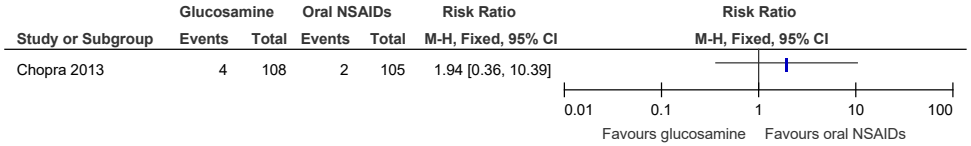
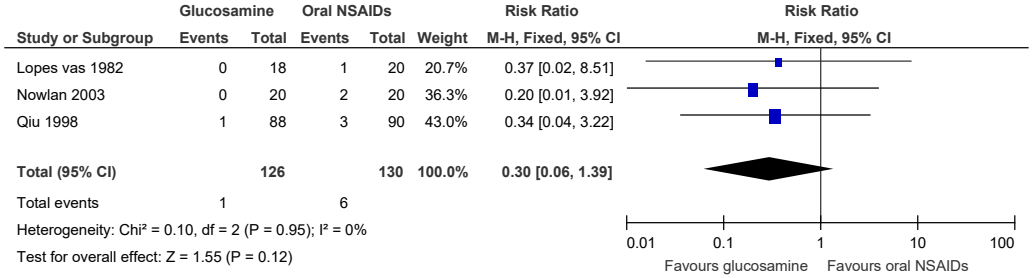


Figure 148: Serious adverse events 4: Central nervous system adverse events at ≤3 months



E.1.17 Glucosamine compared to placebo

Figure 149: Quality of life (EQ-5D, 0-1, high is good, change score) at >3 months

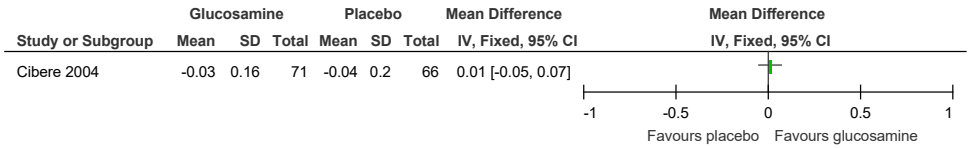


Figure 150: Quality of life (SF-12 physical component summary, 0-100, high is good, final value) at >3 months

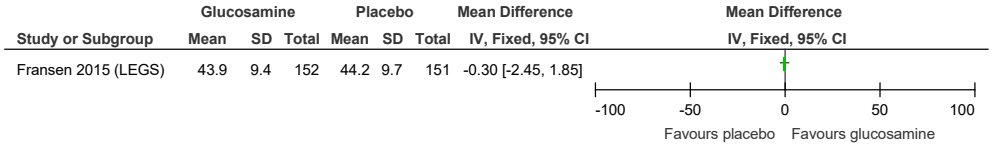


Figure 151: Quality of life (SF-12 mental component summary, 0-100, high is good, final value) at >3 months

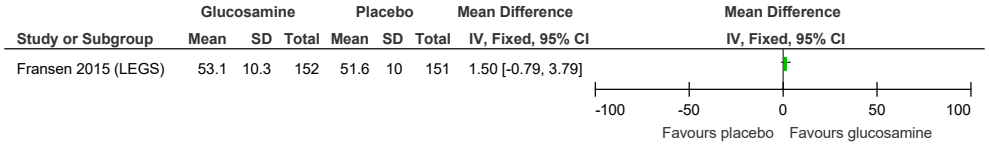


Figure 152: Pain (WOMAC, VAS, 0-100, final values and change scores, high is poor) at ≤3 months

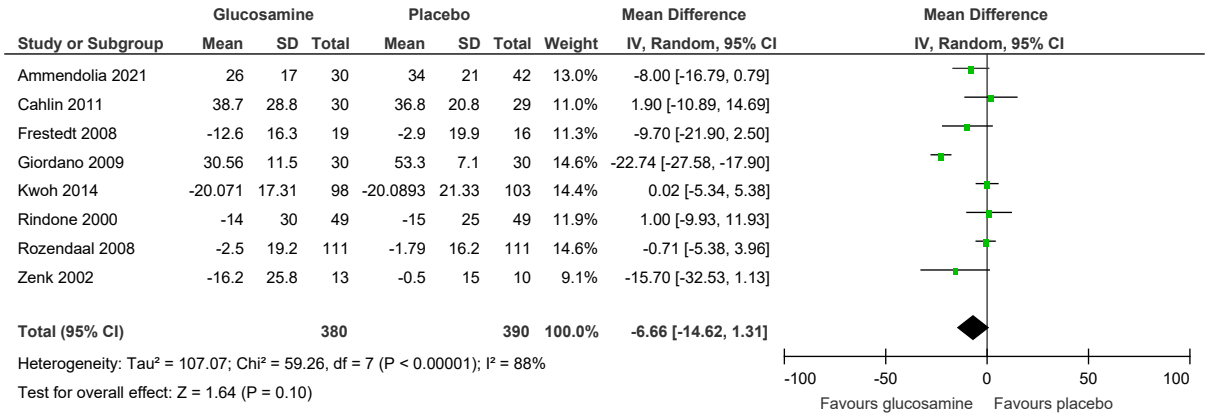


Figure 153: Pain (WOMAC, 0-20, high is poor, final value) at ≤3 months

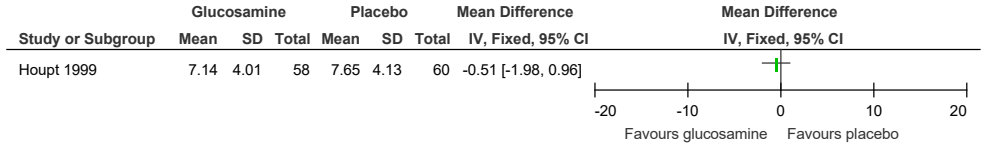


Figure 154: Pain (WOMAC [different scale ranges], high is poor, change scores) at >3 months

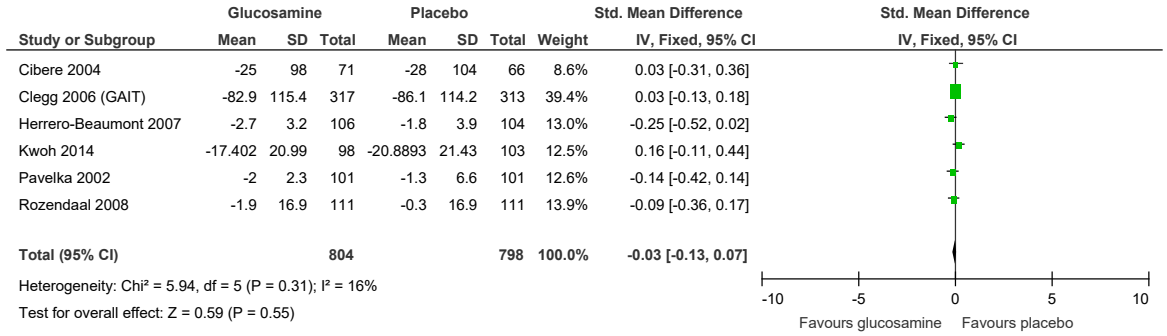


Figure 155: Pain (WOMAC [different scale ranges], high is poor, final values) at >3 months

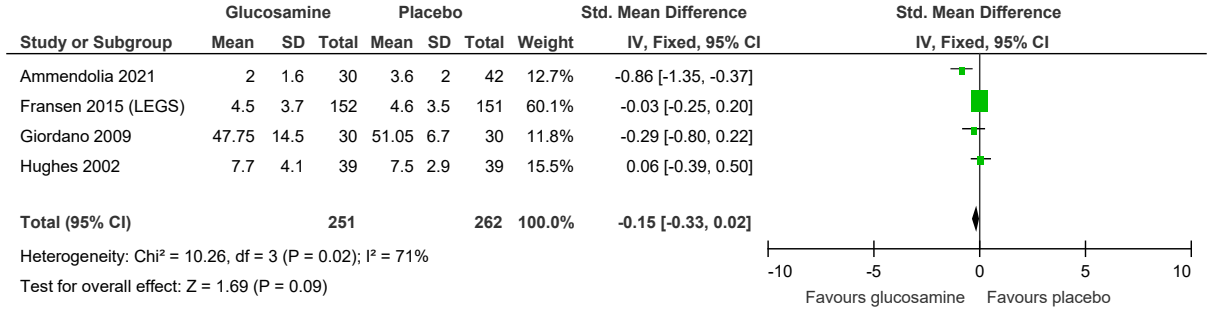


Figure 156: Physical function (WOMAC, 0-100, high is poor, final value and change scores) at ≤3 months

Study or Subgroup	Glucosamine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Frestedt 2008	-10.5	24	19	-7	18.4	16	12.7%	-3.50 [-17.56, 10.56]
Giordano 2009	38.2	13.2	30	55.1	14.9	30	21.8%	-16.90 [-24.02, -9.78]
Kwoh 2014	-18.0873	17.85	98	-18.718	22.3	103	24.1%	0.63 [-4.94, 6.20]
Rozendaal 2008	-3.29	14.9	111	-1.08	12.7	111	26.7%	-2.21 [-5.85, 1.43]
Zenk 2002	2.3	12	10	13.2	23.5	23	14.8%	-10.90 [-23.05, 1.25]
Total (95% CI)			**268**			**283**	**100.0%**	**-6.17 [-12.84, 0.49]**

Heterogeneity: Tau² = 39.90; Chi² = 17.42, df = 4 (P = 0.002); I² = 77%

Test for overall effect: Z = 1.81 (P = 0.07)

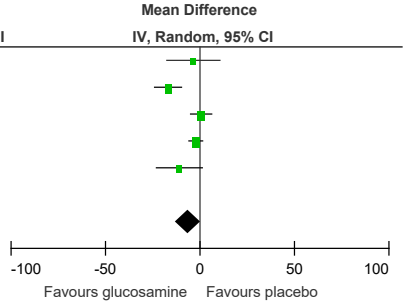


Figure 157: Physical function (WOMAC, 0-68, high is poor, final value) at ≤3 months

Study or Subgroup	Glucosamine Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Houpt 1999	25.98	14.7	58	27.17	14.1	60	-1.19 [-6.39, 4.01]

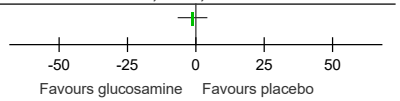


Figure 158: Physical function (WOMAC [different scale ranges], high is poor, change scores) at >3 months

Study or Subgroup	Glucosamine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cibere 2004	-58	270	71	-63	318	66	12.9%	0.02 [-0.32, 0.35]
Clegg 2006 (GAIT)	-222.3	388.3	317	-227.4	362.7	313	23.3%	0.01 [-0.14, 0.17]
Herrero-Beaumont 2007	-9.2	10.5	106	-5.5	11.5	104	16.0%	-0.33 [-0.61, -0.06]
Kwoh 2014	-15.4138	21.34	98	-19.404	21.21	103	15.7%	0.19 [-0.09, 0.46]
Pavelka 2002	-5.8	6.9	101	-3.7	6.2	101	15.7%	-0.32 [-0.60, -0.04]
Rozendaal 2008	-1.69	13.7	111	0.38	13.7	111	16.5%	-0.15 [-0.41, 0.11]
Total (95% CI)			**804**			**798**	**100.0%**	**-0.09 [-0.25, 0.07]**

Heterogeneity: Tau² = 0.02; Chi² = 11.73, df = 5 (P = 0.04); I² = 57%

Test for overall effect: Z = 1.15 (P = 0.25)

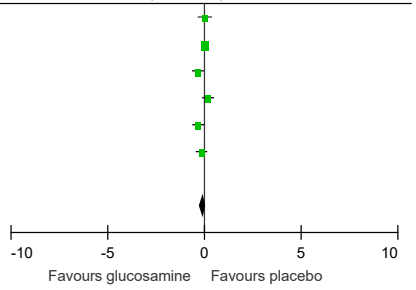


Figure 159: Physical function (WOMAC [different scale ranges], high is poor, final values) at >3 months

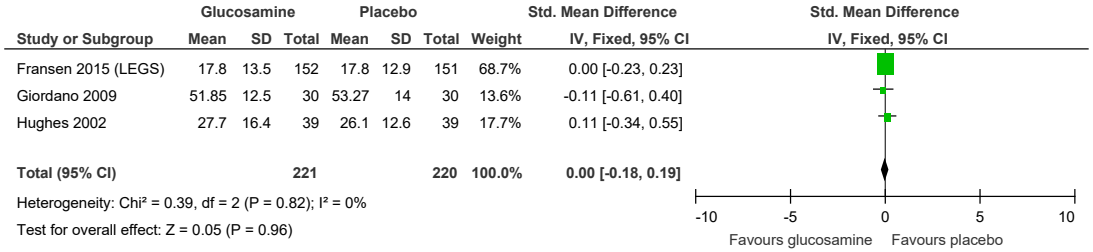


Figure 160: Osteoarthritis flares at >3 months

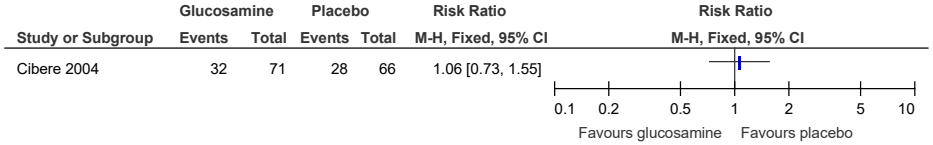


Figure 161: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months

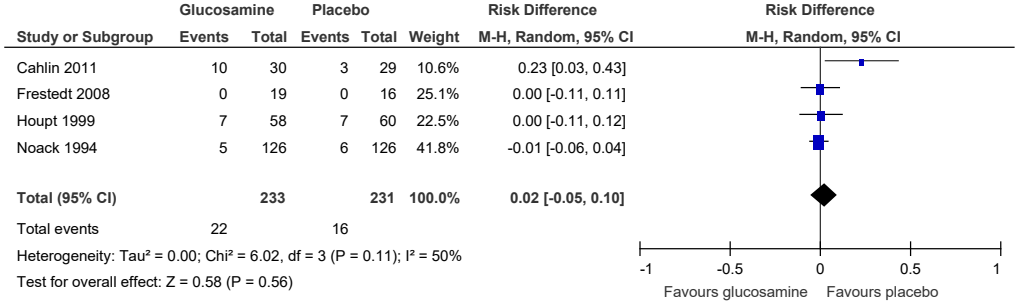


Figure 162: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at >3 months

Figure 163: Serious adverse events 2: Cardiovascular adverse events at ≤3 months

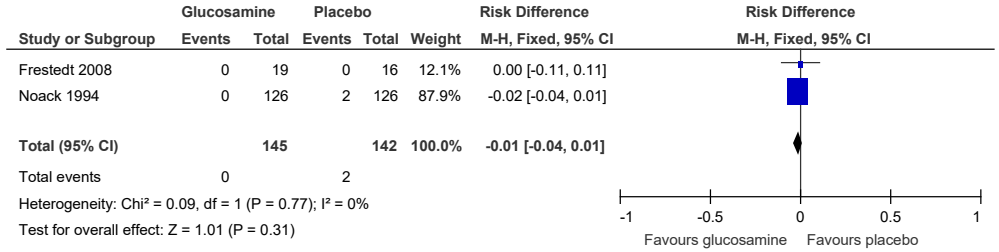


Figure 164: Serious adverse events 2: Cardiovascular adverse events at >3 months

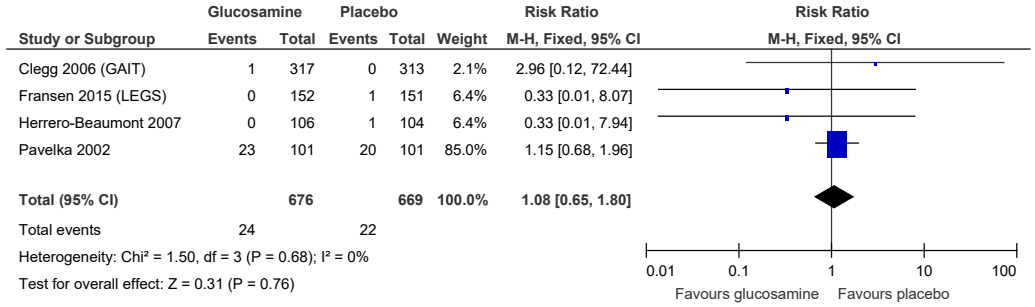


Figure 165: Serious adverse events 3: Hepatorenal adverse events at >3 months

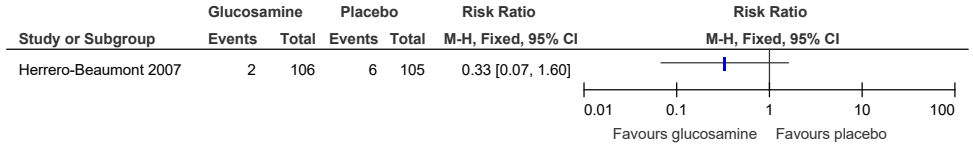


Figure 166: Serious adverse events 4: Central nervous system adverse events at ≤3 months

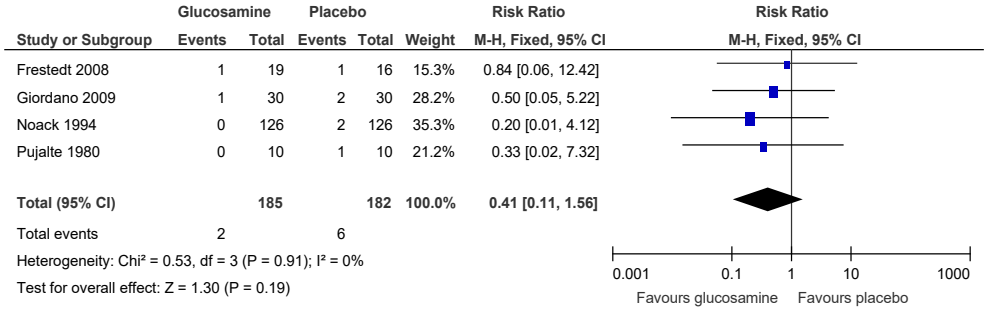
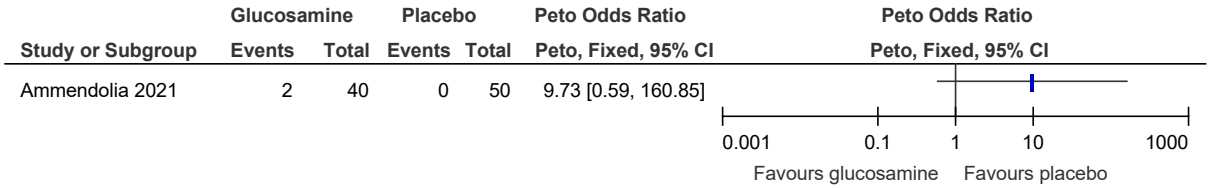


Figure 167: Serious adverse events 4: Central nervous system adverse events at ≤3 months



E.2 Topical (local) (including comparisons to oral formulations)

E.2.1 Capsaicin compared to placebo in knee osteoarthritis

Figure 168: Pain (WOMAC, 0-20, high is poor, change score) at ≤3 months

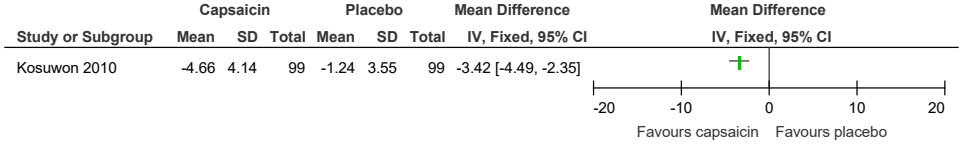


Figure 169: Physical function (WOMAC, 0-68, high is poor, change score) at ≤3 months

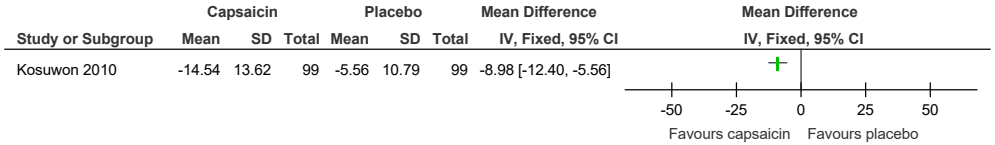


Figure 170: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months

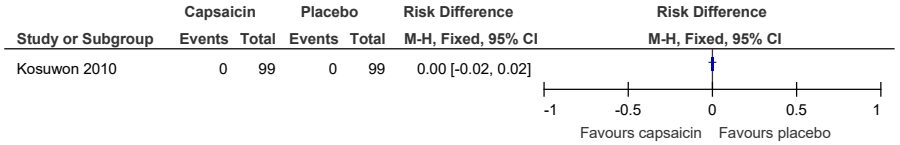


Figure 171: Serious adverse events 2: Cardiovascular adverse events at ≤3 months

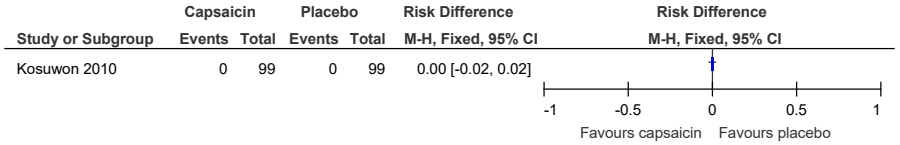


Figure 172: Serious adverse events 3: Hepatorenal adverse events at ≤3 months

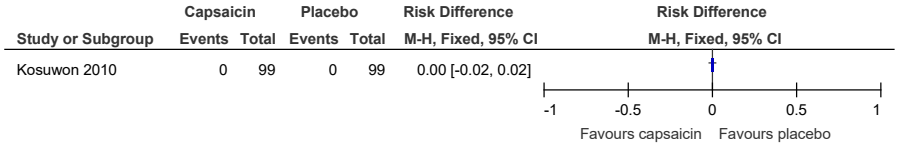
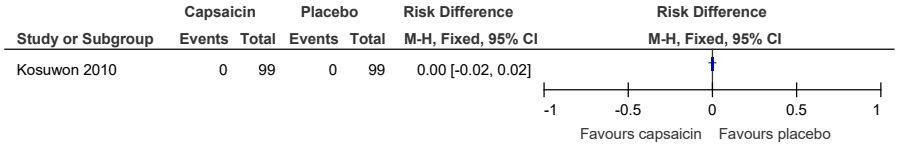
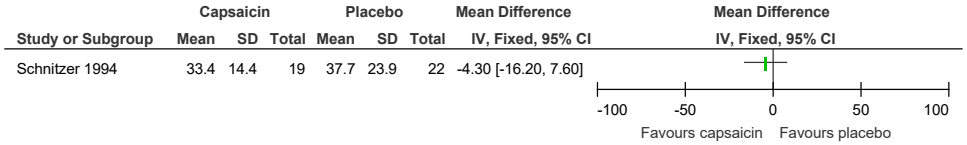


Figure 173: Serious adverse events 4: Central nervous system adverse events at ≤3 months



E.2.2 Capsaicin compared to placebo in hand osteoarthritis

Figure 174: Pain (VAS, 0-100, high is poor, final value) at ≤3 months



E.2.3 Topical non-steroidal anti-inflammatory drugs compared to oral non-steroidal anti-inflammatory drugs in knee osteoarthritis

Figure 175: Quality of life (SF-36 physical component summary, SF-12 physical component summary, 0-100, high is good, change score) at ≤3 months

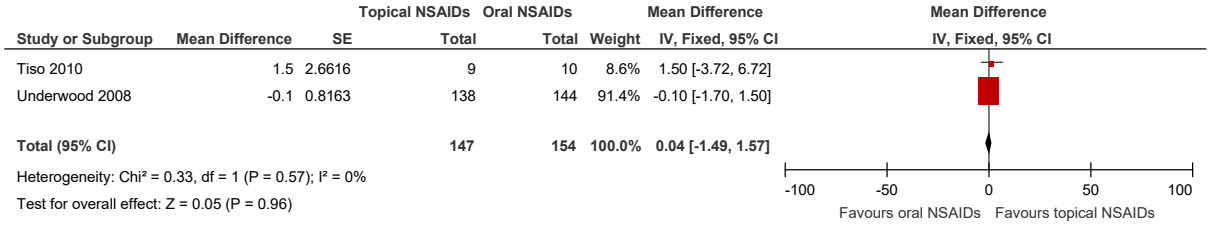


Figure 176: Quality of life (SF-36 mental component summary, SF-12 mental component summary 0-100, high is good, change score) at ≤3 months

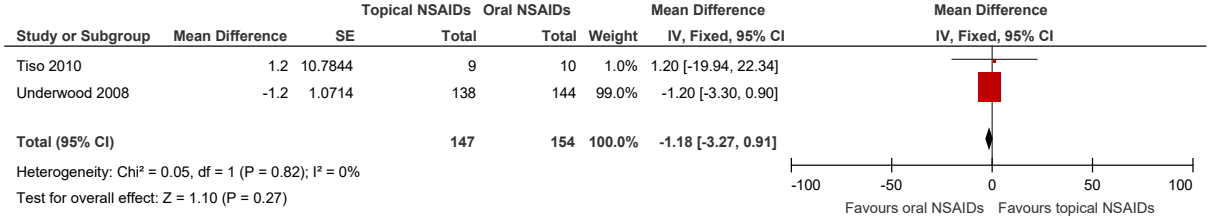


Figure 177: Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at >3 months

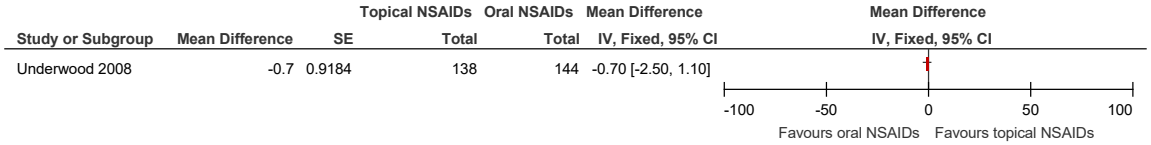


Figure 178: Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at >3 months

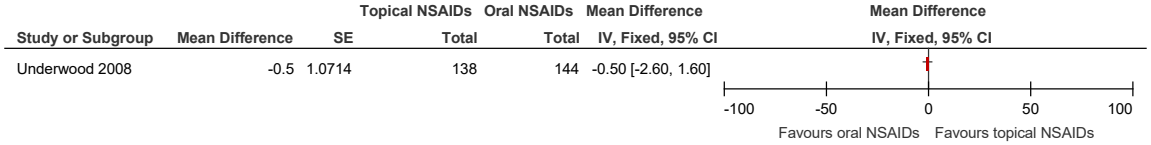


Figure 179: Pain (WOMAC pain subscale [different scale ranges], high is poor, change scores) at ≤3 months

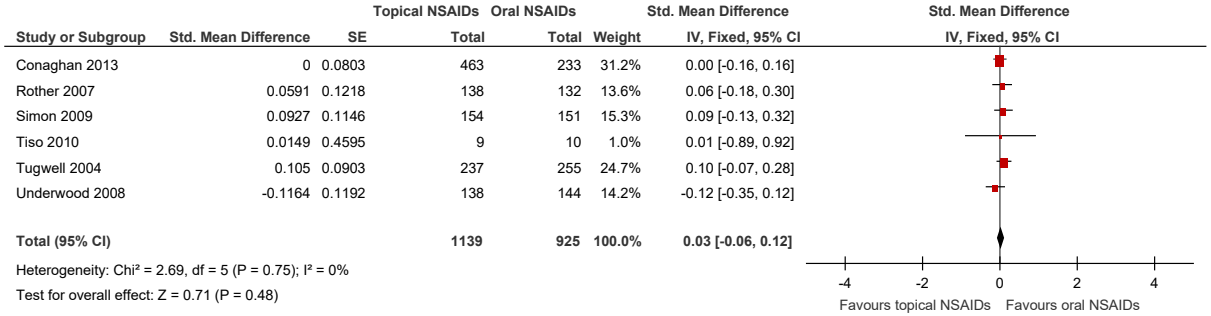


Figure 180: Pain (WOMAC pain subscale, 0-100, high is poor, change score) at >3 months

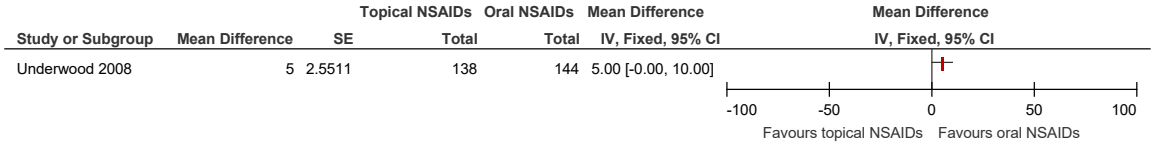


Figure 181: Physical function (WOMAC physical function subscale [different scale ranges], high is poor, change scores) at ≤3 months

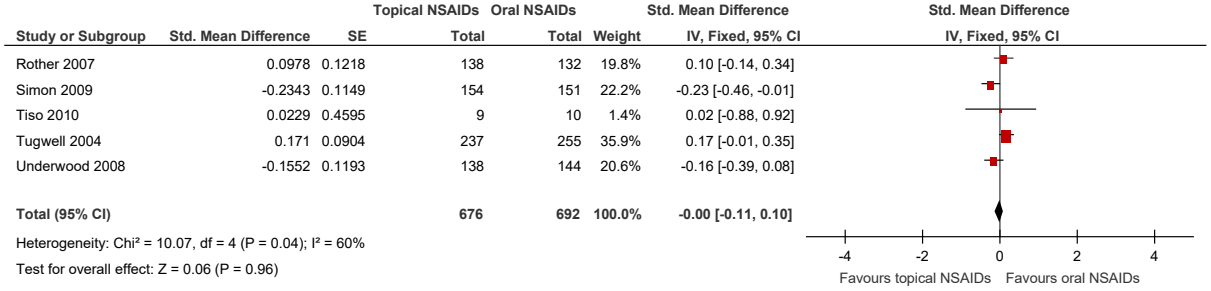


Figure 182: Physical function (WOMAC physical function subscale, 0-100, high is poor, change score) at >3 months

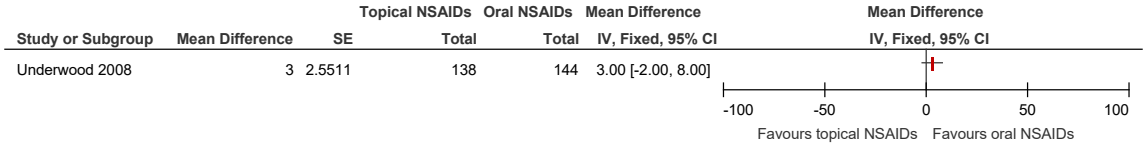


Figure 183: Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months

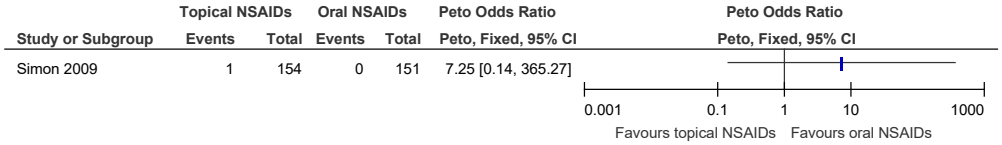


Figure 184: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months

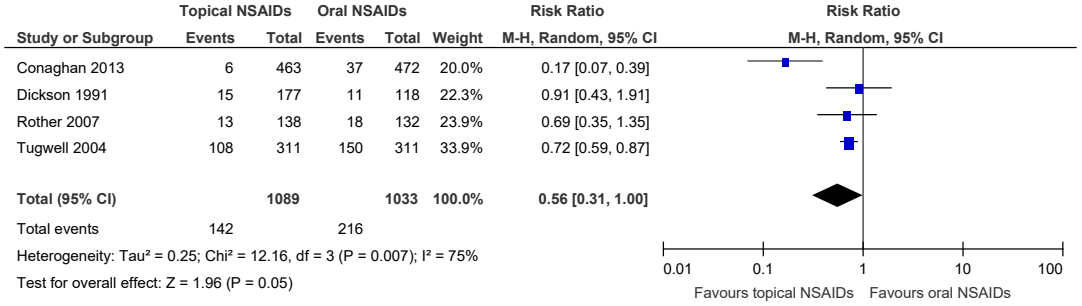


Figure 185: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at >3 months

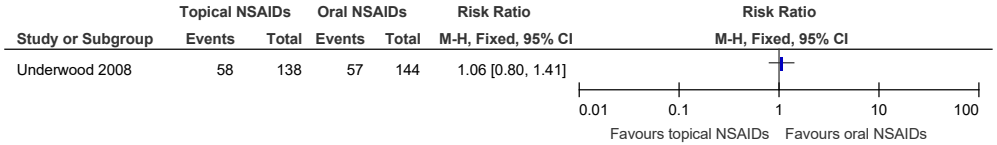


Figure 186: Serious adverse events 2: Cardiovascular adverse events at ≤3 months

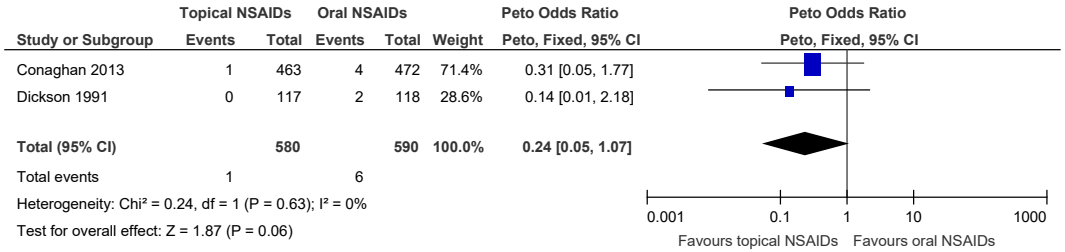
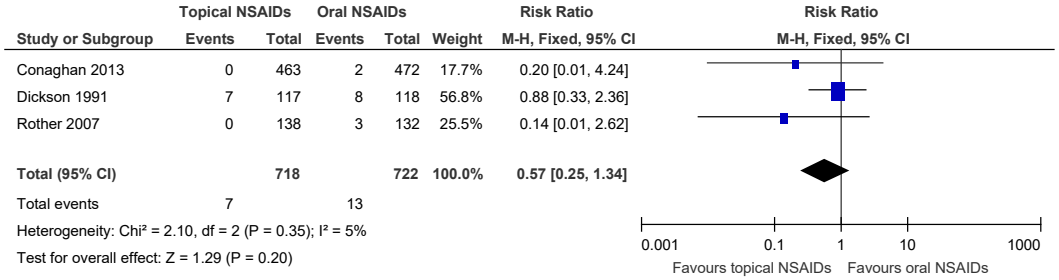
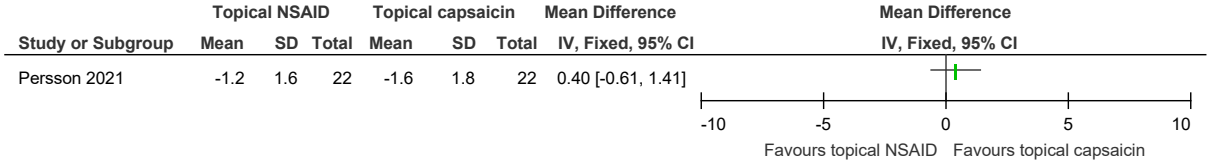


Figure 187: Serious adverse events 4: Central nervous system adverse events at ≤3 months



E.2.4 Topical non-steroidal anti-inflammatory drugs compared to oral non-steroidal anti-inflammatory drugs in knee osteoarthritis

Figure 188: Pain (NRS, 0-10, high is poor, change score) at ≤3 months



E.2.5 Topical non-steroidal anti-inflammatory drugs compared to placebo in knee osteoarthritis

Figure 189: Pain (WOMAC pain subscale, VAS, 0-100, high is poor, final values and change scores) at ≤3 months

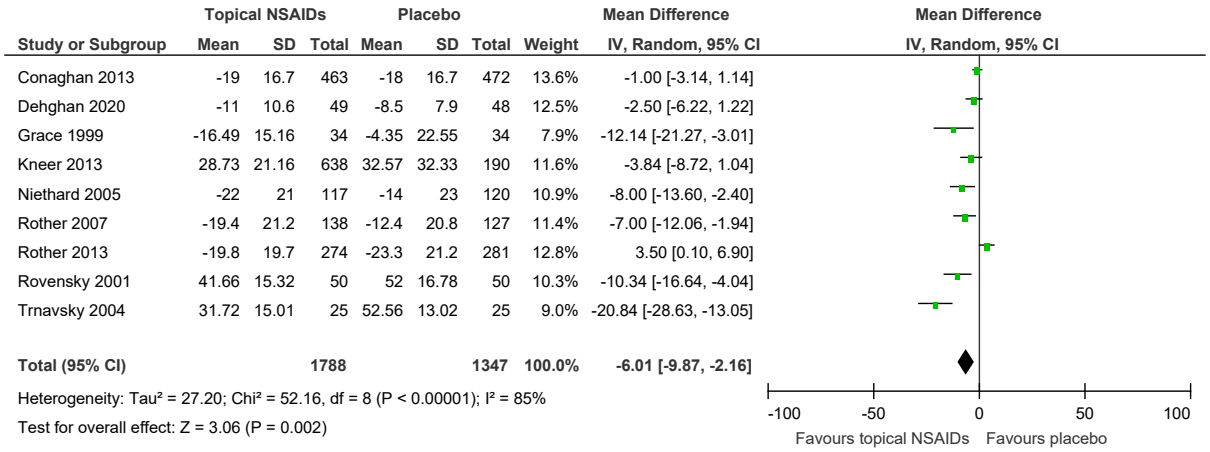


Figure 190: Pain (WOMAC pain subscale, 0-20, high is poor, change scores) at ≤3 months

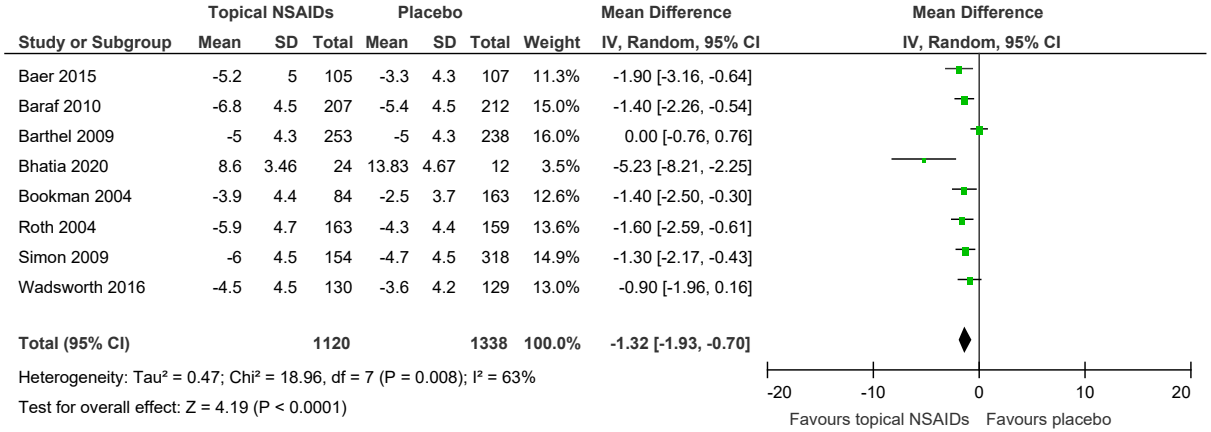


Figure 191: Physical function (WOMAC physical function subscale [different scale ranges], high is poor, change scores) at ≤3 months

	Topical NSAIDs			Placebo				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Baer 2015	-13.4	16.3	105	-6.9	13.2	107	8.1%	-0.44 [-0.71, -0.16]
Baraf 2010	-21.5	15.3	207	-16.8	15.7	212	9.5%	-0.30 [-0.50, -0.11]
Barthel 2009	-15	13.7	253	-10.9	13.7	238	9.7%	-0.30 [-0.48, -0.12]
Bookman 2004	-11.6	14.7	84	-6.4	11.6	163	8.2%	-0.41 [-0.67, -0.14]
Dehghan 2020	-32.04	18.38	49	-11.13	14.8	48	5.6%	-1.24 [-1.68, -0.81]
Grace 1999	-11.96	13.37	34	-3.17	17.72	34	5.0%	-0.55 [-1.04, -0.07]
Niethard 2005	-23	21	117	-16	22	120	8.4%	-0.32 [-0.58, -0.07]
Roth 2004	-15.4	15.3	162	-10.1	13.9	159	9.0%	-0.36 [-0.58, -0.14]
Rother 2007	-16	20.3	138	-12.3	19.2	127	8.6%	-0.19 [-0.43, 0.06]
Rother 2013	-2.02	2.07	274	-2.32	2.23	281	9.9%	0.14 [-0.03, 0.31]
Simon 2009	-15.8	15.1	154	-12.2	14.7	318	9.5%	-0.24 [-0.44, -0.05]
Wadsworth 2016	-14.3	14.7	130	-11.5	13.8	129	8.6%	-0.20 [-0.44, 0.05]
Total (95% CI)			**1707**			**1936**	**100.0%**	**-0.32 [-0.47, -0.18]**

Heterogeneity: Tau² = 0.05; Chi² = 47.79, df = 11 (P < 0.00001); I² = 77%

Test for overall effect: Z = 4.44 (P < 0.00001)

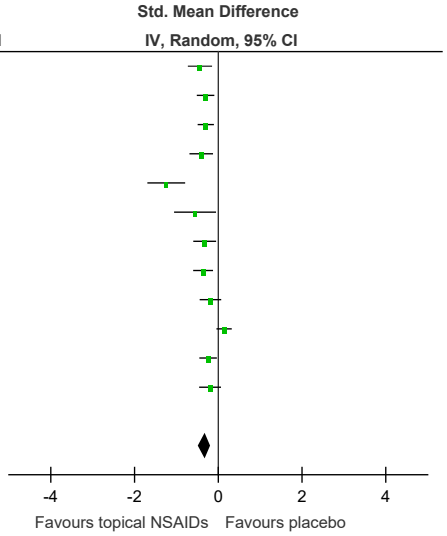


Figure 192: Physical function (WOMAC physical function subscale, 0-100, high is poor, final value) at ≤3 months

	Topical NSAIDs			Placebo			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Kneer 2013	30.25	20.78	638	33.16	21.75	190	-2.91 [-6.40, 0.58]

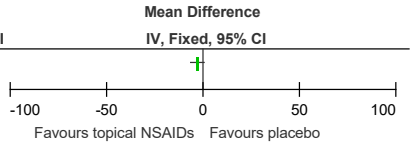


Figure 193: Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months

Study or Subgroup	Topical NSAIDs Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Baer 2015	0	107	1	109	25.8%	0.14 [0.00, 6.95]
Roth 2004	0	164	2	162	51.5%	0.13 [0.01, 2.13]
Simon 2009	1	154	0	318	22.7%	21.43 [0.33, 1401.53]
Total (95% CI)		**425**		**589**	**100.0%**	**0.43 [0.06, 3.12]**
Total events	1		3			

Heterogeneity: Chi² = 4.37, df = 2 (P = 0.11); I² = 54%

Test for overall effect: Z = 0.84 (P = 0.40)

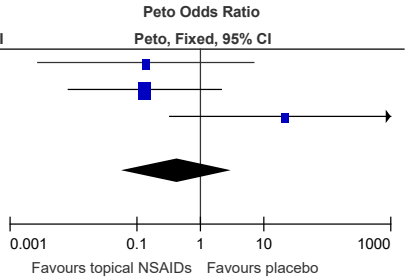


Figure 194: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months

Study or Subgroup	Topical NSAIDs Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Baraf 2010	11	208	9	212	11.5%	0.01 [-0.03, 0.05]
Barthel 2009	15	254	12	238	13.5%	0.01 [-0.03, 0.05]
Conaghan 2013	6	463	9	472	25.7%	-0.01 [-0.02, 0.01]
Grace 1999	1	38	2	36	2.0%	-0.03 [-0.12, 0.06]
Kneer 2013	22	667	9	199	16.8%	-0.01 [-0.04, 0.02]
Niethard 2005	0	117	2	121	6.5%	-0.02 [-0.04, 0.01]
Rother 2007	13	138	12	127	7.3%	-0.00 [-0.07, 0.07]
Rother 2013	2	274	2	281	15.2%	0.00 [-0.01, 0.01]
Trnavsky 2004	0	25	0	25	1.4%	0.00 [-0.07, 0.07]
Total (95% CI)		**2184**		**1711**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	70		57			

Heterogeneity: Chi² = 2.66, df = 8 (P = 0.95); I² = 0%

Test for overall effect: Z = 0.49 (P = 0.62)

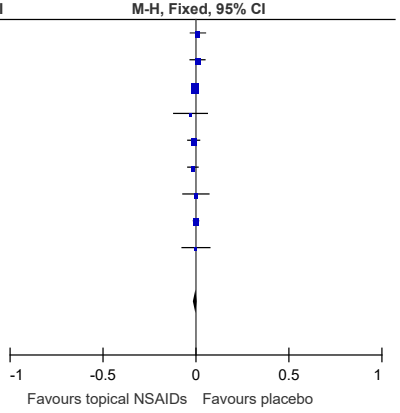


Figure 195: Serious adverse events 2: Cardiovascular adverse events at ≤3 months

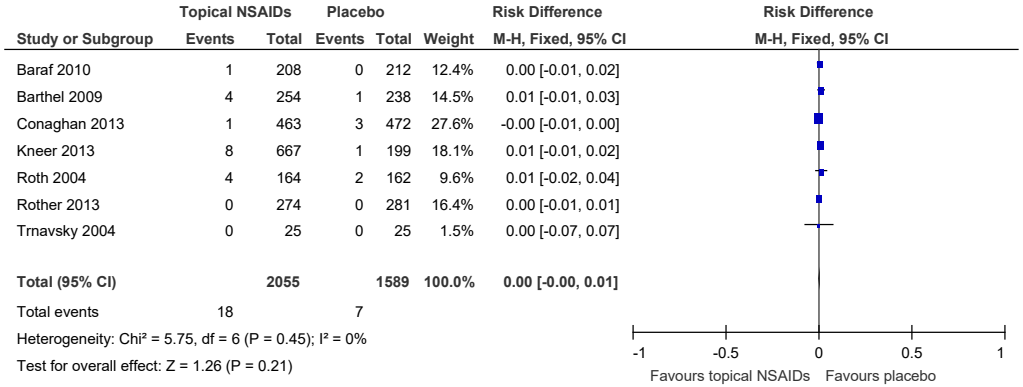


Figure 196: Serious adverse events 3: Hepatorenal adverse events at ≤3 months

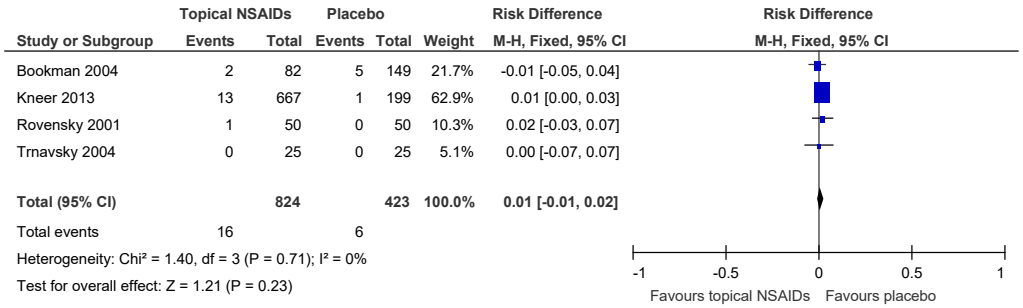
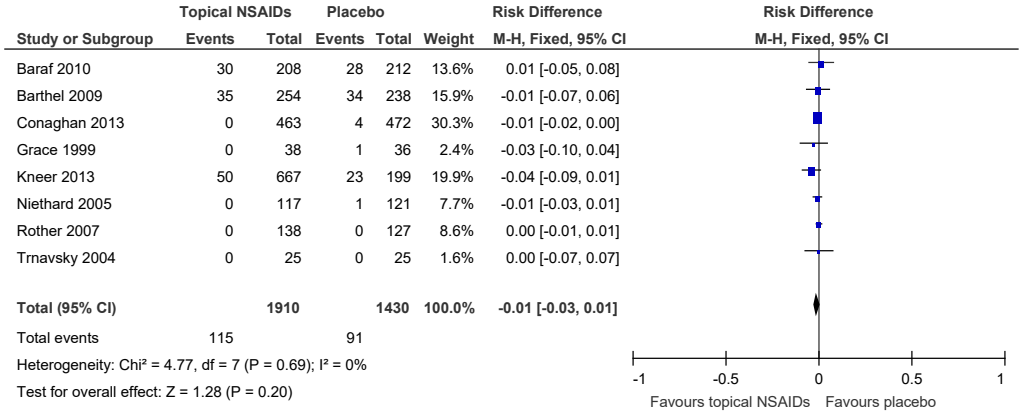


Figure 197: Serious adverse events 4: Central nervous system adverse events at ≤3 months



E.2.6 Topical non-steroidal anti-inflammatory drugs compared to placebo in hand osteoarthritis

Figure 198: Pain (AUSCAN pain index, 0-100, high is poor, change score) at ≤3 months

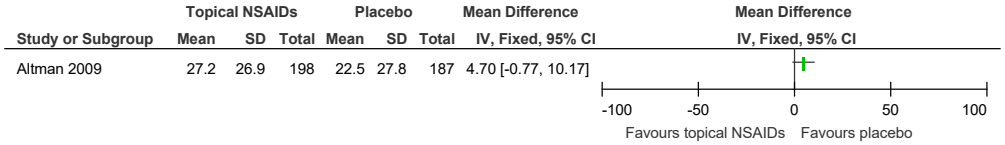


Figure 199: Physical function (AUSCAN functional index, 0-100, high is poor, change score) at ≤3 months

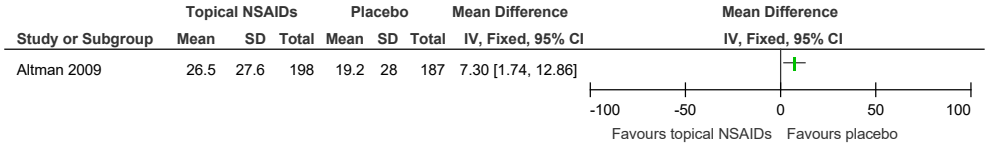


Figure 200: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months

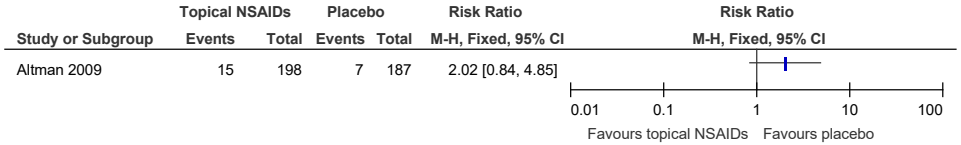
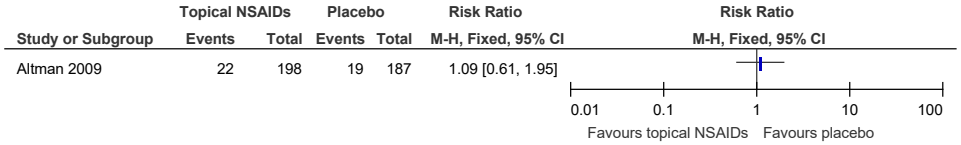


Figure 201: Serious adverse events 4: Central nervous system adverse events at ≤3 months



E.3 Topical (systemic) (including comparisons to oral formulations)

E.3.1 Transdermal strong opioids compared to oral strong opioids

Figure 202: Pain (NRS, 0-10, high is poor, final value) at ≤3 months

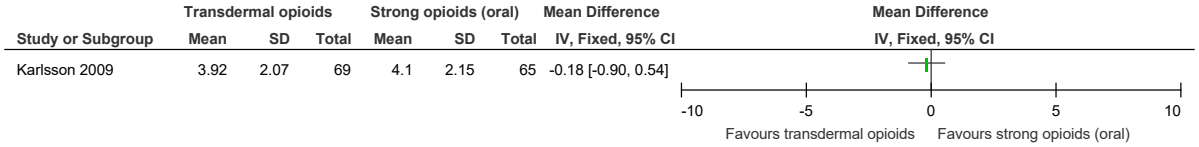
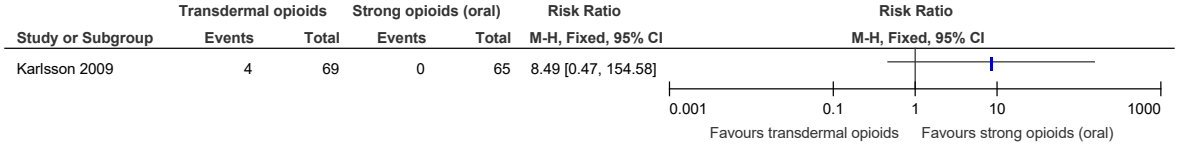


Figure 203: Serious adverse events 2: Cardiovascular adverse events at ≤3 months



E.3.2 Transdermal strong opioids compared to placebo

Figure 204: Quality of life (SF-36 pain index, 0-100, high is good, change score) at ≤3 months

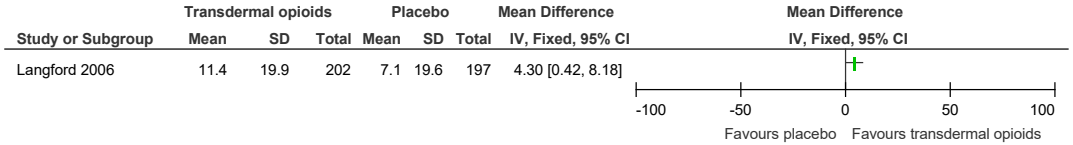


Figure 205: Quality of life (SF-36 physical functioning, 0-100, high is good, change score) at ≤3 months

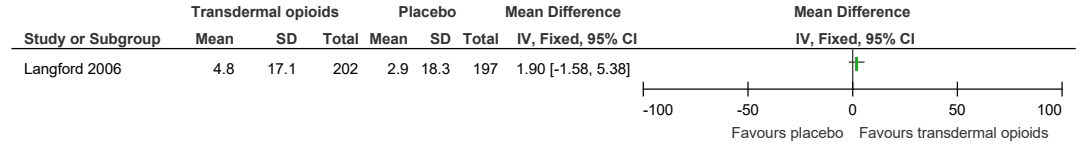


Figure 206: Quality of life (SF-36 role physical, 0-100, high is good, change score) at ≤3 months

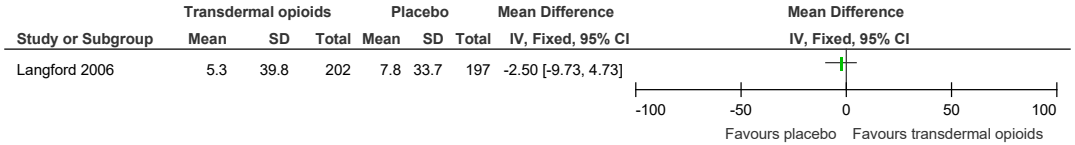


Figure 207: Quality of life (SF-36 vitality, 0-100, high is good, change score) at ≤3 months

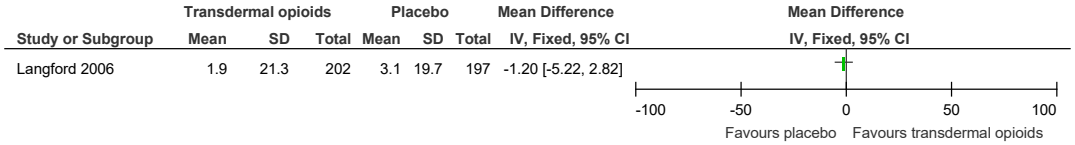


Figure 208: Quality of life (SF-36 general health, 0-100, high is good, change score) at ≤3 months

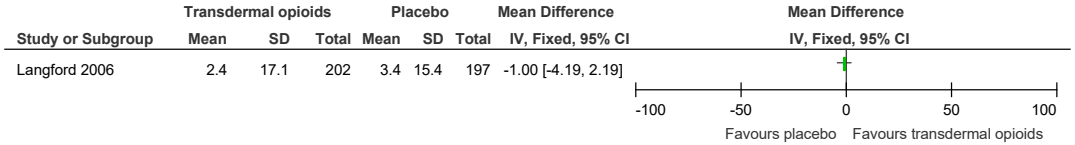


Figure 209: Quality of life (SF-36 mental health, 0-100, high is good, change score) at ≤3 months

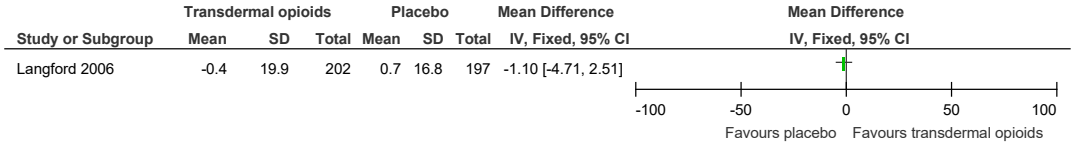


Figure 210: Quality of life (SF-36 role emotional, 0-100, high is good, change score) at ≤3 months

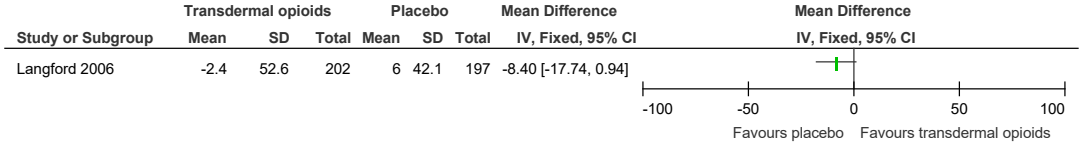


Figure 211: Quality of life (SF-36 social functioning, 0-100, high is good, change score) at ≤3 months

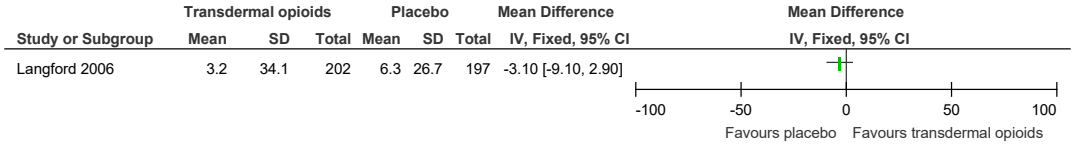


Figure 212: Pain (WOMAC, NRS [different scale ranges], high is poor, change scores) at ≤3 months

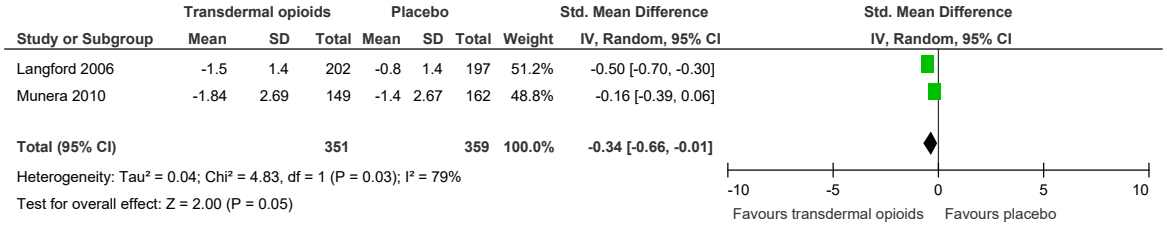


Figure 213: Pain (WOMAC, 0-20, high is poor, change score) at >3 months

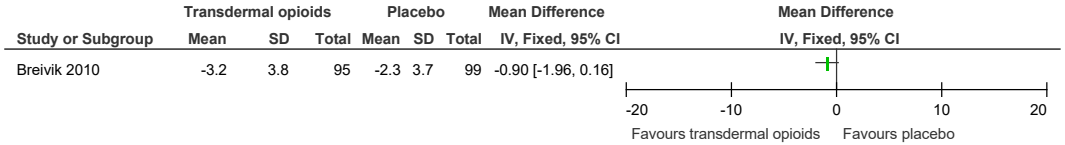


Figure 214: Physical function (WOMAC, unclear scale range, high is poor, change score) at ≤3 months

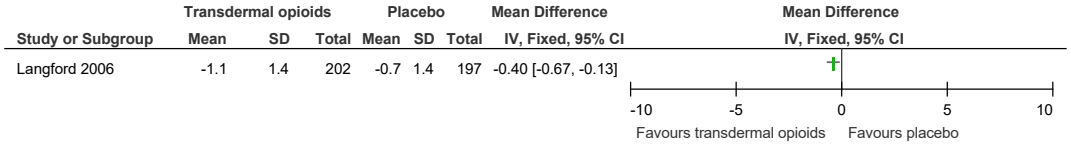


Figure 215: Physical function (WOMAC, 0-68, high is poor, change score) at >3 months

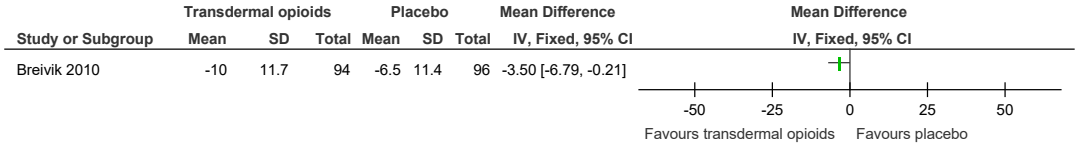


Figure 216: Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at >3 months

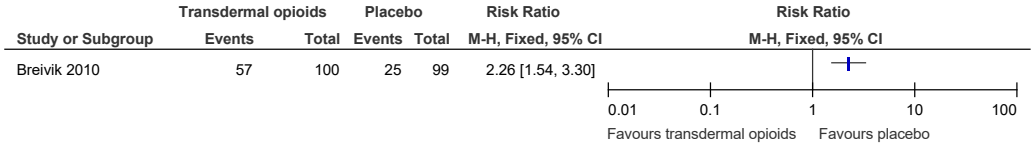
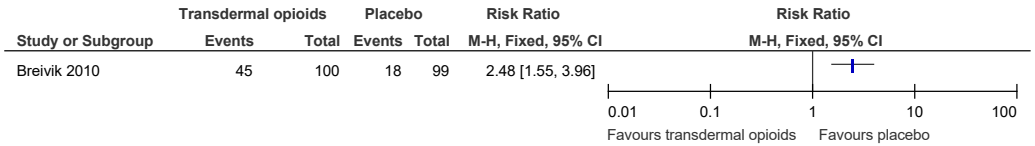


Figure 217: Serious adverse events 4: Central nervous system adverse events at >3 months



Appendix F – GRADE tables

F.1 Oral

F.1.1 Paracetamol compared to placebo

Table 1: Clinical evidence profile: paracetamol compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	paracetamol	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life (Nottingham health profile energy subscale, 0-100, high is good, change score) at ≤3 months (follow up: 12 weeks; assessed with: Nottingham health profile energy subscale)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	267	275	-	MD **0.28 higher** (0.07 higher to 0.49 higher)	⨁⨁◯◯ LOW	CRITICAL
Pain (WOMAC, Multidimensional Health Assessment Questionnaire [different scale ranges], high is poor, change scores) at ≤3 months (follow up: mean 12 weeks; assessed with: WOMAC, Multidimensional Health Assessment Questionnaire)												
6	randomised trials	very serious [a]	not serious	not serious	not serious	none	2071	1588	-	SMD **0.05 lower** (0.11 lower to 0.02 higher)	⨁⨁◯◯ LOW	CRITICAL
Pain (WOMAC, 0-20, high is poor, change score) at >3 months (follow up: 26 weeks; assessed with: WOMAC)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	108	104	-	MD **0.6 lower** (1.56 lower to 0.36 higher)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC [different scale ranges], high is poor, change scores) at ≤3 months (follow up: mean 12 weeks; assessed with: WOMAC)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	paracetamol	placebo	Relative (95% CI)	Absolute (95% CI)		
5	randomised trials	very serious [a]	not serious	not serious	not serious	none	1468	1069	-	SMD **0.09 lower** (0.17 lower to 0.01 lower)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC, 0-68, high is poor, change score) at >3 months (follow up: 26 weeks; assessed with: WOMAC)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	108	104	-	MD **3.2 lower** (6.12 lower to 0.28 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months (follow up: 2 weeks)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	0/148 (0.0%)	0.0%	**RR 0.00** (-0.01 to 0.01)	**0 fewer per 1,000** (from 10 fewer to 10 more) [c]	⨁⨁⨁◯ MODERATE	IMPORTANT
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months (follow up: mean 7 weeks)												
4	randomised trials	serious [a]	not serious	not serious	serious [b]	none	170/1502 (11.3%)	9.5%	**RR 1.16** (0.92 to 1.46)	**15 more per 1,000** (from 8 fewer to 48 more)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events 2: Cardiovascular adverse events at ≤3 months (follow up: mean 9 weeks)												
3	randomised trials	serious [a]	not serious	not serious	serious [b]	none	13/885 (1.5%)	0.9%	**RR 1.00** (0.09 to 1.03)	**0 fewer per 1,000** (from 8 fewer to 0 fewer) [c]	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events 2: Cardiovascular adverse events at >3 months (follow up: 26 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	paracetamol	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	1/108 (0.9%)	1.0%	**RR 0.96** (0.06 to 15.19)	**0 fewer per 1,000** (from 9 fewer to 142 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 3: Hepatorenal adverse events at ≤3 months (follow up: mean 12 weeks)												
3	randomised trials	serious [a]	not serious	not serious	not serious	none	37/1055 (3.5%)	0.7%	**RR 6.10** (2.35 to 15.84)	**36 more per 1,000** (from 9 more to 104 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Serious adverse events 3: Hepatorenal adverse events at >3 months (follow up: 26 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	21/108 (19.4%)	5.8%	**RR 3.37** (1.42 to 8.02)	**137 more per 1,000** (from 24 more to 407 more)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events 4: Central nervous system adverse events at ≤3 months (follow up: mean 8 weeks)												
6	randomised trials	very serious [a]	serious [d]	not serious	serious [b]	none	101/2239 (4.5%)	5.8%	**RR 0.91** (0.59 to 1.42)	**5 fewer per 1,000** (from 24 fewer to 24 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio

Explanations

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

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

c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

d. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

F.1.2 Oral non-steroidal anti-inflammatory drugs compared to paracetamol

Table 2: Clinical evidence profile: oral non-steroidal anti-inflammatory drugs compared to paracetamol

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral non-steroidal anti-inflammatory drugs	paracetamol	Relative (95% CI)	Absolute (95% CI)		
Quality of life (EQ-5D, 0-1, high is good, final value) at ≤3 months (follow up: 12 weeks; assessed with: EQ-5D)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	52	52	-	MD **0** (0.06 lower to 0.06 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (WOMAC, VAS, MDHAQ, Hospital assessment questionnaire pain score [different scale ranges], high is poor, change scores) at ≤3 months (follow up: mean 7 weeks; assessed with: WOMAC, VAS, MDHAQ, Hospital assessment questionnaire pain score)												
9	randomised trials	serious [a]	not serious	not serious	not serious	none	1906	1461	-	SMD **0.15 lower** (0.22 lower to 0.09 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Pain (KOOS, VAS, 0-100, high is poor, final values) at ≤3 months (follow up: mean 7 weeks; assessed with: KOOS, VAS)												
2	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	67	67	-	MD **3.47 higher** (3.46 lower to 10.41 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (VAS, 0-10, high is poor, change score) at >3 months (follow up: 24 months; assessed with: VAS)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	24	27	-	MD **1 lower** (2.52 lower to 0.52 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Physical function (WOMAC, Hospital assessment questionnaire disability score [different scale ranges], high is poor, change scores) at ≤3 months (follow up: mean 7 weeks; assessed with: WOMAC, Hospital assessment questionnaire disability score)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral non-steroidal anti-inflammatory drugs	paracetamol	Relative (95% CI)	Absolute (95% CI)		
7	randomised trials	very serious [a]	not serious	not serious	not serious	none	1115	780	-	SMD **0.23 lower** (0.32 lower to 0.13 lower)	⨁⨁◯◯ LOW	CRITICAL
Physical function (KOOS, 0-100, high is poor, final value) at ≤3 months (follow up: 12 weeks; assessed with: KOOS)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	52	52	-	MD **3 higher** (4.63 lower to 10.63 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months (follow up: 2 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	3/162 (1.9%)	0.0%	**Peto OR 6.86** (0.71 to 66.61)	**20 more per 1,000** (from 10 fewer to 40 more) [c]	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months (follow up: mean 5 weeks)												
6	randomised trials	serious [a]	not serious	not serious	serious [b]	none	189/1252 (15.1%)	128/1089 (11.8%)	**RR 1.26** (1.04 to 1.58)	**31 more per 1,000** (from 5 more to 68 more)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at >3 months (follow up: 24 months)												
1	randomised trials	very serious [a]	not serious	serious [d]	serious [b]	none	17/90 (18.9%)	6.8%	**RR 2.77** (1.15 to 6.70)	**120 more per 1,000** (from 10 more to 388 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 2: Cardiovascular adverse events at ≤3 months (follow up: mean 5 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral non-steroidal anti-inflammatory drugs	paracetamol	Relative (95% CI)	Absolute (95% CI)		
5	randomised trials	very serious [a]	serious [e]	not serious	very serious [b]	none	24/970 (2.5%)	12/641 (1.9%)	**RR 1.1** (0.6 to 2.0)	**10 more per 1,000** (from 10 fewer to 20 more) [c]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 2: Cardiovascular adverse events at >3 months (follow up: mean 18 months)												
2	randomised trials	very serious [a]	serious [f]	not serious	very serious [b]	none	13/374 (3.5%)	2.2%	**RR 1.74** (0.32 to 9.45)	**16 more per 1,000** (from 15 fewer to 186 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 3: Hepatorenal adverse events at ≤3 months (follow up: mean 4 weeks)												
3	randomised trials	very serious [a]	serious [e]	not serious	very serious [b]	none	1/316 (0.3%)	1.2%	**Peto OR 0.40** (0.04 to 4.04)	**0 fewer per 1,000** (from 20 fewer to 10 more) [c]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 3: Hepatorenal adverse events at >3 months (follow up: 24 months)												
1	randomised trials	very serious [a]	not serious	serious [d]	very serious [b]	none	1/90 (1.1%)	0.0%	**Peto OR 7.23** (0.14 to 364.29)	**10 more per 1,000** (from 20 fewer to 40 more) [c]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 4: Central nervous system adverse events at ≤3 months (follow up: mean 5 weeks)												
6	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	77/1693 (4.5%)	61/1272 (4.8%)	**RR 0.96** (0.69 to 1.34)	**2 fewer per 1,000** (from 15 fewer to 16 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 4: Central nervous system adverse events at >3 months (follow up: 24 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral non-steroidal anti-inflammatory drugs	paracetamol	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [d]	very serious [b]	none	0/90 (0.0%)	1.1%	**Peto OR 0.13** (0.00 to 6.67)	**10 fewer per 1,000** (from 40 fewer to 20 more) [c]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio

Explanations

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

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

c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

d. Downgraded by 1 or 2 increments because of outcome indirectness

e. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

f. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

F.1.3 Oral non-steroidal anti-inflammatory drugs compared to placebo

Table 3: Clinical evidence profile: oral non-steroidal anti-inflammatory drugs compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral non-steroidal anti-inflammatory drugs	placebo	Relative (95% CI)	Absolute (95% CI)		

Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at ≤3 months (follow up: mean 13 weeks; assessed with: SF-36 physical component summary)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral non-steroidal anti-inflammatory drugs	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	387	342	-	MD **2.89 higher** (1.67 higher to 4.12 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at ≤3 months (follow up: mean 13 weeks; assessed with: SF-36 mental component summary)												
2	randomised trials	very serious [a]	not serious	not serious	not serious	none	387	342	-	MD **0.38 higher** (0.86 lower to 1.61 higher)	⨁⨁◯◯ LOW	CRITICAL
Quality of life (SF-36 bodily pain subscale, 0-100, high is good, change score) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 bodily pain subscale)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	202	103	-	MD **9.1 higher** (3.85 higher to 14.35 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 physical functioning subscale, 0-100, high is good, change score) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 physical functioning subscale)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	202	103	-	MD **7 higher** (1.59 higher to 12.41 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 role physical subscale, 0-100, high is good, change score) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 role physical subscale)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	202	103	-	MD **6.2 higher** (0.31 higher to 12.09 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 vitality subscale, 0-100, high is good, change score) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 vitality subscale)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	202	103	-	MD **5.9 higher** (1.72 higher to 10.08 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral non-steroidal anti-inflammatory drugs	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life (SF-36 general health subscale, 0-100, high is good, change score) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 general health subscale)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	202	103	-	MD **2.1 higher** (2.02 lower to 6.22 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 mental health subscale, 0-100, high is good, change score) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 mental health subscale)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	202	103	-	MD **2.4 higher** (1.53 lower to 6.33 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 role emotional subscale, 0-100, high is good, change score) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 role emotional subscale)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	202	103	-	MD **2.1 higher** (3.82 lower to 8.02 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 social functioning subscale, 0-100, high is good, change score) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 social functioning subscale)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	202	103	-	MD **4.6 higher** (0.83 lower to 10.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (WOMAC, VAS [different scale ranges], high is poor, change scores) at ≤3 months (follow up: mean 9 weeks; assessed with: WOMAC, VAS)												
45	randomised trials	very serious [a]	very serious [c]	not serious	not serious	none	13962	7792	-	SMD **0.37 lower** (0.45 lower to 0.28 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months (follow up: mean 5 weeks; assessed with: WOMAC, VAS)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral non-steroidal anti-inflammatory drugs	placebo	Relative (95% CI)	Absolute (95% CI)		
11	randomised trials	very serious [a]	serious [c]	not serious	serious [b]	none	2102	1209	-	SMD **0.46 lower** (0.61 lower to 0.3 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (WOMAC, 0-500, high is poor, change score) at >3 months (follow up: 24 weeks; assessed with: WOMAC)												
1	randomised trials	not serious	not serious	not serious	not serious	none	318	313	-	MD **13.9 lower** (30.87 lower to 3.07 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
Physical function (WOMAC [different scale ranges], high is poor, change scores) at ≤3 months (follow up: mean 9 weeks; assessed with: WOMAC)												
31	randomised trials	very serious [a]	not serious	not serious	not serious	none	8746	5398	-	SMD **0.32 lower** (0.37 lower to 0.27 lower)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC [different scale ranges], high is poor, final values) at ≤3 months (follow up: mean 8 weeks; assessed with: WOMAC)												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	1043	331	-	SMD **0.47 lower** (0.6 lower to 0.35 lower)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months (follow up: mean 8 weeks)												
19	randomised trials	very serious [a]	serious [d]	not serious	not serious	none	296/6511 (4.5%)	51/3442 (1.5%)	**RD 0.02** (0.01 to 0.03)	**20 more per 1,000** (from 30 more to 10 more) [e]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months (follow up: mean 7 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral non-steroidal anti-inflammatory drugs	placebo	Relative (95% CI)	Absolute (95% CI)		
47	randomised trials	very serious [a]	serious [d]	not serious	not serious	none	2104/14989 (14.0%)	866/7705 (11.2%)	**RD 0.01** (0.01 to 0.02)	**10 more per 1,000** (from 20 more to 10 more) [e]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at >3 months (follow up: 24 months)												
1	randomised trials	very serious [a]	not serious	serious [f]	very serious [b]	none	6/45 (13.3%)	11.4%	**RR 1.17** (0.39 to 3.57)	**19 more per 1,000** (from 70 fewer to 293 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 2: Cardiovascular adverse events at ≤3 months (follow up: mean 8 weeks)												
27	randomised trials	very serious [a]	serious [d]	not serious	serious [b]	none	151/9342 (1.6%)	77/4905 (1.6%)	**RR 1.15** (0.84 to 1.56)	**2 more per 1,000** (from 3 fewer to 9 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 2: Cardiovascular adverse events at >3 months (follow up: mean 13 months)												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	13/520 (2.5%)	9/616 (1.5%)	**RR 2.30** (0.99 to 5.36)	**20 more per 1,000** (from 0 fewer to 30 more) [e]	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events 3: Hepatorenal adverse events at ≤3 months (follow up: mean 7 weeks)												
12	randomised trials	very serious [a]	serious [d]	not serious	not serious	none	48/3595 (1.3%)	16/2178 (0.7%)	**RD 0.00** (0.00 to 0.00)	**0 fewer per 1,000** (from 0 fewer to 0 fewer) [e]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 3: Hepatorenal adverse events at >3 months (follow up: 24 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral non-steroidal anti-inflammatory drugs	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	2/45 (4.4%)	2.3%	**RR 1.96** (0.18 to 20.80)	**22 more per 1,000** (from 19 fewer to 455 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 4: Central nervous system adverse events at ≤3 months (follow up: mean 7 weeks)												
39	randomised trials	very serious [a]	not serious	not serious	not serious	none	878/11337 (7.7%)	543/6902 (7.9%)	**RR 0.89** (0.81 to 0.99)	**9 fewer per 1,000** (from 15 fewer to 1 fewer)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio

Explanations

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

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

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

e. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

f. Downgraded by 1 or 2 increments because of outcome indirectness

F.1.4 Non-steroidal anti-inflammatory drugs and gastroprotection compared to paracetamol

Table 4: Clinical evidence profile: non-steroidal anti-inflammatory drugs and gastroprotection compared to paracetamol

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	non-steroidal anti-inflammatory drugs and gastroprotection	paracetamol	Relative (95% CI)	Absolute (95% CI)		
Quality of life (SF-36 bodily pain subscale, 0-100, high is good, change score) at ≤3 months (follow up: 6 weeks; assessed with: SF-36 bodily pain subscale)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	218	218	-	MD **3.83 higher** (2.36 higher to 5.3 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (MDHAQ VAS, 0-100, high is poor, change score) at ≤3 months (follow up: 6 weeks; assessed with: MDHAQ VAS)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	218	218	-	MD **14.6 lower** (18.15 lower to 11.05 lower)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	1/218 (0.5%)	0.0%	**Peto OR 7.39** (0.15 to 372.38)	**0 fewer per 1,000** (from 10 fewer to 20 more) [c]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 2: Cardiovascular adverse events at ≤3 months (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	2/218 (0.9%)	0.5%	**RR 2.00** (0.18 to 21.89)	**5 more per 1,000** (from 4 fewer to 104 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 3: Hepatorenal adverse events at ≤3 months (follow up: 6 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	non-steroidal anti-inflammatory drugs and gastroprotection	paracetamol	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	22/218 (10.1%)	4.6%	**RR 2.20** (1.07 to 4.54)	**55 more per 1,000** (from 3 more to 163 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Serious adverse events 4: Central nervous system adverse events at ≤3 months (follow up: 6 weeks)

1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	5/218 (2.3%)	3.2%	**RR 0.71** (0.23 to 2.22)	**9 fewer per 1,000** (from 25 fewer to 39 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

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

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

c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

F.1.5 Non-steroidal anti-inflammatory drugs and gastroprotection compared to oral non-steroidal anti-inflammatory drugs

Table 5: Clinical evidence profile: non-steroidal anti-inflammatory drugs and gastroprotection compared to oral non-steroidal anti-inflammatory drugs

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	non-steroidal anti-inflammatory drugs and gastroprotection	oral non-steroidal anti-inflammatory drugs	Relative (95% CI)	Absolute (95% CI)		
Pain (VAS, 0-10, high is poor, change score) at <3 months (follow-up: 6 weeks; assessed with: VAS)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	327	154	-	MD **0.02 lower** (0.6 lower to 0.56 higher)	⨁⨁◯◯ Low	CRITICAL
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at <3 months (follow-up: mean 7 weeks)												
4	randomised trials	serious[a]	serious[b]	not serious	serious[c]	none	113/1133 (10.0%)	176/1174 (15.0%)	**RR 0.56** (0.35 to 0.91)	**66 fewer per 1,000** (from 97 fewer to 13 fewer)	⨁◯◯◯ Very low	IMPORTANT
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at >3 months (follow-up: 26 weeks)												
1	randomised trials	serious[a]	not serious	serious[d]	not serious	none	81/2246 (3.6%)	0.9%	**RR 4.04** (2.48 to 6.56)	**27 more per 1,000** (from 13 more to 50 more)	⨁⨁◯◯ Low	IMPORTANT
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at <3 months (follow-up: 12 weeks)												
1	randomised trials	not serious	not serious	serious[d]	serious[c]	none	87/490 (17.8%)	19.3%	**RR 0.92** (0.71 to 1.20)	**15 fewer per 1,000** (from 56 fewer to 39 more)	⨁⨁◯◯ Low	IMPORTANT
Serious adverse events 2: Cardiovascular adverse events at <3 months (follow-up: mean 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	non-steroidal anti-inflammatory drugs and gastroprotection	oral non-steroidal anti-inflammatory drugs	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	not serious	not serious	serious[c]	none	16/1019 (1.6%)	6/1004 (0.6%)	**RR 2.52** (1.03 to 6.21)	**9 more per 1,000** (from 0 fewer to 31 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Serious adverse events 3: Hepatorenal adverse events at <3 months (follow-up: 6 weeks)												
1	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	5/327 (1.5%)	1.3%	**RR 1.18** (0.23 to 6.00)	**2 more per 1,000** (from 10 fewer to 65 more)	⨁◯◯◯ Very low	IMPORTANT
Serious adverse events 4: Central nervous system adverse events at <3 months (follow-up: 4 weeks)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	12/178 (6.7%)	10.9%	**RR 0.62** (0.31 to 1.22)	**41 fewer per 1,000** (from 75 fewer to 24 more)	⨁⨁◯◯ Low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

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

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

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

d. Downgraded by 1 or 2 increments because of population indirectness

F.1.6 Non-steroidal anti-inflammatory drugs and gastroprotection compared to placebo

Table 6: Clinical evidence profile: non-steroidal anti-inflammatory drugs and gastroprotection compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	non-steroidal anti-inflammatory drugs and gastroprotection	placebo	Relative (95% CI)	Absolute (95% CI)		
Pain (VAS, 0-10, high is poor, change score) at ≤3 months (follow up: 6 weeks; assessed with: VAS)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	327	91	-	MD **1.59 lower** (2.29 lower to 0.89 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months (follow up: 6 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	22/327 (6.7%)	3.3%	**RR 2.04** (0.62 to 6.67)	**34 more per 1,000** (from 13 fewer to 187 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months (follow up: 12 weeks)												
1	randomised trials	not serious	not serious	serious [c]	serious [b]	none	87/490 (17.8%)	19.9%	**RR 0.89** (0.65 to 1.22)	**22 fewer per 1,000** (from 70 fewer to 44 more)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events 2: Cardiovascular adverse events at ≤3 months (follow up: 12 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	15/490 (3.1%)	1.2%	**RR 2.51** (0.73 to 8.59)	**18 more per 1,000** (from 3 fewer to 91 more)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events 3: Hepatorenal adverse events at ≤3 months (follow up: 6 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	non-steroidal anti-inflammatory drugs and gastroprotection	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	5/327 (1.5%)	0.0%	**Peto OR** 3.64 (0.43 to 30.72)	**20 more per 1,000** (from 10 fewer to 40 more) [d]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

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

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

c. Downgraded by 1 or 2 increments because of outcome indirectness

d. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

F.1.7 Weak opioids compared to placebo

Table 7: Clinical evidence profile: weak opioids compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	weak opioids	placebo	Relative (95% CI)	Absolute (95% CI)		

Pain (WOMAC, 0-500, high is poor, change score) at ≤3 months (follow up: 4 weeks; assessed with: WOMAC)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	weak opioids	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	31	35	-	MD **86.9 lower** (135.16 lower to 38.64 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Physical function (WOMAC, 0-1700, high is poor, change score) at ≤3 months (follow up: 4 weeks; assessed with: WOMAC)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	31	35	-	MD **300.7 lower** (470.41 lower to 130.99 lower)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

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

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

F.1.8 Strong opioids compared to oral non-steroidal anti-inflammatory drugs

Table 8: Clinical evidence profile: strong opioids compared to oral non-steroidal anti-inflammatory drugs

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	strong opioids	oral non-steroidal anti-inflammatory drugs	Relative (95% CI)	Absolute (95% CI)		
Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 physical component summary)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	strong opioids	oral non-steroidal anti-inflammatory drugs	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	599	202	-	MD **2.1 lower** (3.46 lower to 0.74 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 mental component summary)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	599	202	-	MD **0.4 lower** (1.76 lower to 0.96 higher)	⨁⨁◯◯ LOW	CRITICAL
Pain (WOMAC, 0-500, high is poor, change scores) at ≤3 months (follow up: mean 9 weeks; assessed with: WOMAC)												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	644	254	-	MD **28.02 higher** (9.75 higher to 46.29 higher)	⨁⨁◯◯ LOW	CRITICAL
Pain (VAS, 0-100, high is poor, final value) at ≤3 months (follow up: 12 weeks; assessed with: VAS)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	108	110	-	MD **0.95 lower** (1.99 lower to 0.09 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Physical function (WOMAC, 0-1700, high is poor, change scores) at ≤3 months (follow up: mean 9 weeks; assessed with: WOMAC)												
2	randomised trials	serious [a]	serious [c]	not serious	serious [b]	none	644	254	-	MD **75.68 higher** (56.61 lower to 207.97 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events 3: Hepatorenal adverse events at ≤3 months (follow up: 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	strong opioids	oral non-steroidal anti-inflammatory drugs	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	3/108 (2.8%)	2.7%	**RR 1.02** (0.21 to 4.94)	**1 more per 1,000** (from 21 fewer to 106 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Serious adverse events 4: Central nervous system adverse events at ≤3 months (follow up: 4 weeks)

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/60 (1.7%)	0/60 (0.0%)	**Peto OR 7.39** (0.15 to 372.38)	**20 fewer per 1,000** (from 30 fewer to 60 more) [d]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

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

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

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

F.1.9 Strong opioids compared to placebo

Table 9: Clinical evidence profile: Strong opioids compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	strong opioids	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life (EQ-5D, 0-1, high is good, change scores) at ≤3 months (follow up: mean 12 weeks; assessed with: EQ-5D)												
2	randomised trials	serious [a]	very serious [b]	not serious	very serious [c]	none	1336	674	-	MD **0** (0.11 lower to 0.11 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 physical component summary, 0-100, high is good, change scores) at ≤3 months (follow up: mean 9 weeks; assessed with: SF-36 physical component summary)												
3	randomised trials	very serious [a]	not serious	not serious	not serious	none	1530	529	-	MD **0.91 higher** (0.05 higher to 1.78 higher)	⨁⨁◯◯ LOW	CRITICAL
Quality of life (SF-36 mental component summary, 0-100, high is good, change scores) at ≤3 months (follow up: mean 9 weeks; assessed with: SF-36 mental component summary)												
3	randomised trials	very serious [a]	serious [b]	not serious	not serious	none	1530	529	-	MD **0.61 lower** (2.19 lower to 0.97 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 pain subscale, 0-100, high is good, final value and change score) at ≤3 months (follow up: mean 8 weeks; assessed with: SF-36 pain subscale)												
2	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	223	230	-	MD **2.07 higher** (0.37 lower to 4.52 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 physical functioning subscale, 0-100, high is good, final value) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 physical functioning subscale)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	strong opioids	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	132	144	-	MD **1.13 lower** (6.3 lower to 4.04 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 vitality subscale, 0-100, high is good, final value) at ≤3 months (follow up: 4 weeks; assessed with: SF-36 vitality subscale)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	94	88	-	MD **2.93 higher** (0.98 lower to 6.84 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 general health perception subscale, 0-100, high is good, final value) at ≤3 months (follow up: 4 weeks; assessed with: SF-36 general health perception subscale)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	94	88	-	MD **2.15 higher** (1.17 lower to 5.47 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 social functioning subscale, 0-100, high is good, final value) at ≤3 months (follow up: 12 weeks; assessed with: SF-36 social functioning subscale)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	132	144	-	MD **2.26 lower** (7.87 lower to 3.35 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (WOMAC, VAS, NRS [different scale ranges], high is poor, change scores) at ≤3 months (follow up: mean 10 weeks; assessed with: WOMAC, VAS, NRS)												
13	randomised trials	serious [a]	very serious [b]	not serious	serious [c]	none	3864	2129	-	SMD **0.35 lower** (0.51 lower to 0.18 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months (follow up: mean 7 weeks; assessed with: WOMAC, VAS)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	strong opioids	placebo	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	259	205	-	SMD **0.34 lower** (0.52 lower to 0.15 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Physical function (WOMAC [different scale ranges], high is poor, change scores) at ≤3 months (follow up: mean 11 weeks; assessed with: WOMAC)												
6	randomised trials	serious [a]	serious [b]	not serious	not serious	none	2036	879	-	SMD **0.2 lower** (0.28 lower to 0.11 lower)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months (follow up: mean 9 weeks; assessed with: WOMAC, VAS)												
2	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	157	154	-	SMD **0.29 lower** (0.51 lower to 0.06 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Psychological distress (negative affect scale, 0-10, high is poor, change score) at ≤3 months (follow up: 2 weeks; assessed with: negative affect scale)												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	56	51	-	MD **0.2 lower** (0.47 lower to 0.07 higher)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months (follow up: mean 9 weeks)												
3	randomised trials	very serious [a]	very serious [b]	not serious	serious [c]	none	846/1438 (58.8%)	324/725 (44.7%)	**RR 1.63** (0.80 to 3.28)	**282 more per 1,000** (from 89 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 2: Cardiovascular adverse events at ≤3 months (follow up: mean 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	strong opioids	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	29/1456 (2.0%)	1.6%	**RR 1.21** (0.54 to 2.70)	**3 more per 1,000** (from 7 fewer to 27 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Serious adverse events 4: Central nervous system adverse events at ≤3 months (follow up: mean 9 weeks)

3	randomised trials	very serious [a]	not serious	not serious	not serious	none	633/1438 (44.0%)	165/725 (22.8%)	**RR 1.93** (1.67 to 2.24)	**212 more per 1,000** (from 152 more to 282 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio

Explanations

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

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

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

F.1.10 Anti-epileptic drugs compared to paracetamol

Table 10: Clinical evidence profile: anti-epileptic drugs compared to paracetamol

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anti-epileptic drugs	paracetamol	Relative (95% CI)	Absolute (95% CI)		

Pain (WOMAC, 0-100, %, high is poor, change score) at <3 months (follow-up: 3 months; assessed with: WOMAC; Scale from: 0 to 100)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anti-epileptic drugs	paracetamol	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	50	50	-	MD **23.62 lower** (28.26 lower to 18.98 lower)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC, 0-100, %, high is poor, change score) at <3 months (follow-up: 3 months; assessed with: WOMAC; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	50	50	-	MD **10.71 lower** (14.12 lower to 7.3 lower)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events 4: Central nervous system adverse events at <3 months (follow-up: 3 months)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	4/50 (8.0%)	0/50 (0.0%)	**Peto OR 7.87** (1.07 to 57.56)	**80 more per 1,000** (from 0 fewer to 160 more)[c]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations

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

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

c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

F.1.11 Anti-epileptic drugs compared to antidepressants

Table 11: Clinical evidence profile: anti-epileptic drugs compared to antidepressants

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anti-epileptic drugs	antidepressants	Relative (95% CI)	Absolute (95% CI)		
Pain (AUSCAN, 0-500, high is poor, change score) at <3 months (follow-up: 13 weeks; assessed with: AUSCAN)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	22	21	-	MD **96.3 lower** (193.56 lower to 0.96 higher)	⨁⨁◯◯ Low	CRITICAL
Pain (WOMAC, 0-100, %, high is poor, change score) at <3 months (follow-up: 3 months; assessed with: WOMAC; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	50	50	-	MD **4.35 higher** (0.16 lower to 8.86 higher)	⨁◯◯◯ Very low	CRITICAL
Physical function (AUSCAN, 0-900, high is poor, change scores) at < 3 months (follow-up: 13 weeks; assessed with: AUSCAN)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	22	21	-	MD **144.6 lower** (284.11 lower to 5.09 lower)	⨁⨁◯◯ Low	CRITICAL
Physical function (WOMAC, 0-100, %, high is poor, change score) at <3 months (follow-up: 3 months; assessed with: WOMAC; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	50	50	-	MD **1.17 lower** (5.23 lower to 2.89 higher)	⨁⨁◯◯ Low	CRITICAL
Psychological distress (HADS depression score, 0-21, high is poor, change score) at <3 months (follow-up: 13 weeks; assessed with: HADS depression score)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	22	21	-	MD **0.48 higher** (1.73 lower to 2.69 higher)	⨁⨁◯◯ Low	IMPORTANT
Psychological distress (HADS anxiety score, 0-21, high is poor, change score) at < 3 months) (follow-up: 13 weeks; assessed with: HADS anxiety score)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anti-epileptic drugs	antidepressants	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	22	21	-	MD **0.8 lower** (2.66 lower to 1.06 higher)	⨁⨁◯◯ Low	IMPORTANT
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at <3 months (follow-up: 13 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	7/22 (31.8%)	85.7%	**RR 0.37** (0.20 to 0.70)	**540 fewer per 1,000** (from 686 fewer to 257 fewer)	⨁⨁◯◯ Low	IMPORTANT
Serious adverse events 2: Cardiovascular adverse events at <3 months (follow-up: 13 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	3/22 (13.6%)	9.5%	**RR 1.43** (0.27 to 7.73)	**41 more per 1,000** (from 69 fewer to 639 more)	⨁◯◯◯ Very low	IMPORTANT
Serious adverse events 4: Central nervous system adverse events at <3 months (follow-up: 3 months)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	4/50 (8.0%)	7/50 (14.0%)	**RR 0.57** (0.18 to 1.83)	**60 fewer per 1,000** (from 115 fewer to 116 more)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

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

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

F.1.12 Anti-epileptic drugs compared to placebo

Table 12: Clinical evidence profile: anti-epileptic drugs compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anti-epileptic drugs	placebo	Relative (95% CI)	Absolute (95% CI)		
Pain (AUSCAN, 0-500, high is poor, change score) at ≤3 months (follow up: 13 weeks; assessed with: AUSCAN)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	22	22	-	MD **85.49 lower** (153.7 lower to 17.28 lower)	⨁⨁◯◯ LOW	CRITICAL
Physical function (AUSCAN, 0-900, high is poor, change score) at ≤3 months (follow up: 13 weeks; assessed with: AUSCAN)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	22	22	-	MD **179.1 lower** (295.82 lower to 62.38 lower)	⨁⨁◯◯ LOW	CRITICAL
Psychological distress (HADS anxiety score, 0-21, high is poor, change score) at ≤3 months (follow up: 13 weeks; assessed with: HADS anxiety score)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	22	22	-	MD **1.32 lower** (2.91 lower to 0.27 higher)	⨁⨁◯◯ LOW	IMPORTANT
Psychological distress (HADS depression score, 0-21, high is poor, change scores) at ≤3 months (follow up: 13 weeks; assessed with: HADS depression score)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	22	22	-	MD **1.15 lower** (2.85 lower to 0.55 higher)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months (follow up: 13 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	anti-epileptic drugs	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	7/22 (31.8%)	22.7%	**RR 1.40** (0.52 to 3.74)	**91 more per 1,000** (from 109 fewer to 622 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 2: Cardiovascular adverse events at ≤3 months (follow up: 13 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	3/22 (13.6%)	4.6%	**RR 3.00** (0.34 to 26.66)	**92 more per 1,000** (from 30 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

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

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

F.1.13 Antidepressants compared to paracetamol

Table 13: Clinical evidence profile: antidepressants compared to paracetamol

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	antidepressant drugs	paracetamol	Relative (95% CI)	Absolute (95% CI)		
Pain (WOMAC, 0-100, %, high is poor, change score) at <3 months (follow-up: 3 months; assessed with: WOMAC; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	antidepressant drugs	paracetamol	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	50	50	-	MD **27.97 % lower** (32.06 lower to 23.88 lower)	⨁⨁◯◯ Low	CRITICAL
Physical function (WOMAC, 0-100, %, high is poor, change score) at <3 months (follow-up: 3 months; assessed with: WOMAC; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	50	50	-	MD **9.54 % lower** (13.55 lower to 5.53 lower)	⨁⨁◯◯ Low	CRITICAL
Serious adverse events 4: Central nervous system adverse events at <3 months (follow-up: 3 months)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	7/50 (14.0%)	0/50 (0.0%)	**OR 8.41** (1.82 to 38.77)	**140 more per 1,000** (from 40 more to 240 more)[b]	⨁⨁◯◯ Low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations

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

b. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

F.1.14 Antidepressants compared to placebo

Table 14: Clinical evidence profile: antidepressants compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	antidepressant drugs	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life (EQ-5D, -0.11-1, high is good, change scores) at <3 months (follow-up: mean 13 weeks; assessed with: EQ-5D)												
3	randomised trials	serious[a]	serious[b]	not serious	serious[c]	none	401	414	-	MD **0.05 higher** (0.01 higher to 0.09 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 physical function, 0-100, high is good, change score) at <3 months (follow-up: 14 weeks; assessed with: SF-36 physical function; Scale from: 0 to 100)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	102	103	-	MD **2.6 higher** (0.02 higher to 5.18 higher)	⨁⨁◯◯ LOW	CRITICAL
Quality of life (SF-36 bodily pain, 0-100, high is good, change score) at <3 months (follow-up: 14 weeks; assessed with: SF-36 bodily pain; Scale from: 0 to 100)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	102	103	-	MD **2.7 higher** (0.21 higher to 5.19 higher)	⨁⨁◯◯ LOW	CRITICAL
Quality of life (SF-36 role physical, 0-100, high is good, change score) at <3 months (follow-up: 14 weeks; assessed with: SF-36 role physical; Scale from: 0 to 100)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	102	103	-	MD **1.9 higher** (1.3 lower to 5.1 higher)	⨁⨁◯◯ LOW	CRITICAL
Quality of life (SF-36 vitality, 0-100, high is good, change score) at <3 months (follow-up: 14 weeks; assessed with: SF-36 vitality; Scale from: 0 to 100)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	102	103	-	MD **0.6 higher** (1.93 lower to 3.13 higher)	⨁⨁◯◯ LOW	CRITICAL
Quality of life (SF-36 general health, 0-100, high is good, change score) at <3 months (follow-up: 14 weeks; assessed with: SF-36 general health; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	antidepressant drugs	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	102	103	-	MD **0.5 lower** (2.57 lower to 1.57 higher)	⨁⨁◯◯ LOW	CRITICAL
Quality of life (SF-36 role emotional, 0-100, high is good, change score) at <3 months (follow-up: 14 weeks; assessed with: SF-36 role emotional; Scale from: 0 to 100)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	102	103	-	MD **1.8 higher** (1.73 lower to 5.33 higher)	⨁⨁◯◯ LOW	CRITICAL
Quality of life (SF-36 mental health, 0-100, high is good, change score) at <3 months (follow-up: 14 weeks; assessed with: SF-36 mental health; Scale from: 0 to 100)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	102	103	-	MD **0.2 lower** (2.75 lower to 2.35 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Quality of life (SF-36 social function, 0-100, high is good, change score) at <3 months (follow-up: 14 weeks; assessed with: SF-36 social function; Scale from: 0 to 100)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	102	103	-	MD **2 higher** (1.56 lower to 5.56 higher)	⨁⨁◯◯ LOW	CRITICAL
Pain (WOMAC, AUSCAN [different scale ranges], high is poor, change scores) at <3 months (follow-up: mean 13 weeks; assessed with: WOMAC, AUSCAN)												
7	randomised trials	serious[a]	not serious	not serious	not serious	none	972	983	-	SMD **0.34 SD lower** (0.43 lower to 0.25 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Pain (WOMAC, 0-20, high is poor, final value) at >3 months (follow-up: 16 weeks)												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	144	144	-	MD **2.4 lower** (3.51 lower to 1.29 lower)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC, AUSCAN [different scale ranges], high is poor, change scores) at <3 months) (follow-up: mean 13 weeks; assessed with: WOMAC, AUSCAN)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	antidepressant drugs	placebo	Relative (95% CI)	Absolute (95% CI)		
6	randomised trials	serious[a]	not serious	not serious	not serious	none	853	862	-	SMD **0.35 SD lower** (0.45 lower to 0.26 lower)	⨁⨁⨁◯ MODERATE	CRITICAL

Physical function (WOMAC, 0-68, high is poor, final value) at >3 months (follow-up: 16 weeks; assessed with: WOMAC)

1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	144	144	-	MD **5.7 lower** (7.81 lower to 3.59 lower)	⨁⨁◯◯ LOW	CRITICAL

Psychological distress (Beck depression Inventory, HADS depression score [different scale ranges], high is poor, change scores) at <3 months (follow-up: mean 13 weeks; assessed with: Beck depression Inventory, HADS depression score)

2	randomised trials	serious[a]	not serious	not serious	not serious	none	98	118	-	SMD **0.07 lower** (0.34 lower to 0.19 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

Psychological distress (HADS anxiety scale, 0-21, high is poor, change scores) at <3 months (follow-up: mean 13 weeks; assessed with: HADS anxiety scale)

2	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	98	118	-	MD **0.63 lower** (1.32 lower to 0.07 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Psychological distress (Geriatric depression scale, 0-15, high is poor, final value) at >3 months (follow-up: 16 weeks; assessed with: Geriatric depression scale)

1	randomised trials	serious[a]	not serious	not serious	not serious	none	144	144	-	MD **4.5 lower** (4.95 lower to 4.05 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT

Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at <3 months (follow-up: mean 12 weeks)

3	randomised trials	very serious[a]	serious[d]	not serious	not serious	none	27/413 (6.5%)	8/410 (2.0%)	**RR 3.33** (1.70 to 6.49)	**50 more per 1,000** (from 30 more to 70 more)[e]	⨁◯◯◯ VERY LOW	IMPORTANT

Serious adverse events 2: Cardiovascular adverse events at <3 months (follow-up: mean 13 weeks)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	antidepressant drugs	placebo	Relative (95% CI)	Absolute (95% CI)		
5	randomised trials	serious[a]	serious[d]	not serious	serious[c]	none	9/690 (1.3%)	2/688 (0.3%)	**RR 3.04** (0.92 to 10.08)	**10 more per 1,000** (from 0 fewer to 20 more)[e]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 3: Hepatic and renal adverse events at <3 months (follow-up: mean 12 weeks)												
3	randomised trials	serious[a]	serious[d]	not serious	very serious[c]	none	1/491 (0.2%)	2/490 (0.4%)	**OR 0.52** (0.05 to 4.96)	**0 fewer per 1,000** (from 10 fewer to 10 more)[e]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 4: Central nervous system adverse events at <3 months (follow-up: mean 12 weeks)												
3	randomised trials	serious[a]	serious[b]	not serious	very serious[c]	none	21/491 (4.3%)	30/490 (6.1%)	**RR 1.02** (0.33 to 3.19)	**1 more per 1,000** (from 41 fewer to 134 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio; **SMD:** standardised mean difference

Explanations

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

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

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

d. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

e. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

F.1.15 Glucosamine compared to paracetamol

Table 15: Clinical evidence profile: glucosamine compared to paracetamol

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	glucosamine	paracetamol	Relative (95% CI)	Absolute (95% CI)		
Pain (WOMAC, 0-20, high is poor, change score) at >3 months (follow up: 26 weeks; assessed with: WOMAC)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	106	108	-	MD **0.3 lower** (1.16 lower to 0.56 higher)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC, 0-68, high is poor, change score) at >3 months (follow up: 26 weeks; assessed with: WOMAC)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	106	108	-	MD **0.5 lower** (3.26 lower to 2.26 higher)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events 2: Cardiovascular adverse events at >3 months (follow up: 26 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	0/106 (0.0%)	0.9%	**Peto OR 0.14** (0.00 to 6.95)	**10 fewer per 1,000** (from 30 fewer to 20 more) [c]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 3: Hepatorenal adverse events at >3 months (follow up: 26 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	2/106 (1.9%)	19.4%	**RR 0.10** (0.02 to 0.40)	**175 fewer per 1,000** (from 190 fewer to 116 fewer)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

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

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

c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

F.1.16 Glucosamine compared to oral non-steroidal anti-inflammatory drugs

Table 16: Clinical evidence profile: Glucosamine compared to oral non-steroidal anti-inflammatory drugs

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	glucosamine	oral non-steroidal anti-inflammatory drugs	Relative (95% CI)	Absolute (95% CI)		
Pain (WOMAC [different scale ranges], high is poor, change scores) at >3 months (follow up: mean 24 weeks; assessed with: WOMAC)												
2	randomised trials	serious [a]	very serious [b]	not serious	serious [c]	none	427	428	-	SMD **0.72 higher** (0.4 lower to 1.84 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Physical function (WOMAC [different scale ranges], high is poor, change scores) at >3 months (follow up: mean 24 weeks; assessed with: WOMAC)												
2	randomised trials	serious [a]	serious [b]	not serious	not serious	none	427	428	-	SMD **0.06 higher** (0.23 lower to 0.34 higher)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months (follow up: 4 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [x]	none	0/100 (0.0%)	1.0%	**Peto OR 0.13** (0.00 to 6.75)	**10 fewer per 1,000** (from 40 fewer to 20 more) [d]	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	glucosamine	oral non-steroidal anti-inflammatory drugs	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months (follow up: mean 7 weeks)												
4	randomised trials	serious [a]	serious [b]	not serious	serious [c]	none	12/226 (5.3%)	15.0%	**RR 0.39** (0.16 to 0.95)	**92 fewer per 1,000** (from 126 fewer to 8 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 2: Cardiovascular adverse events at ≤3 months (follow up: mean 8 weeks)												
2	randomised trials	serious [a]	serious [e]	not serious	very serious [c]	none	1/108 (0.9%)	2.2%	**RR 0.55** (0.02 to 14.10)	**20 fewer per 1,000** (from 100 fewer to 70 more) [d]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 2: Cardiovascular adverse events at >3 months (follow up: 24 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious [c]	none	1/317 (0.3%)	0.3%	**RR 1.00** (0.06 to 15.97)	**0 fewer per 1,000** (from 3 fewer to 45 more)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events 3: Hepatorenal adverse events at ≤3 months (follow up: 4 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	0/88 (0.0%)	1.1%	**Peto OR 0.14** (0.00 to 6.98)	**10 fewer per 1,000** (from 40 fewer to 20 more) [d]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 3: Hepatorenal adverse events at >3 months (follow up: mean 24 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	4/108 (3.7%)	2/105 (1.9%)	**RR 1.94** (0.36 to 10.39)	**18 more per 1,000** (from 12 fewer to 179 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	glucosamine	oral non-steroidal anti-inflammatory drugs	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events 4: Central nervous system adverse events at ≤3 months (follow up: mean 8 weeks)												
3	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	1/126 (0.8%)	5.0%	**RR 0.30** (0.06 to 1.39)	**40 fewer per 1,000** (from 80 fewer to 10 more) [d]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **SMD:** Standardised mean difference; **RR:** Risk ratio

Explanations

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

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

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

d. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

e. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

F.1.17 Glucosamine compared to placebo

Table 17: Clinical evidence profile: glucosamine compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	glucosamine	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life (EQ-5D, 0-1, high is good, change score) at >3 months (follow-up: 26 weeks; assessed with: EQ-5D)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	glucosamine	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	71	66	-	MD **0.01 higher** (0.05 lower to 0.07 higher)	⨁◯◯◯ Very low	CRITICAL
Quality of life (SF-12 physical component summary, 0-100, high is good, final value) at >3 months (follow-up: 24 months; assessed with: SF-12 physical component summary)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	152	151	-	MD **0.3 lower** (2.45 lower to 1.85 higher)	⨁⨁◯◯ Low	CRITICAL
Quality of life (SF-12 mental component summary, 0-100, high is good, final value) at >3 months (follow-up: 24 months; assessed with: SF-12 mental component summary)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	152	151	-	MD **1.5 higher** (0.79 lower to 3.79 higher)	⨁⨁◯◯ Low	CRITICAL
Pain (WOMAC, VAS, 0-100, final values and change scores, high is poor) at <3 months (follow-up: mean 10 weeks; assessed with: WOMAC, VAS)												
8	randomised trials	serious[a]	serious[c]	not serious	serious[b]	none	380	390	-	MD **6.66 lower** (14.62 lower to 1.31 higher)	⨁◯◯◯ Very low	CRITICAL
Pain (WOMAC, 0-20, high is poor, final value) at <3 months (follow-up: 8 weeks; assessed with: WOMAC)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	58	60	-	MD **0.51 lower** (1.98 lower to 0.96 higher)	⨁⨁◯◯ Low	CRITICAL
Pain (WOMAC [different scale ranges], high is poor, change scores) at >3 months (follow-up: mean 60 weeks; assessed with: WOMAC)												
6	randomised trials	serious[a]	not serious	not serious	not serious	none	804	798	-	SMD **0.03 lower** (0.13 lower to 0.07 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Pain (WOMAC [different scale ranges], high is poor, final values) at >3 months (follow-up: mean 19.5 months; assessed with: WOMAC)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	glucosamine	placebo	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	serious[a]	not serious	not serious	not serious	none	251	262	-	SMD **0.15 SD lower** (0.33 lower to 0.02 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Physical function (WOMAC, 0-100, high is poor, final value and change scores) at <3 months (follow-up: mean 11 weeks; assessed with: WOMAC)												
5	randomised trials	serious[a]	not serious	not serious	serious[b]	none	268	283	-	MD **6.17 lower** (12.84 lower to 0.49 higher)	⨁⨁◯◯ Low	CRITICAL
Physical function (WOMAC, 0-68, high is poor, final value) at <3 months (follow-up: 8 weeks; assessed with: WOMAC)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	58	60	-	MD **1.19 lower** (6.39 lower to 4.01 higher)	⨁⨁◯◯ Low	CRITICAL
Physical function (WOMAC [different scale ranges], high is poor, change scores) at >3 months (follow-up: mean 60 weeks; assessed with: WOMAC)												
6	randomised trials	serious[a]	serious[c]	not serious	not serious	none	804	798	-	SMD **0.09 lower** (0.25 lower to 0.07 higher)	⨁⨁◯◯ Low	CRITICAL
Physical function (WOMAC [different scale ranges], high is poor, final values) at >3 months (follow-up: mean 51 weeks; assessed with: WOMAC)												
3	randomised trials	serious[a]	not serious	not serious	not serious	none	221	220	-	SMD **0** (0.18 lower to 0.19 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Osteoarthritis flares at >3 months (follow-up: 26 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	32/71 (45.1%)	42.4%	**RR 1.06** (0.73 to 1.55)	**25 more per 1,000** (from 114 fewer to 233 more)	⨁⨁◯◯ Low	IMPORTANT

Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at <3 months (follow-up: mean 8 weeks)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	glucosamine	placebo	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	very serious[a]	serious[d]	not serious	very serious[e]	none	22/233 (9.4%)	7.6%	**RR 1.37** (0.71 to 2.01)	**20 more per 1,000** (from 50 fewer to 100 more)[f]	⨁◯◯◯ Very low	IMPORTANT
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at >3 months (follow-up: 6 months)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	2/40 (5.0%)	0/50 (0.0%)	**OR 9.73** (0.59 to 160.85)	**50 more per 1,000** (from 30 fewer to 130 more)[f]	⨁◯◯◯ Very low	IMPORTANT
Serious adverse events 2: Cardiovascular adverse events at <3 months (follow-up: mean 8 weeks)												
2	randomised trials	serious[a]	not serious	not serious	very serious[e]	none	0/145 (0.0%)	0.8%	**RR 0.01** (-1.84 to 1.71)	**10 fewer per 1,000** (from 40 fewer to 10 more)[f]	⨁◯◯◯ Very low	IMPORTANT
Serious adverse events 2: Cardiovascular adverse events at >3 months (follow-up: mean 76 weeks)												
4	randomised trials	serious[a]	serious[d]	not serious	very serious[e]	none	24/676 (3.6%)	0.8%	**RR 1.08** (0.65 to 1.80)	**1 more per 1,000** (from 3 fewer to 6 more)	⨁◯◯◯ Very low	IMPORTANT
Serious adverse events 3: Hepatorenal adverse events at >3 months (follow-up: 26 weeks)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	2/106 (1.9%)	5.7%	**RR 0.33** (0.07 to 1.60)	**38 fewer per 1,000** (from 53 fewer to 34 more)	⨁◯◯◯ Very low	IMPORTANT
Serious adverse events 4: Central nervous system adverse events at <3 months (follow-up: mean 9 weeks)												
4	randomised trials	serious[a]	serious[d]	not serious	very serious[e]	none	2/185 (1.1%)	6/182 (3.3%)	**RR 0.41** (0.11 to 1.56)	**19 fewer per 1,000** (from 29 fewer to 18 more)	⨁◯◯◯ Very low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	glucosamine	placebo	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events 4: Central nervous system adverse events at >3 months (follow-up: 6 months)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	2/40 (5.0%)	0/50 (0.0%)	**OR 9.73** (0.59 to 160.85)	**50 more per 1,000** (from 30 fewer to 130 more)[f]	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio; **SMD:** standardised mean difference

Explanations

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

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

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

e. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

f. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

F.2 Topical (local) (including comparisons to oral formulations)

F.2.1 Capsaicin compared to placebo in knee osteoarthritis

Table 18: Clinical evidence profile: capsaicin compared to placebo in knee osteoarthritis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	capsaicin	placebo	Relative (95% CI)	Absolute (95% CI)		
Pain (WOMAC, 0-20, high is poor, change score) at ≤3 months (follow up: 4 weeks; assessed with: WOMAC)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	99	99	-	MD **3.42 lower** (4.49 lower to 2.35 lower)	⨁⨁⨁⨁ HIGH	CRITICAL
Physical function (WOMAC, 0-68, high is poor, change score) at ≤3 months (follow up: 4 weeks; assessed with: WOMAC)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	99	99	-	MD **8.98 lower** (12.4 lower to 5.56 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months (follow up: 4 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	0/99 (0.0%)	0.0%	**RR 0.00** (-0.02 to 0.02)	**0 fewer per 1,000** (from 20 fewer to 20 more) [d]	⨁⨁⨁◯ MODERATE	IMPORTANT
Serious adverse events 2: Cardiovascular adverse events at ≤3 months (follow up: 4 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	0/99 (0.0%)	0.0%	**RR 0.00** (-0.02 to 0.02)	**0 fewer per 1,000** (from 20 fewer to 20 more) [d]	⨁⨁⨁◯ MODERATE	IMPORTANT
Serious adverse events 3: Hepatorenal adverse events at ≤3 months (follow up: 4 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	capsaicin	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	0/99 (0.0%)	0.0%	**RR 0.00** (-0.02 to 0.02)	**0 fewer per 1,000** (from 20 fewer to 20 more) [d]	⨁⨁⨁◯ MODERATE	IMPORTANT

Serious adverse events 4: Central nervous system adverse events at ≤3 months (follow up: 4 weeks)

1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	0/99 (0.0%)	0.0%	**RR 0.00** (-0.02 to 0.02)	**0 fewer per 1,000** (from 20 fewer to 20 more) [d]	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

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

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

c. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

d. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

F.2.2 Capsaicin compared to placebo in hand osteoarthritis

Table 19: Clinical evidence profile: capsaicin compared to placebo in hand osteoarthritis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	capsaicin	placebo	Relative (95% CI)	Absolute (95% CI)		
Pain (visual analogue scale, 0-100, high is poor, final value) at ≤3 months (follow up: 9 weeks; assessed with: visual analogue scale)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	19	22	-	MD **4.3 lower** (16.2 lower to 7.6 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

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

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

F.2.3 Topical non-steroidal anti-inflammatory drugs compared to oral non-steroidal anti-inflammatory drugs in knee osteoarthritis

Table 20: Clinical evidence profile: Topical non-steroidal anti-inflammatory drugs compared to oral non-steroidal anti-inflammatory drugs in knee osteoarthritis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	topical non-steroidal anti-inflammatory drugs	oral non-steroidal anti-inflammatory drugs	Relative (95% CI)	Absolute (95% CI)		
Quality of life (SF-36 physical component summary, SF-12 physical component summary, 0-100, high is good, change score) at <3 months (follow up: mean 7 weeks; assessed with: SF-36 physical component summary, SF-12 physical component summary; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	topical non-steroidal anti-inflammatory drugs	oral non-steroidal anti-inflammatory drugs	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a]	not serious	not serious	not serious	none	147	154	-	MD **0.04 higher** (1.49 lower to 1.57 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Quality of life (SF-36 mental component summary, SF-12 mental component summary, 0-100, high is good, change score) at <3 months (follow up: mean 7 weeks; assessed with: SF-36 mental component summary, SF-12 mental component summary; Scale from: 0 to 100)												
2	randomised trials	serious [a]	not serious	not serious	not serious	none	147	154	-	MD **1.18 lower** (3.27 lower to 0.91 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at >3 months (follow up: 24 months; assessed with: SF-36 physical component summary; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	138	144	-	MD **0.7 lower** (2.5 lower to 1.1 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at >3 months (follow up: 24 months; assessed with: SF-36 mental component summary; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	138	144	-	MD **0.5 lower** (2.6 lower to 1.6 higher)	⨁⨁◯◯ LOW	CRITICAL
Pain (WOMAC pain subscale [different scale ranges], high is poor, change scores) at <3 months (follow up: mean 9 weeks; assessed with: WOMAC pain subscale)												
6	randomised trials	serious [a]	not serious	not serious	not serious	none	1139	925	-	SMD **0.03 higher** (0.06 lower to 0.12 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Pain (WOMAC pain subscale, 0-100, high is poor, change score) at >3 months (follow up: 24 months; assessed with: WOMAC pain subscale; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	topical non-steroidal anti-inflammatory drugs	oral non-steroidal anti-inflammatory drugs	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	138	144	-	MD **5 higher** (0 to 10 higher)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC physical function subscale [different scale ranges], high is poor, change scores) at <3 months (follow up: mean 9 weeks; assessed with: WOMAC physical function subscale)												
5	randomised trials	serious [a]	serious [c]	not serious	not serious	none	676	692	-	SMD **0** (0.11 lower to 0.1 higher)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC physical function subscale, 0-100, high is poor, change score) at >3 months (follow up: 24 months; assessed with: WOMAC physical function subscale; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	138	144	-	MD **3 higher** (2 lower to 8 higher)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at <3 months (follow up: 12 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/154 (0.6%)	0.0%	**Peto OR 7.25** (0.14 to 365.27)	**10 more per 1,000** (from 10 fewer to 20 more) [d]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at <3 months (follow up: mean 9 weeks)												
4	randomised trials	very serious [a]	serious [c]	not serious	serious [b]	none	142/1089 (13.0%)	216/1033 (20.9%)	**RR 0.56** (0.31 to 1.00)	**92 fewer per 1,000** (from 144 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at >3 months (follow up: 24 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	topical non-steroidal anti-inflammatory drugs	oral non-steroidal anti-inflammatory drugs	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	58/138 (42.0%)	39.6%	**RR 1.06** (0.80 to 1.41)	**24 more per 1,000** (from 79 fewer to 162 more)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events 2: Cardiovascular adverse events at <3 months (follow up: mean 8 weeks)												
2	randomised trials	serious [a]	serious [e]	not serious	serious [b]	none	1/580 (0.2%)	6/590 (1.0%)	**Peto OR 0.24** (0.05 to 1.07)	**20 fewer per 1,000** (from 30 fewer to 0 fewer) [d]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 4: Central nervous system adverse events at <3 months (follow up: mean 7 weeks)												
3	randomised trials	very serious [a]	serious [e]	not serious	very serious [b]	none	7/718 (1.0%)	13/722 (1.8%)	**RR 0.57** (0.25 to 1.34)	**8 fewer per 1,000** (from 14 fewer to 6 more) [d]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio

Explanations

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

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

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

e. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

F.2.4 Topical non-steroidal anti-inflammatory drugs compared to capsaicin in knee osteoarthritis

Table 21: Clinical evidence profile: Topical non-steroidal anti-inflammatory drugs compared to capsaicin in knee osteoarthritis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	topical non-steroidal anti-inflammatory drugs	capsaicin	Relative (95% CI)	Absolute (95% CI)		
Pain (NRS, 0-10, high is poor, change score) at <3 months (follow-up: 12 weeks; assessed with: NRS; Scale from: 0 to 10)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	22	22	-	MD **0.4 higher** (0.61 lower to 1.41 higher)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

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

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

F.2.5 Topical non-steroidal anti-inflammatory drugs compared to placebo in knee osteoarthritis

Table 22: Clinical evidence profile: topical non-steroidal anti-inflammatory drugs compared to placebo in knee osteoarthritis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	topical non-steroidal anti-inflammatory drugs	placebo	Relative (95% CI)	Absolute (95% CI)		
Pain (WOMAC, VAS, 0-100, high is poor, final values and change scores) at <3 months (follow-up: mean 6 weeks; assessed with: WOMAC, VAS)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	topical non-steroidal anti-inflammatory drugs	placebo	Relative (95% CI)	Absolute (95% CI)		
9	randomised trials	serious[a]	very serious[b]	not serious	serious[c]	none	1788	1347	-	MD **6.01 lower** (9.87 lower to 2.16 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (WOMAC pain subscale, 0-20, high is poor, change scores) at <3 months (follow-up: mean 9 weeks; assessed with: WOMAC pain subscale)												
8	randomised trials	serious[a]	not serious	not serious	not serious	none	1120	1338	-	MD **1.32 lower** (1.93 lower to 0.7 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Physical function (WOMAC physical function subscale [different scale ranges], high is poor, change scores) at <3 months (follow-up: mean 8 weeks; assessed with: WOMAC physical function subscale)												
12	randomised trials	serious[a]	serious[b]	not serious	not serious	none	1707	1936	-	SMD **0.32 SD lower** (0.47 lower to 0.18 lower)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC physical function subscale, 0-100, high is poor, final value) at <3 months (follow-up: 12 weeks; assessed with: WOMAC physical function subscale)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	638	190	-	MD **2.91 lower** (6.4 lower to 0.58 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at <3 months (follow-up: mean 10 weeks)												
3	randomised trials	serious[a]	serious[d]	not serious	very serious[c]	none	1/425 (0.2%)	0.9%	**Peto OR 0.43** (0.06 to 3.12)	**0 fewer per 1,000** (from 10 fewer to 10 more)[e]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at <3 months (follow-up: mean 8 weeks)												
9	randomised trials	very serious[a]	serious[d]	not serious	very serious[f]	none	70/2184 (3.2%)	57/1711 (3.3%)	**RR 0.91** (0.70 to 1.30)	**0 fewer per 1,000** (from 10 fewer to 10 more)[e]	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	topical non-steroidal anti-inflammatory drugs	placebo	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events 2: Cardiovascular adverse events at <3 months (follow-up: mean 10 weeks)												
7	randomised trials	very serious[a]	serious[d]	not serious	very serious[f]	none	18/2055 (0.9%)	7/1589 (0.4%)	**RR 1.70** (1.00 to 2.57)	**0 fewer per 1,000** (from 0 fewer to 10 more)[e]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 3: Hepatorenal adverse events at <3 months (follow-up: mean 5 weeks)												
4	randomised trials	not serious	serious[d]	not serious	very serious[f]	none	16/824 (1.9%)	0.3%	**RR 1.65** (0.29 to 2.41)	**10 more per 1,000** (from 10 fewer to 20 more)[e]	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 4: Central nervous system adverse events at <3 months (follow-up: mean 11 weeks)												
8	randomised trials	serious[a]	serious[d]	not serious	very serious[f]	none	115/1910 (6.0%)	1.8%	**RR 0.83** (0.53 to 1.16)	**10 fewer per 1,000** (from 30 fewer to 10 more)[e]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardised mean difference

Explanations

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

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

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

d. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

e. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

f. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

F.2.6 Topical non-steroidal anti-inflammatory drugs compared to placebo in hand osteoarthritis

Table 23: Clinical evidence profile: topical non-steroidal anti-inflammatory drugs compared to placebo in hand osteoarthritis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	topical non-steroidal anti-inflammatory drugs	placebo	Relative (95% CI)	Absolute (95% CI)		
Pain (AUSCAN pain index, 0-100, high is poor, change score) at ≤3 months (follow up: 8 weeks; assessed with: AUSCAN pain index)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	198	187	-	MD **4.7 higher** (0.77 lower to 10.17 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Physical function (AUSCAN functional index, 0-100, high is poor, change score) at ≤3 months (follow up: 8 weeks; assessed with: AUSCAN functional index)												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	198	187	-	MD **7.3 higher** (1.74 higher to 12.86 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months (follow up: 8 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	15/198 (7.6%)	3.7%	**RR 2.02** (0.84 to 4.85)	**38 more per 1,000** (from 6 fewer to 142 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Serious adverse events 4: Central nervous system adverse events at ≤3 months (follow up: 8 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	22/198 (11.1%)	10.2%	**RR 1.09** (0.61 to 1.95)	**9 more per 1,000** (from 40 fewer to 97 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

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

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

F.3 Topical (systemic) (including comparisons to oral formulations)

F.3.1 Transdermal strong opioids compared to oral strong opioids

Table 24: Clinical evidence profile: transdermal strong opioids compared to oral strong opioids

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	transdermal strong opioids	oral strong opioids	Relative (95% CI)	Absolute (95% CI)		
Pain (NRS, 0-10, high is poor, final value) at ≤3 months (follow up: 12 weeks; assessed with: NRS)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	69	65	-	MD **0.18 lower** (0.9 lower to 0.54 higher)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events 2: Cardiovascular adverse events at ≤3 months (follow up: 12 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	4/69 (5.8%)	0.0%	**RR 8.49** (0.47 to 154.58)	**60 more per 1,000** (from 0 fewer to 120 more) [c]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

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

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

c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

F.3.2 Transdermal strong opioids compared to placebo

Table 25: Clinical evidence profile: transdermal strong opioids compared to placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	transdermal strong opioids	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life (SF-36 pain index, 0-100, high is good, change score) at ≤3 months (follow up: 6 weeks; assessed with: SF-36 pain index)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	202	197	-	MD **4.3 higher** (0.42 higher to 8.18 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 physical functioning, 0-100, high is good, change score) at ≤3 months (follow up: 6 weeks; assessed with: SF-36 physical functioning)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	202	197	-	MD **1.9 higher** (1.58 lower to 5.38 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 role physical, 0-100, high is good, change score) at ≤3 months (follow up: 6 weeks; assessed with: SF-36 role physical)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	202	197	-	MD **2.5 lower** (9.73 lower to 4.73 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 vitality, 0-100, high is good, change score) at ≤3 months (follow up: 6 weeks; assessed with: SF-36 vitality)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	202	197	-	MD **1.2 lower** (5.22 lower to 2.82 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 general health, 0-100, high is good, change score) at ≤3 months (follow up: 6 weeks; assessed with: SF-36 general health)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	transdermal strong opioids	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	202	197	-	MD **1 lower** (4.19 lower to 2.19 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 mental health, 0-100, high is good, change score) at ≤3 months (follow up: 6 weeks; assessed with: SF-36 mental health)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	202	197	-	MD **1.1 lower** (4.71 lower to 2.51 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 role emotional, 0-100, high is good, change score) at ≤3 months (follow up: 6 weeks; assessed with: SF-36 role emotional)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	202	197	-	MD **8.4 lower** (17.74 lower to 0.94 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (SF-36 social functioning, 0-100, high is good, change score) at ≤3 months (follow up: 6 weeks; assessed with: SF-36 social functioning)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	202	197	-	MD **3.1 lower** (9.1 lower to 2.9 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (WOMAC, NRS [different scale ranges], high is poor, change scores) at ≤3 months (follow up: 5 weeks; assessed with: WOMAC, NRS)												
2	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	351	359	-	SMD **0.34 lower** (0.66 lower to 0.01 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Pain (WOMAC, 0-20, high is poor, change score) at >3 months (follow up: 24 weeks; assessed with: WOMAC)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	95	99	-	MD **0.9 lower** (1.96 lower to 0.16 higher)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC, unclear scale range, high is poor, change score) at ≤3 months (follow up: 6 weeks; assessed with: WOMAC)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	transdermal strong opioids	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	202	197	-	MD **0.4 lower** (0.67 lower to 0.13 lower)	⨁⨁◯◯ LOW	CRITICAL
Physical function (WOMAC, 0-68, high is poor, change score) at >3 months (follow up: 24 weeks; assessed with: WOMAC)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	94	96	-	MD **3.5 lower** (6.79 lower to 0.21 lower)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at >3 months (follow up: 24 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	57/100 (57.0%)	25.3%	**RR 2.26** (1.54 to 3.30)	**319 more per 1,000** (from 137 more to 582 more)	⨁⨁◯◯ LOW	IMPORTANT
Serious adverse events 4: Central nervous system adverse events at >3 months (follow up: 24 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	45/100 (45.0%)	18.2%	**RR 2.48** (1.55 to 3.96)	**269 more per 1,000** (from 100 more to 539 more)	⨁⨁◯◯ LOW	IMPORTANT

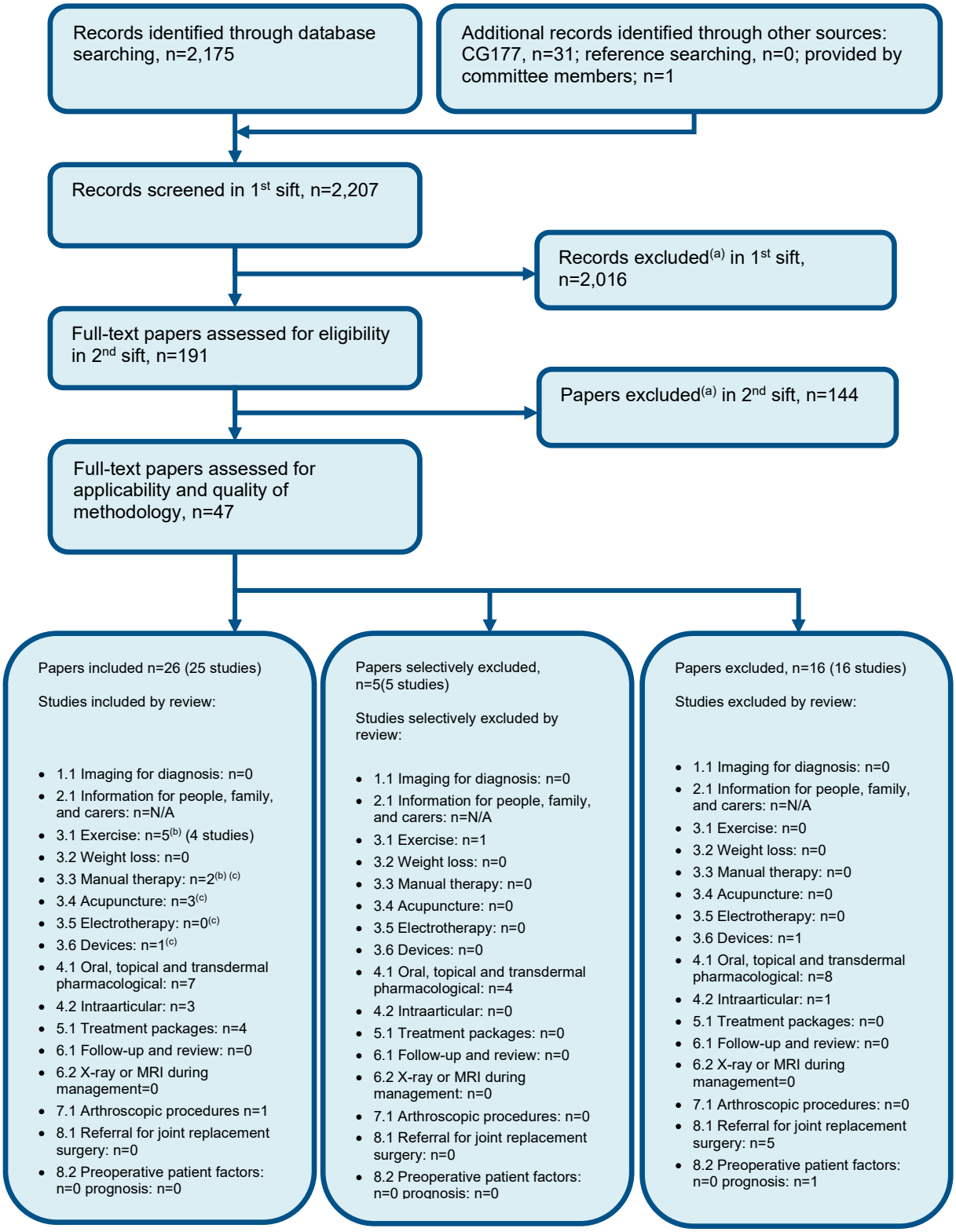
CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio

Explanations

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

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

Appendix G – Economic evidence study selection



(a) Non-relevant population, intervention, comparison, design or setting; non-English language.
(b) Two articles identified were applicable to Q3.1 and Q3.3, for the purposes of this diagram they have been included under Q3.1 only.
(c) One article identified was applicable to Q3.3, Q3.4, Q3.5 and Q3.6, for the purposes of this diagram it has been included under Q3.3 only.

Appendix H – Economic evidence tables

Oral analgesics

Study	Chen 2009[95]						
		Costs[(b)]		Health Outcomes	Cost effectiveness[(c)]		
Study details	Population & Interventions	Int.	Total cost	Total QALYs	Inc. cost	Inc. QALYs	ICER
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model with a 3 months cycle length in which patient might experience gastrointestinal (GI) or cardiovascular events. Treatment may be withdrawn and/or PPI may be added if gastrointestinal adverse event occurs. Only one new event (GI or MI) can occur in any 3-month cycle. Assumed second MIs are fatal. Assumed that NSAIDs do not protect against risk of MI. At each cycle, patients	**Population:** People with osteoarthritis and rheumatoid arthritis (majority osteoarthritis) **Cohort settings:** Start age: 58 Male: NR **1:** NSAID - diclofenac **2:** NSAID - ibuprofen **3:** NSAID - celecoxib (low dose) **4:** NSAID - celecoxib (high dose) **5:** NSAID - etodolac (branded) **6:** NSAID - etodolac (generic) **7:** NSAID - etoricoxib **8**: NSAID - lumiracoxib **9:** NSAID – meloxicam (low dose) **10:** NSAID - meloxicam (high dose) **11:** NSAID - rofecoxib **12:** NSAID - valdecoxib **13:** NSAID with gastroprotection - diclofenac + PPI **14:** NSAID with gastroprotection - ibuprofen + PPI	2 1 6 9 13 14 10 5 8 3 12 7 11 4	£520 £531 £786 £806 £971 £981 £1,006 £1,142 £1,227 £1,455 £1,486 £1,526 £1,560 £2,565	3.192 3.187 3.202 3.214 3.218 3.214 3.214 3.202 3.197 3.201 3.214 3.219 3.198 3.201	- Dominated Ext Dom £286 £165 Dominated Dominated Dominated Dominated Dominated Dominated £555 Dominated Dominated	- Dominated Ext Dom 0.023 0.004 Dominated Dominated Dominated Dominated Dominated Dominated 0.001 Dominated Dominated	- Dominated Ext dominated £12,557 £43,606 Dominated Dominated Dominated Dominated Dominated Dominated £459,083 Dominated Dominated
		Currency & cost year: 2008 UK pounds **Cost components incorporated:** Prescriptions, consultations, diagnostic tests, hospital admissions,			**Analysis of uncertainty:** Multiple deterministic sensitivity analyses were undertaken in which low dose meloxicam remains the most cost effective option. A scenario analysis was undertaken for populations with increased risk of GI events (for example, people with a known previous GI event). In this population diclofenac with gastroprotection is found to be the most cost effective treatment. (ICER £13,397 compared to low dose meloxicam).		

are subject to age-specific mortality. **Perspective:** UK NHS **Time horizon:** 5 years **Treatment effect duration:** Treatment duration[(a)] **Discounting:** Costs: 3.5%; Outcomes: 3.5%		equipment and aids.		
Data sources				
Health outcomes: Where available meta-analysed data from RCTs was used to estimate adverse event rates: any gastrointestinal event (dyspepsia, perforation, symptomatic ulcers, or bleeding) and myocardial infarction. Baseline event data estimated from non-aspirin users in a large RCT (CLASS). Utilities for health states were elicited from general population survey (n=60) in Sudbury, Ontario using the standard gamble and rating scale techniques. **Quality-of-life weights:** Not specified. **Cost sources:** Boehringer Ingelheim submission, British National Formulary (year unclear).				
Comments				
Source of funding: NHS R&D HTA Programme (project number 03/34/01). **Limitations:** Study does not include all comparators being assessed in the review. 2008 units costs may not reflect the current NHS context. Unclear how utilities were derived to calculate QALYs. Mixed arthritis population in RCTs used to determine treatment effect, although most people have osteoarthritis. Further RCTs have been published for some of the comparators and therefore treatment effects may not reflect the full body of evidence. Unclear sources for resource use associated with adverse events. **Other:** None.				
Overall applicability:[(d)] Directly applicable **Overall quality:**[(e)] Potentially serious limitations				

Abbreviations: CUA= cost–utility analysis; GI= gastrointestinal; ICER= incremental cost-effectiveness ratio; Inc.= incremental; Int.= intervention; MI= myocardial infarction; NHS= National Health Service; NR= not reported; NSAID= non-steroidal anti-inflammatory drug; PPI= proton pump inhibitor; QALYs= quality-adjusted life years; RCT= randomised controlled trial; UK= United Kingdom; WOMAC= Western Ontario and McMaster Universities osteoarthritis index.

(a) Assumed that treatment effects do not persist after treatment is terminated. However, the model does include the continuing effect on a person's remaining lifetime of any adverse events that have occurred within the treatment period.

(b) Intervention number in order of least to most costly

(c) Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more costly and is less effective) or subject to extended dominance (the strategy is more costly and more effective but the incremental cost effectiveness ratio is higher than the next most effective option and so it would never be the most cost effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option.

(d) Directly applicable / Partially applicable / Not applicable

(e) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Latimer 2009[298]					
Study details	**Population & Interventions**	**Costs[(d)]**		**Health outcomes**	**Cost effectiveness[(e)]**		
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** NICE CG59 guideline model. Markov model with health states representing the most frequent and severe adverse events: dyspepsia; symptomatic ulcer; complicated gastrointestinal perforation, ulcer, or bleed; myocardial infarction; stroke; and heart failure. **Perspective:** UK NHS **Time horizon:** Lifetime **Treatment effect duration:**[(a)] 3 months **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Population:** People with symptomatic osteoarthritis **Cohort settings:** Start age: 55 Male: NR **1:** No treatment **2:** Paracetamol **Intervention 3:** NSAID - diclofenac 100mg **4:** NSAID - naproxen 750mg **5:** NSAID – ibuprofen 1200mg **6:** NSAID - etoricoxib 30mg **7:** NSAID - celecoxib 200mg **8:** NSAID with gastroprotection - diclofenac 100mg + PPI **9:** NSAID with gastroprotection - naproxen, 750mg + PPI **10:** NSAID with gastroprotection - ibuprofen 1200mg + PPI **11:** NSAID with gastroprotection - etoricoxib 30mg + PPI **12:** NSAID with gastroprotection - celecoxib 200mg + PPI	**Int.**	**Total costs (mean per person)**	**QALY gain (mean per person)**	**Inc. cost**	**Inc. QALY**	**ICER**
		1	£0	0.0000	-	-	-
		2	£13	0.0010	Ext Dom	Ext Dom	Ext Dom
		3	NR	NR	NR	NR	NR
		4	NR	NR	NR	NR	NR
		5	NR	NR	NR	NR	NR
		8	£20	0.0028	£20	0.0028	£6,976
		9	£30	0.0035	Ext Dom	Ext Dom	Ext Dom
		10	£35	0.0039	Ext Dom	Ext Dom	Ext Dom
		6	NR	NR	NR	NR	NR
		7	NR	NR	NR	NR	NR
		11	£58	0.0073	£38	0.0045	£8,597
		12	£79	0.0093	£21	0.0020	£10,724
		Currency & cost year: 2008 UK pounds **Cost components incorporated:** Drugs, treatment of side effects, outpatient and GP consultations.			It was noted that interventions 3,4, 5, 6 and 7 accumulate fewer QALYs and similar costs to interventions 8, 9, 10, 11 and 12, respectively. Therefore, the addition of a proton pump inhibitor is highly cost effective. Consequently, interventions 3, 4, 5, 6 and 7 were not reported in the incremental analysis. **Analysis of uncertainty:** Multiple deterministic sensitivity analyses were undertaken. Celecoxib + PPI remains the most cost effective option when using observational data for adverse events. When assume same stroke risk for both celecoxib and etoricoxib (from MEDAL trial),		

				etoricoxib + PPI becomes most cost effective option. A scenario analysis was also undertaken adjusting the starting age of the population to 65 to reflect a population with greater baseline gastrointestinal and cardiovascular risk. In this population, celecoxib + PPI remains the most cost effective option.
Data sources				
Health outcomes: Three large RCTs (TARGET, CLASS and MEDAL) reporting adverse events: gastrointestinal (dyspepsia, symptomatic ulcer, and gastrointestinal bleed) and cardiovascular (myocardial infarction, stroke, and heart failure). **Quality-of-life weights:** Utility estimates for treatments and no adverse events were derived using a mapping technique from a meta-analysis of WOMAC scores. Utility weights for adverse events were identified in the literature. All identified estimates were multiplied by general UK population age-specific utility scores. **Cost sources:** NHS Reference Costs 2007/08, British National Formulary 2008				
Comments				
Source of funding: National Institute for Health and Clinical Excellence. **Limitations:** Study does not include all comparators being assessed in the review. 2008 units costs may not reflect the current NHS context. Utilities were not derived directly from EQ-5D questionnaire, but from mapping from WOMAC. Further RCTs have been published for some of the comparators and therefore treatment effects may not reflect the full body of evidence. Unclear source of estimates for resource use. **Other:** None.				
Overall applicability:[b] Directly applicable **Overall quality:**[c] Potentially Serious limitations				

Abbreviations: CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); GP= general practitioner; ICER= incremental cost-effectiveness ratio; Inc.= incremental; Int.= intervention; NHS= National Health Service; NR= not reported; NSAID= non-steroidal anti-inflammatory drug; PPI= proton pump inhibitor; QALYs= quality-adjusted life years; RCT= randomised controlled trial; UK= United Kingdom; WOMAC= Western Ontario and McMaster Universities osteoarthritis index.

(a) Assumed that treatment effects do not persist after treatment is terminated. However, the model does include the continuing effect on a person's remaining lifetime of any adverse events that have occurred within the treatment period.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

(d) Intervention number in order of least to most costly

(e) Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more costly and is less effective) or subject to extended dominance (the strategy is more costly and more effective but the incremental cost effectiveness ratio is higher than the next most effective option and so it would never be the most cost effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option.

Study	NICE Osteoarthritis clinical guidelines 2014					
Study details	**Population & Interventions**	**Costs[d]**		**Health outcomes**	**Cost effectiveness[e]**		
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** The NICE CG59 guideline model was updated to incorporate new efficacy and adverse event evidence for paracetamol and fixed-dose combination products containing NSAIDs and PPI. Markov model with health states representing the most frequent and severe adverse events: dyspepsia; symptomatic ulcer; complicated gastrointestinal event; myocardial infarction; stroke; heart failure and chronic kidney disease. **Perspective:** UK NHS	**Population:** People with osteoarthritis **Cohort settings:** Start age: 55-64 Male: NR **1:** No treatment **2:** Paracetamol 3000mg **3:** NSAID - diclofenac 100mg **4:** NSAID - naproxen 750mg **5:** NSAID - ibuprofen 1200mg **6:** NSAID - etoricoxib 30mg **7:** NSAID - celecoxib 200mg **8:** NSAID with gastroprotection - diclofenac 100mg + PPI **9:** NSAID with gastroprotection - naproxen, 750mg + PPI **10:** NSAID with gastroprotection - ibuprofen 1200mg + PPI **11:** NSAID with gastroprotection - etoricoxib 30mg + PPI **12:** NSAID with gastroprotection - celecoxib 200mg + PPI	**Int.**	**Total costs (mean per person)**	**QALY gain (mean per person)**	**Inc. cost**	**Inc. QALY**	**ICER**
		1	£1,612	11.2632	-	-	-
		8	£1,631	11.2697	£19	0.0065	£2,923
		2	£1,633	11.2591	Dominated	Dominated	Dominated
		3	£1,642	11.2572	Dominated	Dominated	Dominated
		10	£1,646	11.2682	Dominated	Dominated	Dominated
		9	£1,648	11.2697	Dominated	Dominated	Dominated
		5	£1,656	11.2564	Dominated	Dominated	Dominated
		4	£1,659	11.2581	Dominated	Dominated	Dominated
		15	£1,667	11.2685	Dominated	Dominated	Dominated
		11	£1,668	11.2725	£37	0.0028	£13,214
		13	£1,673	11.2685	Dominated	Dominated	Dominated
		14	£1,676	11.2689	Dominated	Dominated	Dominated
		6	£1,678	11.2604	Dominated	Dominated	Dominated
		12	£1,684	11.2724	Dominated	Dominated	Dominated
		7	£1,692	11.2611	Dominated	Dominated	Dominated
		Currency & cost year: 2012 UK pounds **Cost components incorporated:** Drugs, diagnostics, treatment of side effects, outpatient and GP consultations.			**Analysis of uncertainty:** The most cost effective option was etoricoxib + PPI, however its probability of cost effectiveness was 10.3%. This highlights the high degree of uncertainty in the results. Cost effectiveness probabilities for other treatment options included: diclofenac + PPI (34.5%), celecoxib + PPI (6.1%), naproxen + PPI (23.5%) and ibuprofen +PPI (6.1%).		

Time horizon: Lifetime **Treatment effect duration:**[(a)] 3 months **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**13:** Fixed-dose NSAID with gastroprotection - Diclofenac 150mg + misoprostol 400mg **14:** Fixed-dose NSAID with gastroprotection - Naproxen 1000mg + esomeprazole 40mg **15:** Fixed-dose NSAID with gastroprotection - Ketoprofen 200mg + omeprazole 20mg			Results for a 2-year treatment duration are similar to those of a 3-month duration with etoricoxib + PPI the most cost effective option. The NSAID + PPI combination was also found to be more cost effective than the NSAID alone due to the reduced adverse events resulting from the PPI over the longer term. . A scenario analysis was also undertaken adjusting the starting age of the population to 65 to reflect a population with greater baseline gastrointestinal and cardiovascular risk. In this population, etoricoxib + PPI remains the most cost effective option.

Data sources
Health outcomes: Adverse event data for NSAIDs and COX-2 inhibitors were taken from three large RCTs (TARGET, CLASS and MEDAL). The main source of adverse event data for paracetamol was an observational study by De Vries 2010. Data for symptomatic ulcers with paracetamol were taken from a study by Rodriguez 2004, while GI symptoms were assumed to be equivalent to ibuprofen. The hazard ratio for moderate CKD due to NSAIDs was based on observational data from Hippisley-Cox 2010, which was subsequently applied to all drugs in the model (including paracetamol). **Quality-of-life weights:** Utility estimates for treatments and no adverse events were derived using a mapping technique from a meta-analysis of WOMAC scores conducted by the NGC. Utility weights for adverse events were identified in the literature. All identified estimates were multiplied by general UK population age-specific utility scores. **Cost sources:** NHS Reference Costs 2011/12, Drug Tariff October 2012, Personal Social Services Research Unit 2012
Comments
Source of funding: National Institute for Health and Clinical Excellence. **Limitations:** Study does not include all comparators being assessed in the review. Unit costs from 2012 may not reflect the current NHS context. Utilities were not derived directly from EQ-5D questionnaire but were mapped from WOMAC. Further RCTs have been published for some of the comparators and therefore treatment effects may not reflect the full body of evidence. Unclear source of estimates for resource use in dyspepsia, symptomatic ulcer and complicated GI events. **Other:** It was assumed there is equal efficacy between NSAIDs and COX-2 inhibitors as well as between different drug doses in the absence of evidence. It was also assumed that treatment with NSAIDs and COX-2 inhibitors is stopped after any serious GI, CV or CKD event, and patients switched to topical ibuprofen.
Overall applicability:[(b)] Directly applicable **Overall quality:**[(c)] Minor limitations

Abbreviations: CKD= chronic kidney disease; COX-2= cyclooxygenase 2; CUA= cost–utility analysis; CV= cardiovascular; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); GI= gastrointestinal; GP= general practitioner; ICER= incremental cost-effectiveness ratio; Inc.= incremental; Int.= Intervention; NGC: National Guideline Centre; NHS= National Health Service; NR= not reported; NSAID= non-steroidal anti-inflammatory drug; OA= osteoarthritis; PPI= proton

pump inhibitor; QALYs= quality-adjusted life years; RCT= randomised controlled trial; UK= United Kingdom; WOMAC= Western Ontario and McMaster Universities osteoarthritis index.

(a) Assumed that treatment effects do not persist after treatment is terminated. However, the model does include the continuing effect on a person's remaining lifetime of any adverse events that have occurred within the treatment period.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

(d) Intervention number in order of least to most costly

(e) Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more costly and is less effective) or subject to extended dominance (the strategy is more costly and more effective but the incremental cost effectiveness ratio is higher than the next most effective option and so it would never be the most cost effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option.

Oral versus topical NSAIDs

Study	Castelnuovo 2008/Underwood 2008[88]			
Study details	**Population & Interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Within-trial analysis of Underwood 2008 [506] **Approach to analysis:** Analysis of individual level quality of life and resource use data adjusted by age and gender, and baseline utility for QALYs. Unit costs applied. Randomised trial and patient preference study undertaken. Data reported here is from the trial data only. **Perspective:** UK NHS and societal perspective (only NHS perspective reported here) **Time horizon:** 12 months **Treatment effect duration:**[(a)] 12 months **Discounting:** Costs: 3.5% (in sensitivity analyses); Outcomes: 3.5% (in sensitivity analyses)	**Population:** People aged 50 years and over who had troublesome pain in or around the knee on most days for at least a month as well as knee pain for >3 months in the preceding year; and had consulted or been prescribed treatment by a GP for knee pain in the preceding 3 years. Radiological diagnosis of OA was not required. **Cohort settings:** Start age: NR Male: NR **Intervention 1:** Topical ibuprofen **Intervention 2:** Oral ibuprofen	**Total costs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental cost: 2−1: £191.40 **Currency & cost year:** UK pounds 2006 **Cost components incorporated:** GP appointments, outpatient consultations, physiotherapy services, diagnostic tests (blood tests, X-rays, gastroscopies, hospital admissions, prescriptions. Societal perspective also included the number and cost of equipment or other aids, privately acquired or dispensed by the NHS, and private treatment (GP and nurse consultations, referrals and hospital admissions, nursing or other help.	**QALY gain (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental QALYs: 2−1: 0.021	**ICER (Intervention 2 versus intervention 1):** £9,114 per QALY gained Probability Intervention 2 cost effective (£30K threshold): 80% **Analysis of uncertainty:** 24-month time horizon shows that oral ibuprofen remains cost effective ICER: £11,976 per QALY gained. Probability Intervention 2 cost effective (£30K threshold): 55% The cost effectiveness of oral ibuprofen remained robust to the following sensitivity analyses: costs of admissions based on actual length of stay reported in discharge notes, excluding high cost individuals, increasing the discount rate to 6%, using the total cost of any drug prescribed (to test assumptions around which costs were related to knee pain).
Data sources				
Health outcomes: QALYs were calculated using patient-level EQ-5D data collected at baseline, 3, 6,12 and 24 months. Area under the curve approach was used and with adjustments for health utility at baseline, age and gender. **Quality-of-life weights:** EQ-5D UK tariff. **Cost sources:** UK national sources such as NHS Reference costs (2005), Prescription Cost Analysis Database (2004) inflated using Healthcare Price Index, and PSSRU (2005).				

Comments
Source of funding: NHS Health Technology Assessment Programme. Goldshield Pharmaceuticals supplied the starter packs of topical ibuprofen. **Limitations:** Study does not include all comparators being assessed in the review. Resource use (2003-2005) and inflated unit costs (2006) may not reflect current UK NHS practice. Within-trial analysis and so may not reflect full body of available evidence for this comparison; 1 of 7 studies included in the clinical review for topical versus oral NSAID. A longer time horizon may be preferable given that oral ibuprofen seems to become less cost effective over time. **Other:** None.
Overall applicability: Partially applicable(b) **Overall quality: Potentially serious limitations**(c)

Abbreviations: CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); GP= general practitioner; ICER= incremental cost-effectiveness ratio; NHS= National Health Service; NR= not reported; NSAID= non-steroidal ant-inflammatory drug; PSSRU= Personal Social Services Research Unit; QALYs= quality-adjusted life years; UK= United Kingdom; WOMAC= Western Ontario and McMaster Universities osteoarthritis index.

(a) Assumed that treatment effects do not persist after treatment is terminated. However, the model does include the continuing effect on a person's remaining lifetime of any adverse events that have occurred within the treatment period.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Glucosamine

Study	Black 2009[55]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Cohort simulation with 12-month cycle length. Rather than using discrete health states, health was modelled along a continuum given the initial baseline level of health status. Two additional discrete health states were used: progression to total knee replacement, and death. Individuals would only remain in the progression to TKR health state for one cycle before returning to non-progressive cohort. Individuals were assumed to remain on glucosamine until death. **Perspective:** UK NHS **Time horizon:** Lifetime **Treatment effect duration:** Lifetime[(a)] **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Population:** People with knee osteoarthritis **Cohort settings:** Start age: NR (mean life expectancy 22.61 years) Male: NR **Intervention 1:** Usual care **Intervention 2:** Usual care plus glucosamine sulphate	**Total costs (mean per patient):** Intervention 1: £4,634 Intervention 2: £7,039 Incremental (2−1): £2,405 (95% CI: NR; p=NR) **Currency & cost year:** 2008 UK pounds **Cost components incorporated:** GP visits, medications, outpatient visits, inpatient care, professions allied to medicine consultations, complementary therapist and X-ray procedures	**QALYs (mean total):** Intervention 1: 8.17 Intervention 2: 8.28 Incremental (2−1): 0.11 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £21,335 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost effective (£20K threshold): 43% **Analysis of uncertainty:** One-way sensitivity analyses undertaken on cost of glucosamine sulphate, discount rate, proportion of patients requiring total knee replacement, healthcare costs, quality of life scores suggest that the results were reasonably robust to the estimates used.
Data sources				
Health outcomes: Used baseline and follow up WOMAC scores data reported in Pavelka 2002 to estimate quality of life. Annual quality of life decrement applied to account for progression in disease. Probability of total knee replacement was derived from Bruyere 2008 (pooled data from two placebo controlled RCTs of glucosamine sulphate). Probability of death was estimated from age-specific all-cause life tables. Quality of life for people prior to total knee replacement was estimated from baseline WOMAC scores was reported in Nunez 2007. **Quality-of-life weights:** Utilities obtained from mapping of				

clinical outcome WOMAC into HUI3 (Grootendorst 2007). **Cost sources:** Resource use estimated from a UK study, Lord 1999- RCT of primary care-based education for knee osteoarthritis with resource use data collected from case notes, supplemented by patient interviews. Unit costs updated to 2007/08 prices. 2007/08 NHS reference costs used to estimate the cost of total knee replacement. UK market prices of glucosamine hydrochloride was used as an estimate of glucosamine sulphate.
Comments
Source of funding: National Institute of Health Research Health Technology Assessment programme **Limitations:** Study does not include all comparators being assessed in the review. Resource use (1999) and unit costs (2008) may not reflect current NHS practice. Utilities were not derived directly from EQ-5D questionnaire in line with NICE reference case but were instead mapped from WOMAC to HUI3. Further RCTs have been published for reporting quality of life and so treatment effects may not reflect the full body of evidence.[82, 184, 293] **Other:** None.
Overall applicability:(b) Directly applicable **Overall quality:**(c) Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; HUI3= health utilities index 3; NHS= National health Service; NR= not reported; RCT= randomised controlled trial; QALYs= quality-adjusted life years; UK= United Kingdom; WOMAC= Western Ontario and McMaster Universities osteoarthritis index.

(a) Annual treatment effects applied throughout lifetime horizon.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Bruyere 2019[75]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Individual patient data simulation. **Approach to analysis:** Simulation of 20,000 utility values based on WOMAC scores reported in 10 clinical trials. Data meta-analysed where possible. Cost of intervention applied. **Perspective:** Unclear **Time horizon:** Various (2, 3, 6 and 36 months) **Treatment effect duration:** Same as study time horizon **Discounting:** Costs: NR; Outcomes: NR	**Population:** People with osteoarthritis **Cohort settings:** Start age: NR Male: NR **Intervention 1:** No treatment (placebo) **Intervention 2: G**lucosamine - prescription crystalline glucosamine sulphate (pCGS) **Intervention 3:** Glucosamine - other forms of glucosamine	**Total costs (median per patient):** 3 months Intervention 1: £0 Intervention 2: £124 Incremental (2−1): £124 (95% CI: NR; p=NR) 6 months Intervention 1: £0 Intervention 2: £247 Incremental (2−1): £247 (95% CI: NR; p=NR) 36 months Intervention 1: £0 Intervention 2: £1,484 Incremental (2−1): £1,484 (95% CI: NR; p=NR) 2 months Intervention 1: £0 Intervention 3: £29 Incremental (3−1): £29 (95% CI: NR; p=NR) 3 months Intervention 1: £0 Intervention 3: £44 Incremental (3−1): £44 (95% CI: NR; p=NR) 6 months	**QALYs (mean change):** 3 months Intervention 1: -0.009275 Intervention 2: 0.016875 Incremental (2−1): 0.02615 (95% CI: NR; p=NR) 6 months Intervention 1: -0.0146125 Intervention 2: 0.0435625 Incremental (2−1): 0.058175 (95% CI: NR; p=NR) 36 months Intervention 1: 0.12872929 Intervention 2: 0.27418931 Incremental (2−1): 0.14546002 (95% CI: NR; p=NR) 2 months Intervention 1: 0.001032 Intervention 3: 0.002344 Incremental (3−1): 0.001312 (95% CI: NR; p=NR) 3 months Intervention 1: 0.0020409 Intervention 3: 0.00303613 Incremental (3−1): 0.00099523 (95% CI: NR; p=NR) 6 months	**ICER (Int. 2 versus Int. 1):** 3 months £4,730 per QALY gained (da) 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): NR 6 months £4,252 per QALY gained (da) 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): NR 36 months £10,203 per QALY gained (da) 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): NR **ICER (Int. 3 versus Int. 1):** 2 months £22,233 per QALY gained (da) 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): NR 3 months £43,990 per QALY gained (da) 95% CI: NR Probability Intervention 3 cost effective (£20K/30K threshold): NR 6 months

		Intervention 1: £0 Intervention 3: £88 Incremental (3−1): £88 (95% CI: NR; p=NR) **Currency & cost year:** Euros 2017 (reported here as 2017 UK pounds[(a)]) **Cost components incorporated:** Cost of glucosamine only.	Intervention 1: 0.00752699 Intervention 2: 0.00423555 Incremental (3−1): - 0.00329144 (95% CI: NR; p=NR)	Intervention 1 dominates intervention 3 (lower costs and higher QALYs) Probability Intervention 3 cost effective (£20K/30K threshold): NR **Analysis of uncertainty:** Sensitivity analysis undertaken adjusting for the fact that different studies used different time points. In this case, longer study data was used at all time points. For example, for a 36 month study, 8.3% of the global effect at month 3 and 16.7% of the global effect at month 6 was used. In this case, pCGS no longer cost effective, and other forms of glucosamine are dominated by placebo at all time points.
Data sources				
Health outcomes: The model simulated individual utility values from 10 clinical trials cited in the meta-analysis of Eriksen 2014 that used WOMAC. [100, 103, 106, 186, 200, 236, 241, 339, 388, 409] It firstly used the SIMNORMAL procedure of SAS® and published summary statistics to simulate WOMAC scores, age and years since osteoarthritis diagnosis. Any simulated values outside permissible ranges were discarded. WOMAC scores were then converted into HUI3 utility values using the equation provided by Grootendorst 2007. This method was validated by comparing to a study where individual health utility values were published and for which access were available to individual WOMAC scores, age and years at baseline and after 3 months of treatment. QALYs were calculated using the area-under-the-curve method. If more than one study was available for a time point, studies were weighted according to the number of subjects included in the trial. Note: of the 10 clinical trials cited in Eriksen 2014 used to calculate WOMAC scores, eight were included in our clinical review, [100, 103, 106, 186, 200, 236, 241, 388] and two were excluded. [339, 409] Of the two excluded, one had no usable outcomes,[409] and the other used an incorrect glucosamine dosage.[339] **Quality-of-life weights:** n/a. **Cost sources:** Selling prices of different formulations in the different countries were obtained from IMS Health Data (December 2017). Prescription crystalline glucosamine was separated from other forms of glucosamine. An overall average price was taken. To reduce variability all prices that were lower than the average price by 50% or greater were excluded. A new average was then calculated which was defined as the 'higher' value cost range. Similarly, all prices higher than the average by 50% or greater were excluded and a new average calculated which was defined as the 'lower' value of the price range. The analysis for glucosamine therefore used three costs; median cost, higher cost and lower cost.			
Comments				

Source of funding: MEDA (marketing authorisation holder of crystalline glucosamine sulphate). **Limitations:** Study does not include all comparators being assessed in the review. Study only incorporates the cost of glucosamine and no other resource use and therefore costs may not be fully represented. Utilities were not derived directly from EQ-5D questionnaire in line with NICE reference case but were instead mapped from WOMAC to HUI3. Our clinical review also identified six studies reporting WOMAC pain scores that were not identified in the study.[82, 243, 293, 415, 429, 574] **Other:** None.

Overall applicability:[(b)] Partially applicable **Overall quality:**[(c)] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HUI3= health utility index 3; ICER= incremental cost-effectiveness ratio; Int.= intervention; NR= not reported; pCGS= prescription crystalline glucosamine sulphate; QALYs= quality-adjusted life years; WOMAC= Western Ontario and McMaster Universities osteoarthritis index.

(a) Converted using PPP

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Scholtissen 2010[454]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Within-trial analysis **Approach to analysis:** Analysis of individual level data for quality of life from single RCT. Drug costs used to estimate costs. **Perspective:** Spanish healthcare system **Time horizon:** 6 months **Treatment effect duration:** 6 months **Discounting:** Costs: n/a; Outcomes: n/a	**Population:** People with symptomatic osteoarthritis **Cohort settings:** Start age: 64 Male: 12% **Intervention 1:** No treatment (placebo) **Intervention 2:** Paracetamol, 3000mg per day **Intervention 3:** Glucosamine, 1500mg once daily	**Total costs (mean per patient):** Intervention 1: £2.68 Intervention 2: £46.91 Intervention 3: £37.56 Incremental (2−1): £44.23 Intervention (3−2): saves £9.41 (95% CI: NR; p=NR) **Currency & cost year:** 2009 Spanish Euros (converted into 2009 UK pounds)[(a)] **Cost components incorporated:** Drug costs only adjusted for compliance. Other healthcare costs were assumed to be comparable between treatment groups.	**QALYs (mean per patient):** Intervention 1: NR Intervention 2: NR Intervention 3: NR Incremental (3−1): 0.01 Incremental (3−2): 0.01 (95% CI: NR; p=NR)	Intervention 2 dominated by intervention 3. ICER (Intervention 3 versus Intervention 1): £3,488 per QALY gained (da) 95% CI: NR Probability Intervention 3 cost effective (€20K (£19K) threshold): 71% **Analysis of uncertainty:** None undertaken.
Data sources				
Health outcomes: Treatment effects on WOMAC scores from the GUIDE trial. **Quality-of-life weights:** WOMAC scores mapped to HUI to determine utility scores. **Cost sources:** Drug costs from Spanish market prices.				
Comments				
Source of funding: ESCEO-Amgen grant from the European Society for Clinical and Economical Aspect of Osteoarthritis and Osteoporosis and by Rottapharm, Italy. **Limitations:** Study does not include all comparators being assessed in the review. Spanish resource use and unit costs (2009) may not reflect current UK NHS practice. Utilities were not derived directly from the EQ-5D questionnaire in line with the NICE reference case but were instead mapped from WOMAC to HUI-3. Time horizon may not capture the change in benefit over time. Treatment effects determined from one trial and so may not reflect the full body of evidence. No analysis of uncertainty undertaken. **Other:** None.				
Overall applicability:[(b)] Partially applicable		**Overall quality:**[(c)] Potentially serious limitations		

Abbreviations: CCA= cost–consequences analysis; CEA= cost-effectiveness analysis; 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years

(a) Converted using PPP

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I – Excluded studies

Clinical studies

Table 26: Studies excluded from the clinical review

Study	Exclusion reason
Aagaard 1975[1]	Abstract only
Abbasifard 2020[2]	Inappropriate comparison
Abdel shaheed 2019[4]	Systematic review; references checked
Abdel shaheed 2021[3]	Not review population (any painful condition included)
Abruzzo 1979[5]	Abstract only
Acevedo 2001[6]	Incorrect interventions (included rofecoxib which is not licensed for use in the United Kingdom)
Adler 2002[7]	Inappropriate comparison (compared tramadol to a different formulation of tramadol)
Afilalo 2009[8]	Abstract only
Agrati 1992[9]	Not available in English language
Algozzine 1982[10]	Incorrect interventions (included trolamine salicylate which is not licensed for use in the United Kingdom)
Allegrini 2009[11]	Incorrect stratum (spinal osteoarthritis). Inappropriate comparison (included transdermal non-steroidal anti-inflammatory drugs, which are not included in the protocol and compared them to topical non-steroidal anti-inflammatory drugs)
Altman 1994[13]	Type of osteoarthritis not clearly defined and so not able to stratify (topical treatment)
Altman 2015[15]	Incorrect study design
Altman 2016[14]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Altman 2018[12]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Amadio 1985[17]	Incorrect stratum (spinal osteoarthritis)
Amadio jr 1983[16]	No usable outcomes (reported adverse events that could not be categorised into the protocol adverse events outcomes without making the number of participants who had any events in that category unclear)
Amako 1978[18]	Not available in English language
Amirpour 2016[19]	Incorrect interventions (included colchicine which is not an included intervention)
Andelman 1980[20]	Incorrect interventions (included zomepirac which is not licensed for use in the United Kingdom)
Anon 1992[153]	Not available in English language
Anon 2004[170]	Report only
Anon 2018[25]	Inappropriate comparison (compared glucosamine and physiotherapy to glucosamine alone, which is not a valid comparison in the protocol)
Anonymous 2002[21]	Article only
Anonymous 2008[22]	Abstract only
Aoki 1992[23]	Not available in English language

Study	Exclusion reason
Aran 2011[24]	Incorrect interventions (included colchicine which is not an included intervention)
Arcangeli 1996[26]	Incorrect stratum (spinal osteoarthritis). Inappropriate comparison (compared different formulations of non-steroidal anti-inflammatory drugs)
Armagan 2015[27]	Incorrect interventions (included home exercise programs compared to glucosamine)
Arti 2012[28]	Inappropriate comparison (compared glucosamine and alendronate to glucosamine alone)
Aylward 1985[29]	Inappropriate comparison (compared two different non-steroidal anti-inflammatory drugs)
Backhouse 1986[30]	Letter only
Bacon 2002[31]	Inappropriate comparison (compared two different formulations of paracetamol)
Bannuru 2014[34]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Bannuru 2015[33]	Systematic review is not relevant to review question or unclear PICO (included intra-articular pharmacological agents, which are considered in a different review question)
Bannuru 2016[32]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Baraf 2007[35]	Incorrect stratum (included spinal osteoarthritis). Wrong comparison (compared two different non-steroidal anti-inflammatory drugs).
Baraf 2011[36]	Post-hoc analysis (a secondary analysis included three trials, two of which are included in this review [Barthel 2010[38] and Barthel 2009[37]], while the third is unpublished evidence.)
Barthel 2010[38]	Post-hoc analysis (a secondary analysis of two trials reporting outcomes which would not be able to be extracted)
Becker 2003[40]	Health economic analysis only (no usable outcomes for clinical evidence)
Becker 2009[39]	Protocol only
Becvár 1996[41]	Abstract only
Bellamy 2006[42]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Bensen 2000[43]	People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, hemochromatosis, haemophilic arthropathy, diseases of childhood that may predispose to osteoarthritis and malignancy)
Berry 1981[45]	Incorrect interventions (included zomepirac which is not licensed for use in the United Kingdom)
Berry 1992[44]	Incorrect interventions (included lornoxicam which is not licensed for use in the United Kingdom)
Bianchi 2003[47]	No usable outcomes (no standard deviation reported and no way to calculate this from the information available)
Bianchi 2004[46]	Not available in English language
Bianchi 2007[48]	Incorrect interventions (included nimesulide which is not licensed for use in the United Kingdom)
Bias 2004[49]	Not guideline condition (included healthy participants). Not review population

Study	Exclusion reason
Bihlet 2020[50]	Inappropriate comparison (all compounds contain a topical non-steroidal anti-inflammatory drugs)
Bin 2007[51]	Inappropriate comparison (compared two different non-steroidal anti-inflammatory drugs)
Biondi 2010[52]	Abstract only
Bird 1995[53]	Incorrect interventions (included pentazocine which is not licensed for use in the United Kingdom)
Bisicchia 2017[54]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Blardi 1992[56]	Incorrect interventions (included nimesulide which is not licensed for use in the United Kingdom)
Blechman 1978[57]	No usable outcomes (no standard deviation reported and no way to calculate this from the information available)
Blechman 1987[58]	No usable outcomes (no standard deviation reported and no way to calculate this from the information available)
Bohlooli 2012[59]	Incorrect interventions (included topical virgin olive oil, which is not included in the protocol)
Boissier 1992[60]	Inappropriate comparison (compared dextropropoxyphene and paracetamol to codeine and paracetamol, dextropropoxyphene is not licensed for use in the United Kingdom)
Bolten 1989[61]	Not available in English language
Bolten 2015[62]	Not guideline condition (included healthy participants). Not review population
Boswell 2008[63]	Pooled analysis of two RCTs with different study designs
Bourgeois 1994[64]	Incorrect interventions (included nimesulide which is not licensed for use in the United Kingdom)
Brereton 2012[66]	Unclear population (for example, the proportion of participants with an osteoarthritis diagnosis not stated)
Bress 1981[67]	Abstract only
Bress 1981[68]	Incorrect interventions (included diflunisal which is not licensed for use in the United Kingdom)
Broll 1986[69]	Inappropriate comparison (compared two different formulations of an non-steroidal anti-inflammatory drugs). Incorrect interventions (included zidometacin which is not licensed for use in the United Kingdom)
Browning 1994[70]	Inappropriate comparison (compared topical and oral non-steroidal anti-inflammatory drugs to oral non-steroidal anti-inflammatory drugs only)
Bruhlmann 2003[72]	Incorrect interventions (included transdermal non-steroidal anti-inflammatory drugs which were not included in the protocol)
Bruhlmann 2006[71]	Incorrect interventions (included transdermal non-steroidal anti-inflammatory drugs which were not included in the protocol)
Bruyere 2003[74]	No relevant outcomes (no standard deviation reported and no way to calculate this from the information available)
Bruyere 2019[75]	Incorrect study design (health economic study only with no usable clinical outcomes)
Burch 2004[77]	Incorrect study design (non-randomised trial)
Burke 1975[79]	Abstract only
Burke 1976[78]	Incorrect interventions (included floctafenine which is not licensed for use in the United Kingdom)

Study	Exclusion reason
Buxton 1978[80]	Unclear population (for example, the proportion of participants with an osteoarthritis diagnosis not stated) (included a mixture of different types of osteoarthritis, included spinal osteoarthritis). Incorrect interventions (included floctafenine which is not licensed for use in the United Kingdom)
Buynak 2015[81]	Not review population (people with low back pain)
Calabro 1977[83]	No usable outcomes (reported adverse events that could not be categorised into the protocol adverse events outcomes without making the number of participants who had any events in that category unclear)
Caldwell 1999[84]	Unclear if blinding sufficient (all participants took part in open-label run in of intervention while taking opioids and then stopped the medicine for some participants. Given that an adverse event with opioids are withdrawal symptoms, this did not appear to maintain blinding and did not appear comparable with other studies)
Cameron 2013[85]	Systematic review is not relevant to review question or unclear PICO (included topical herbal remedies, which were not included in our protocol)
Campbell 2017[86]	Not review population (included people with other pain conditions)
Cannon 2000[87]	Incorrect interventions (included rofecoxib which is not licensed for use in the United Kingdom)
Cazzagon 1976[89]	Incorrect stratum (included people with spinal osteoarthritis). Incorrect interventions (included diftalone which is not licensed for use in the United Kingdom)
Cen 2018[90]	Inappropriate comparison (compared glucosamine and intraarticular hyaluronic acid to intraarticular hyaluronic acid alone). Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Cepeda 2006[91]	Systematic review is not relevant to review question or unclear PICO (Cochrane review, included a different definition of outcomes [for example: serious adverse events])
Chandanwale 2014[92]	People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, hemochromatosis, haemophilic arthropathy, diseases of childhood that may predispose to osteoarthritis and malignancy). Inappropriate comparison (compared tramadol and diclofenac to tramadol and paracetamol, which is not a comparison included in the protocol)
Chen 2019[94]	Systematic review; references checked (insufficient quality assessment)
Chen 2019[93]	Systematic review; references checked (insufficient quality assessment)
Cheung 2010[96]	People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, hemochromatosis, haemophilic arthropathy, diseases of childhood that may predispose to osteoarthritis and malignancy)
Chiozzini 1988[97]	Abstract only
Choi 2007[98]	Inappropriate comparison (compares tramadol and paracetamol to a different method of delivering the combination)

Study	Exclusion reason
Choi 2017[99]	Systematic review is not relevant to review question or unclear PICO. Incorrect interventions (included moxibustion which is not included in the protocol)
Chopra 2011[101]	Dose of glucosamine is below the licensed dose (1178 mg/day)
Choquette 2008[102]	Incorrect study design
Cibere 2005[104]	No usable outcomes (no standard deviation reported and no way to calculate this from the information available)
Cirillo 1978[105]	Incorrect interventions (included diflunisal which is not licensed for use in the United Kingdom)
Coats 2004[107]	Not guideline condition. Not review population (other pain conditions). Inappropriate comparison (included valdecoxib which is not licensed for use in the United Kingdom)
Conaghan 2011[108]	Incorrect interventions (included transdermal opioids and paracetamol compared to weak opioids and paracetamol, which is not included in the protocol)
Concoff 2017[109]	Systematic review is not relevant to review question or unclear PICO (included intra-articular pharmacological agents, which are considered in a different review question)
Corsinovi 2009[110]	Inappropriate comparison (compared strong opioids and paracetamol to weak opioids and paracetamol)
Crolle 1980[111]	Incorrect interventions (included intramuscular and intra-articular glucosamine which is not included in the protocol)
Da 2012[114]	Systematic review is not relevant to review question or unclear PICO (included doxycycline which is not included in the protocol)
Da 2014[113]	Systematic review is not relevant to review question or unclear PICO (did not include tramadol as an opioid, included outcomes that were not included in this review)
Da costa 2017[116]	Systematic review is not relevant to review question or unclear PICO (included outcomes that were not included in this review, compared different doses of medicines which were examined by class effect in this review)
da Costa 2021[115]	Systematic review; references checked (systematic review was a network meta analysis with significantly different methodology, including the inclusion of medications not licensed for use in the UK, a different outcome prioritisation system, using different definitions for outcomes and using a different minimally important clinical difference definition)
Dahlberg 2009[117]	Inappropriate comparison (compared two non-steroidal anti-inflammatory drugs)
Dai 2019[118]	Inappropriate comparison (compared two hyaluronic acid products). Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
D'ambrosio 1981[112]	Incorrect interventions (included intra-venous/intra-muscular piperazine/chlorbutanol which are not included in the protocol)
Datto 2013[119]	Systematic review is not relevant to review question or unclear PICO (included only specific non-steroidal anti-inflammatory drugs and gastroprotection combinations)
Day 2000[120]	Incorrect interventions (included rofecoxib which is not licensed for use in the United Kingdom)
De 2012[126]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)

Study	Exclusion reason
De beer jde 2005[121]	Post-operative analgesia. Inappropriate comparison (compared oxycodone to standard therapy, which was not included in the protocol)
De miquel 1987[123]	Incorrect interventions (included piketoprofen and hydroxyphenylbutazone which are not licensed for use in the United Kingdom)
De moor 1990[124]	Abstract only
De pouvourville 1991[125]	Not available in English language
De vos 2017[127]	No appropriate outcomes (no standard deviation reported and no way to calculate this from the information available)
Debelle 1981[128]	No appropriate outcomes (no standard deviation reported and no way to calculate this from the information available)
Decousus 1990[129]	Abstract only
Delfino 1996[130]	Not available in English language
Deng 2016[131]	Systematic review is not relevant to review question or unclear PICO (combined sites of osteoarthritis)
Dequeker 1998[132]	Inappropriate comparison (compared two non-steroidal anti-inflammatory drugs)
Derry 2016[133]	Systematic review is not relevant to review question or unclear PICO (Cochrane review, included people with chronic musculoskeletal pain, including conditions other than osteoarthritis)
Detora 2001[134]	Incorrect interventions (included rofecoxib, which is not licensed for use in the United Kingdom)
Di rienzo businco 2004[135]	Unclear population (for example, the proportion of participants with an osteoarthritis diagnosis not stated) (included people with temporomandibular joint dysfunction, not specified as osteoarthritis)
Dieu-donne 2016[136]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Ding 1996[137]	Not available in English language
Ding 2005[138]	Not available in English language
Doak 1992[139]	No usable outcomes (no standard deviation reported and no way to calculate this from the information available)
Doherty 1992[140]	No usable outcomes (no standard deviation reported and no way to calculate this from the information available)
Doi 2010[141]	Inappropriate comparison (included transdermal non-steroidal anti-inflammatory drugs compared to oral non-steroidal anti-inflammatory drugs)
Dolanc 1982[142]	Not available in English language
Douglas 2014[143]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Dreiser 1993[145]	Not available in English language
Dreiser 1993[144]	Not available in English language
Dreiser 1993[146]	Incorrect interventions (included nimesulide which is not licensed for use in the United Kingdom)
Dreiser 1993[147]	Incorrect interventions (included transdermal non-steroidal anti-inflammatory drugs)
Drovanti 1980[148]	Incorrect stratum (spinal osteoarthritis)
Durg 2019[149]	Incorrect interventions (included oxaceprol which is not licensed for use in the United Kingdom)

Study	Exclusion reason
Durmus 2012[151]	Inappropriate comparison (compared exercise with glucosamine to exercise alone)
Durmus 2013[150]	Inappropriate comparison (compared exercise with glucosamine to exercise alone)
Eberhardt 1995[152]	Not available in English language
Eggertsen 2012[154]	Not review population (people without osteoarthritis)
Ehrich 1999[156]	Incorrect interventions (included rofecoxib which is not licensed for use in the United Kingdom)
Ehrich 2001[155]	Incorrect interventions (included rofecoxib which is not licensed for use in the United Kingdom)
El mehairy 1974[157]	Incorrect interventions (included niflumic acid and phenylbutazone which are not licensed for use in the United Kingdom)
Emery 2008[158]	Inappropriate comparison (compared two non-steroidal anti-inflammatory drugs)
Emkey 2004[159]	Inappropriate comparison (compared tramadol and paracetamol to placebo)
Enomoto 2018[160]	Post-hoc analysis. No useable outcomes (no standard deviation reported and no way to calculate this from the information available)
Ergun 2007[161]	Incorrect interventions (included nimesulide which is not licensed for use in the United Kingdom)
Eriksen 2014[162]	Systematic review is not relevant to review question or unclear PICO (includes analysis that we were not conducting for this review, does not limit the dose of glucosamine)
Erturk 1998[163]	Not available in English language
Essex 2012[164]	Inappropriate comparison (compares two non-steroidal anti-inflammatory drugs)
Essex 2013[166]	Abstract only
Essex 2014[165]	Inappropriate comparison (compares two different delivery methods of an non-steroidal anti-inflammatory drugs)
Etropolski 2009[168]	Abstract only
Etropolski 2011[462]	Unclear population (for example, the proportion of participants with an osteoarthritis diagnosis not stated) (unclear disease, does not exclude rheumatoid arthritis)
Euppayo 2017[169]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Farkouh 2004[172]	Incorrect interventions (included lumiracoxib which is not licensed for use in the United Kingdom)
Farkouh 2007[171]	Incorrect interventions (included lumiracoxib which is not licensed for use in the United Kingdom)
Faundez 2016[173]	Not in English language
Felden 2014[174]	Not guideline condition. Not review population (included healthy participants). Inappropriate comparison (compared two non-steroidal anti-inflammatory drugs)
Ferreira 2018[175]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Fidelholtz 2011[176]	Abstract only
Fidelix 2014[177]	Systematic review is not relevant to review question or unclear PICO (included diacerin which is not included in the protocol)
Filatova 2017[179]	Not available in English language

Study	Exclusion reason
Filatova 2021[178]	Conference abstract only
Fish 2008[180]	Inappropriate comparison (compared capsaicin to mobilisation and a combination of the two)
Fleischmann 2008[181]	Inappropriate comparison (included lumiracoxib which is not licensed for use in the United Kingdom)
Forster 2001[182]	Not available in English language
Fowler 2015[183]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Frestedt 2009[185]	Incorrect interventions (included aquamin which is not in the protocol)
Fujii 2014[187]	Incorrect interventions (included loxoprofen which is not licensed for use in the United Kingdom)
Gajria 2008[188]	Inappropriate comparison (compared different formulations of an non-steroidal anti-inflammatory drugs)
Galeazzi 1993[189]	Unclear population (for example, the proportion of participants with an osteoarthritis diagnosis not stated). People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, hemochromatosis, haemophilic arthropathy, diseases of childhood that may predispose to osteoarthritis and malignancy). Incorrect interventions (included transdermal non-steroidal anti-inflammatory drugs)
Galer 2004[191]	Incorrect study design (non-randomised study)
Galer 2011[190]	Includes healthy people. Inappropriate comparison (compares two different formulations of an non-steroidal anti-inflammatory drugs)
Gammaitoni 2004[192]	Wrong study type
Garg 2014[193]	Systematic review is not relevant to review question or unclear PICO
Garner 2005[194]	Systematic review is not relevant to review question or unclear PICO. Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Geis 1993[195]	Letter only
Germain 1985[196]	Abstract only
Giacovazzo 1992[197]	Inappropriate comparison (compares two non-steroidal anti-inflammatory drugs). Unclear population (for example, the proportion of participants with an osteoarthritis diagnosis not stated)
Gillgrass 1984[198]	No usable outcomes (no standard deviation reported and no way to calculate this from the information available)
Gimenez 2014[199]	No relevant outcomes (fMRI study, included radiological outcomes)
Glave 1994[201]	Not available in English language
Golding 1978[202]	No usable outcomes (reported adverse events that could not be categorised into the protocol adverse events outcomes without making the number of participants who had any events in that category unclear)
Goldstein 2001[204]	Wrong population (includes people with rheumatoid arthritis equalling 40% of the study population)
Goldstein 2005[203]	Inappropriate comparison (compared two non-steroidal anti-inflammatory drugs, one was not licensed for use in the United Kingdom)

Study	Exclusion reason
Goldstein 2007[205]	Inappropriate comparison (compares two non-steroidal anti-inflammatory drugs to two non-steroidal anti-inflammatory drugs and gastroprotection)
Gor 2016[206]	Inappropriate comparison (compared topical and oral non-steroidal anti-inflammatory drugs to oral non-steroidal anti-inflammatory drugs only)
Gottesdiener 2003[207]	Erratum only
Grayson 1978[208]	Inappropriate comparison (compared two non-steroidal anti-inflammatory drugs, one of which was not licensed for use in the United Kingdom)
Gregori 2018[209]	Systematic review with different definition of time periods for outcomes. References checked.
Grifka 2004[210]	Incorrect interventions (included lumiracoxib which is not licensed for use in the United Kingdom)
Grond 2009[212]	Not available in English language
Grond 2009[211]	Abstract only
Gross 1983[213]	Not available in English language
Guedes 2018[214]	Not available in English language
Guidolin 2018[215]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Guyot 2017[216]	Systematic review; references checked (compared different types of non-steroidal anti-inflammatory drugs)
Haghighat 2013[217]	Not review population (temporomandibular joint disorders)
Hale 2007[218]	Inappropriate comparison (compared two formulations of an non-steroidal anti-inflammatory drugs)
Hale 2009[219]	Unclear population (for example, the proportion of participants with an osteoarthritis diagnosis not stated). Inappropriate comparison (compares two strong opioids)
Han 2000[220]	Not available in English language
Han 2017[221]	Systematic review is not relevant to review question or unclear PICO. Incorrect interventions (included strontium ranolate which is not licensed for use in the United Kingdom)
Harrison-munoz 2017[222]	Not available in English language
Hartrick 2009[223]	No usable outcomes (reported adverse events that could not be categorised into the protocol adverse events outcomes without making the number of participants who had any events in that category unclear)
Hasegawa 2013[224]	People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, hemochromatosis, haemophilic arthropathy, diseases of childhood that may predispose to osteoarthritis and malignancy)
Hawel 2002[225]	Abstract only
Hawel 2003[226]	Inappropriate comparison (compares two non-steroidal anti-inflammatory drugs)
Hawkey 2000[227]	No usable outcomes (no standard deviation reported and no way to calculate this from the information available)
Hawkey 2004[228]	Unclear population (for example, the proportion of participants with an osteoarthritis diagnosis not stated) (includes people with spinal osteoarthritis)
Hawkey 2008[229]	Post-hoc analysis (of Schnitzer 2004[449])

Study	Exclusion reason
Hayllar 1996[230]	Incorrect interventions (included flosulide which is not licensed for use in the United Kingdom)
He 2017[231]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Henriksen 2016[233]	Systematic review; references checked (included exercise as an intervention)
Henriksen 2019[232]	Insufficient follow up (<1 week)
Hepguler 1994[234]	Not available in English language
Herrera 2003[235]	Incorrect interventions (Rofecoxib and Nimesulide are not licensed for use in the United Kingdom)
Hochberg 2016[237]	Inappropriate comparison (compared glucosamine and chondroitin to an non-steroidal anti-inflammatory drugs)
Holt 2015[238]	Incorrect study design (secondary analysis of pooled analyses)
Honvo 2019[239]	Systematic review; references checked
Hosie 1996[240]	Inappropriate comparison (compares two non-steroidal anti-inflammatory drugs)
Huang 2011[242]	Not available in English language
Hunt 2003[244]	Not review population (people with rheumatoid arthritis)
Huskisson 1979[247]	No usable outcomes (no standard deviation reported and no way to calculate this from the information available)
Huskisson 1992[245]	Unclear population (for example, the proportion of participants with an osteoarthritis diagnosis not stated). People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, hemochromatosis, haemophilic arthropathy, diseases of childhood that may predispose to osteoarthritis and malignancy). Inappropriate comparison (compares two non-steroidal anti-inflammatory drugs)
Huskisson 1995[246]	No usable outcomes (outcomes relate to imaging progression)
Itoh 2018[248]	Post-hoc analysis (secondary analysis of another trial)
Iturriaga 2017[249]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Iyengar 2013[250]	No usable outcomes (no standard deviation reported and no way to calculate this from the information available)
Jamali, 2020[251]	Wrong intervention (curcumin ointment)
James 1993[253]	Inappropriate comparison (compared and non-steroidal anti-inflammatory drugs and weak opioid compared to an non-steroidal anti-inflammatory drugs alone)
James 2010[252]	Incorrect interventions (compared two routes of the same strong opioid, included sublingual buprenorphine)
Jensen 1994[254]	Incorrect interventions (included dextropropoxyphene which is not licensed for use in the United Kingdom)
Jones 2019[255]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Jung 2018[256]	Systematic review is not relevant to review question or unclear PICO (included non-licensed form of non-steroidal anti-inflammatory drugs)
Jüni 2015[257]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)

Study	Exclusion reason
K. a. g. e. y. a. m. a. takamasa 1983[491]	Not available in English language
Kafil 2003[258]	Incorrect interventions (included nimesulide which is not licensed for use in the United Kingdom)
Kageyama 1984[261]	Not available in English language
Kageyama 1985[263]	Not available in English language
Kageyama 1985[262]	Not available in English language
Kageyama 1986[259]	Not available in English language
Kageyama 1986[260]	Not available in English language
Kamath 2003[264]	No usable outcomes (included cost-effectiveness data only)
Karlsson 2009[265]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Katz 2010[267]	Inappropriate comparison (compared strong opioid and opioid antagonist to strong opioid only)
Katz 2010[266]	Inappropriate comparison (compared strong opioid and opioid antagonist to strong opioid only)
Kavanagh 2009[268]	Abstract only
Kavanagh 2012[269]	Inappropriate comparison (compared two strong opioids)
Kellner 2013[270]	No useable outcomes (no standard deviation reported and no way to calculate this from the information available)
Kelly 2009[272]	Not available in English language
Kelly 2009[273]	Abstract only
Kelly 2010[274]	Abstract only
Kelly 2010[271]	Abstract only
Khong 1991[275]	Inappropriate comparison (compared two different formulations of an non-steroidal anti-inflammatory drugs)
Kilminster 1999[276]	Inappropriate comparison (compared two different formulations of an non-steroidal anti-inflammatory drugs)
Kim 2012[277]	Not available in English language
Kivitz 2006[279]	No usable outcomes (no standard deviation reported and no way to calculate this from the information available)
Kivitz 2008[278]	Post-hoc analysis (post hoc analysis completed due to early termination of the trial)
Kjaersgaard-andersen 1990[280]	No usable outcomes (outcomes reported in a manner that cannot be meta-analysed)
Knapik 2018[281]	Systematic review; references checked (inadequate quality assessment)
Kongtharvonskul 2015[282]	Systematic review is not relevant to review question or unclear PICO (included diacerein which is not included in the protocol)
Kongtharvonskul 2016[283]	Inappropriate comparison (compares glucosamine and diacerein to glucosamine and placebo)
Krebs 2018[284]	Not review population (low back pain)
Kress 2017[285]	Not review population (mixture of pain causing conditions). Inappropriate comparison (compares weak opioid and paracetamol to paracetamol alone)
Kriegel 2001[286]	Incorrect interventions (included nimesulide which is not licensed for use in the United Kingdom)
Kroon 2016[287]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)

Study	Exclusion reason
Kroon 2018[288]	Systematic review is not relevant to review question or unclear PICO (mixture of interventions, inadequate quality assessment)
Kruger 2007[289]	Incorrect interventions (included oxaceprol which is not licensed for use in the United Kingdom)
Kulkarni 2012[290]	Incorrect interventions (compares two different formulations for glucosamine)
Kuntz 1976[291]	Incorrect interventions (included benorylate which is not licensed for use in the United Kingdom)
Kuperwasser 2009[292]	Abstract only
Kwong 2013[294]	No usable outcomes (secondary analysis of Hartrick 2009[223])
Laine 2007[295]	Not review population (people with rheumatoid arthritis)
Lange 2010[296]	Abstract only
Laslett 2014[297]	Systematic review; references checked (inadequate quality assessment)
Latimer 2009[298]	Economic model of previous NICE guideline update
Le loet 2005[299]	Incorrect study design (non-randomised)
Lee 1985[300]	Incorrect interventions (included diflunisal which is not licensed for use in the United Kingdom)
Lee 1986[301]	Incorrect interventions (included diflunisal which is not licensed for use in the United Kingdom)
Leeb 2004[302]	Not available in English language
Lehn 1992[303]	Inappropriate comparison (compares two different formulations of non-steroidal anti-inflammatory drugs)
Leighton 2018[304]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Leite 2018[306]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Leopoldino 2019[307]	Systematic review is not relevant to review question or unclear PICO (Cochrane review, included different definitions of outcomes and only specific sites of osteoarthritis)
Lepisto 1978[308]	Incorrect study design (non-randomised)
Lequesne 1997[309]	Incorrect interventions (included floctafenine which is not licensed for use in the United Kingdom)
Leung 2015[311]	Protocol only
Leung 2018[310]	Incorrect interventions (included colchicine which is not included in the protocol)
Levy 2009[312]	Incorrect interventions (included flavocoxid which is not licensed for use in the United Kingdom)
Li 2011[313]	Not available in English language
Lindén 1994[314]	Abstract only
Lisse 2001[315]	Subgroup analysis where it is unclear what the original trial was
Lisse 2003[316]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Lloyd 1992[317]	Inappropriate comparison (compares weak opioid and paracetamol to weak opioid only)
Louthrenoo 2007[318]	Incorrect interventions (included diacerein which is not licensed for use in the United Kingdom)
Lubis 2017[319]	Incorrect study design (pooled analysis with insufficient information about methods to permit extraction)

Study	Exclusion reason
Lussier 1980[320]	Incorrect interventions (included floctafenine which is not licensed for use in the United Kingdom). Inappropriate comparison (compared two non-steroidal anti-inflammatory drugs).
Lussier 1983[321]	Not guideline condition (health participants). Not review population
Lyttle 2016[322]	Protocol only
Macdonald 2007[324]	Abstract only
Macdonald 2007[327]	Incorrect interventions (included lumiracoxib which is not licensed for use in the United Kingdom)
Macdonald 2008[325]	Incorrect interventions (included lumiracoxib which is not licensed for use in the United Kingdom)
Macdonald 2010[326]	Incorrect interventions (included lumiracoxib which is not licensed for use in the United Kingdom)
Macdonald 2017[323]	Inappropriate comparison (compared an non-steroidal anti-inflammatory drugs to standard care)
Machado 2015[328]	Systematic review is not relevant to review question or unclear PICO. Incorrect stratum (spinal osteoarthritis)
Maheu 2019[330]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Malik 2017[331]	Inappropriate comparison (compared two non-steroidal anti-inflammatory drugs)
Marcolongo 1977[332]	No usable outcomes
Marini 2012[333]	Incorrect interventions (included palmitoylethanolamide which is not included in the protocol)
Markenson 2005[334]	Incorrect stratum (included people with rheumatoid arthritis)
Marshall 2006[335]	Incorrect interventions (combination of oxycodone and paracetamol compared to standard care)
Matsunaga 1977[337]	Not available in English language
Matsunaga 1983[336]	Not available in English language
Matts 1983[338]	Unclear population (for example, the proportion of participants with an osteoarthritis diagnosis not stated) (people with rheumatoid arthritis). Inappropriate comparison (compared paracetamol and antiemetic to paracetamol alone)
Mcalindon 2004[339]	Dose of glucosamine is below the licensed dose (1178 mg/day)
Mccabe 2016[340]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Mccarthy 1992[341]	People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, hemochromatosis, haemophilic arthropathy, diseases of childhood that may predispose to osteoarthritis and malignancy) (included people with rheumatoid arthritis)
Mccleane 2000[342]	Unable to stratify by population due to an insufficient number of people having the same type of osteoarthritis
Mckenna 1998[344]	People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, hemochromatosis, haemophilic arthropathy, diseases of childhood that may predispose to osteoarthritis and malignancy) (included people with rheumatoid arthritis)
Melo 2018[345]	Systematic review; references checked (inadequate quality assessment)

Study	Exclusion reason
Micca 2013[346]	Post-hoc analysis (of two other studies)
Mochizuki 2016[347]	Not guideline condition. Not review population (perioperative). Inappropriate comparison (compared strong opioid and paracetamol to non-steroidal anti-inflammatory drugs alone)
Moldez 2018[348]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Mongin 2004[349]	Inappropriate comparison (compares two different strong opioid regimens)
Monticone 2016[350]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Moorthy 2016[351]	Inappropriate comparison (compares two strong opioids)
Moskowitz 2006[352]	Incorrect interventions (included valdecoxib and rofecoxib which are not licensed for use in the United Kingdom)
Mu 2016[353]	Incorrect interventions (included loxoprofen which is not licensed for use in the United Kingdom)
Mukhopadhyay 2018[354]	Incorrect interventions (included oxaceprol which is not licensed for use in the United Kingdom)
Mullican 2001[355]	Inappropriate comparison (compared strong opioid and paracetamol to weak opioid and paracetamol)
Murphy 1978[356]	Not review population (included people with a range of non-osteoarthritis pathologies. Inappropriate comparison (compared non-steroidal anti-inflammatory drugs and paracetamol to weak opioid)
Myers 2014[357]	Systematic review; references checked (inadequate quality assessment)
Myllykangas-luosujarvi 2002[358]	Incorrect interventions (included rofecoxib which is not licensed for use in the United Kingdom)
Myrer 2004[359]	Incorrect interventions (included herbal topical therapies which are not in the inclusion criteria)
Nagaya 1984[360]	Not available in English language
Nakata 2018[361]	Systematic review; references checked (inadequate quality assessment)
Nct 2009[362]	Trial registry record only
Nct 2013[363]	Trial registry record only
Ng 2010[364]	Wrong comparison (exercise with glucosamine compared to a different dose of exercise with glucosamine)
Nissen 2016[365]	Inappropriate comparison (compares three non-steroidal anti-inflammatory drugs)
Noble 2010[366]	Systematic review is not relevant to review question or unclear PICO (Cochrane review, includes any person with chronic noncancer pain, not just osteoarthritis)
Ogata 2018[368]	Systematic review; references checked (inadequate quality assessment)
O'hanlon 2016[367]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Ohtori 2013[369]	Incorrect interventions (compares non-steroidal anti-inflammatory drugs and antiepileptic drugs to non-steroidal anti-inflammatory drugs only)
Olejarova 2008[370]	Not available in English language

Study	Exclusion reason
Omololu 2005[371]	Inappropriate comparison (compares two non-steroidal anti-inflammatory drugs)
Osani 2019[372]	Systematic review; references checked (inadequate quality assessment)
Osani 2019[374]	Systematic review; references checked (inadequate quality assessment)
Osani, 2021[373]	Systematic review; references checked
Osteras 2017[375]	Incorrect interventions (included exercise)
Ottillinger 2001[376]	Incorrect interventions (included not licensed medicines)
Pai 2014[377]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Paik 2019[378]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Papalia 2017[380]	Loan not available
Papalia 2017[379]	Loan not available
Pareek 2009[382]	Inappropriate comparison (compared non-steroidal anti-inflammatory drugs and paracetamol to non-steroidal anti-inflammatory drugs alone)
Pareek 2010[381]	Inappropriate comparison (compared non-steroidal anti-inflammatory drugs and paracetamol to non-steroidal anti-inflammatory drugs alone)
Park 2008[385]	Not available in English language
Park 2012[383]	Inappropriate comparison (compared weak opioid and paracetamol to non-steroidal anti-inflammatory drugs)
Park 2020[384]	Incorrect stratum (population is spinal osteoarthritis)
Patel 2017[386]	Systematic review; references checked (inadequate quality assessment)
Pavelka jr 1995[387]	Not available in English language
Pavlicević 2011[389]	Not available in English language
Peeva 2009[391]	Abstract only
Peeva 2010[392]	Inappropriate comparison (included strong opioid and paracetamol to non-steroidal anti-inflammatory drugs)
Persson 2016[393]	Protocol
Persson 2018[394]	Incorrect interventions (included disease modifying agents of rheumatic disease)
Persson 2018[396]	Individual patient data meta-analysis. Includes studies where there were comparators not included in this review (homeopathic remedies, chamomile oil, arnica, dwarf elder gel), includes forms of intervention not included in this review (for example: non-steroidal anti-inflammatory drugs patches) and includes an outcome where the types of scales used to populate it were different from those agreed for in this review (prioritising VAS scores for a pain outcome, rather than WOMAC/KOOS subscales).
Persson 2020[395]	Not review population (mixed osteoarthritis for topical analgesia)
Petersen 2011[397]	Incorrect interventions (medicines with exercise)
Petrick 1983[398]	Incorrect interventions (included meclofenamate which is not licensed for use in the United Kingdom)
Pope 2004[399]	Inappropriate comparison (compares diclofenac and misoprostal to standard care)
Prabhu 2008[400]	Insufficient information on methodology of the study

Study	Exclusion reason
Puljak 2017[401]	Systematic review is not relevant to review question or unclear PICO (Cochrane review, includes only one type of non-steroidal anti-inflammatory drugs and compares it to other types of non-steroidal anti-inflammatory drugs, uses different outcomes)
Qiu 2005[402]	Not available in English language
Quiding 1992[403]	Insufficient follow up (<1 week)
Ran 2018[404]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Rasmussen 2018[405]	Commentary only
Rau 1989[406]	Not available in English language
Rau 1989[407]	Not available in English language
Rauschkolb 2009[408]	Abstract only
Reginster 2001[409]	No usable outcomes (reported adverse events that could not be categorised into the protocol adverse events outcomes without making the number of participants who had any events in that category unclear)
Reginster 2007[410]	Incorrect study design (pooled analysis of two RCTs but has an open phase extension period where people taking placebo were randomised again into the non-steroidal anti-inflammatory drugs groups)
Reicin 2002[411]	Incorrect interventions (included rofecoxib which is not licensed for use in the United Kingdom)
Renda 2006[412]	No relevant outcomes (no standard deviation reported and no way to calculate this from the information available)
Richette 2015[413]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Riera 2017[414]	Protocol only
Ripa 2012[416]	Incorrect interventions (includes a strong opioid and paracetamol compared to a transdermal opioid)
Risser 2013[417]	Post-hoc analysis (secondary analysis of other trials)
Rodriguez-merchan 2016[418]	Incorrect study design (review of systematic reviews)
Rose 1991[419]	Not available in English language
Rosenthal 2004[420]	Inappropriate comparison (included tramadol and paracetamol compared to paracetamol and placebo)
Ross 2008[421]	Report only
Roth 1995[422]	No relevant outcomes (does not include patient validated measures for pain agreed for use in this guideline)
Roth 1998[423]	Inappropriate comparison (compares strong opioids and non-steroidal anti-inflammatory drugs to non-steroidal anti-inflammatory drugs and placebo)
Roth 2000[424]	Incorrect stratum (includes people with osteoarthritis of the spine or back)
Roth 2012[425]	Post-hoc subgroup analysis of original trial
Rothacker 1994[426]	No relevant outcomes (reported adverse events that could not be categorised into the protocol adverse events outcomes without making the number of participants who had any events in that category unclear)
Rothacker 1998[427]	No useable outcomes (no standard deviation reported and no way to calculate this from the information available)
Rovetta 2001[428]	Not available in English language

Study	Exclusion reason
Runhaar 2016[430]	Not review population (people without osteoarthritis)
Runhaar 2017[431]	Systematic review is not relevant to review question or unclear PICO (subgroup analysis of a set of trials)
Runkel 1999[432]	Commentary only
Ruschitzka 2017[433]	Inappropriate comparison (compares multiple non-steroidal anti-inflammatory drugs)
Saag 2000[434]	Incorrect interventions (included rofecoxib which is not licensed for use in the United Kingdom)
Saggioro 1991[435]	Not review population (included people with rheumatoid arthritis)
Salmon 2018[436]	Incorrect interventions (included intraarticular hyaluronic acid and disease modifying osteoarthritis drugs)
Saltzman 2017[437]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Salzman 1983[438]	Incorrect interventions (included dextropropoxyphene and suprofen which are not licensed for use in the United Kingdom)
Sanders 2015[439]	No relevant outcomes (no standard deviation reported and no way to calculate this from the information available)
Santos 2015[440]	Systematic review is not relevant to review question or unclear PICO (Cochrane Review, population included people without osteoarthritis)
Sardana 2017[441]	Systematic review; references checked (quality assessment inadequate)
Sarzi-puttini 2014[442]	Systematic review is not relevant to review question or unclear PICO (wrong comparison, comparing different types of non-steroidal anti-inflammatory drugs)
Scheiman 2006[444]	People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, hemochromatosis, haemophilic arthropathy, diseases of childhood that may predispose to osteoarthritis and malignancy)
Schiff 2004[445]	Post-hoc analysis (pooled analysis of 2 RCTs)
Schimke 1990[446]	Abstract only
Schneider 1990[447]	Inappropriate comparison (compares different types of non-steroidal anti-inflammatory drugs)
Schnitzer 1995[448]	No usable outcomes (reported adverse events that could not be categorised into the protocol adverse events outcomes without making the number of participants who had any events in that category unclear)
Schnitzer 1995[452]	Inappropriate comparison (compares different types of non-steroidal anti-inflammatory drugs)
Schnitzer 1999[450]	Inappropriate comparison (compares strong opioids and non-steroidal anti-inflammatory drugs to strong opioids and placebo)
Schnitzer 2004[449]	Incorrect interventions (compared different types of non-steroidal anti-inflammatory drugs)
Schnitzer 2009[453]	Incorrect interventions (included rofecoxib which is not licensed for use in the United Kingdom)
Schnitzer 2012[451]	Incorrect interventions (included zucapsaicin which is not licensed for use in the United Kingdom)
Seideman 1993[456]	Inappropriate comparison (compares non-steroidal anti-inflammatory drugs and paracetamol to non-steroidal anti-inflammatory drugs alone)

Study	Exclusion reason
Selvan 2012[457]	Inappropriate comparison (compares glucosamine and non-steroidal anti-inflammatory drugs to glucosamine alone)
Shackel 1997[458]	Incorrect interventions (included copper salicylate gel which is not licensed for use in the United Kingdom)
Shah 2001[459]	Inappropriate comparison (compared non-licensed medicines with non-steroidal anti-inflammatory drugs)
Shahine 2014[460]	Inappropriate comparison (compares glucosamine and ibuprofen with ibuprofen alone)
Shand 1986[461]	Systematic review; references checked (inadequate quality assessment)
Shannon 2005[583]	Abstract only
Shen 2006[463]	Incorrect interventions (included rofecoxib which is not licensed for use in osteoarthritis)
Shewale 2017[464]	Incorrect study design. Incorrect interventions (intra-articular injections only)
Shimojo 1999[465]	Not available in English language
Shinde 2017[466]	Unclear population (chronic musculoskeletal pain)
Shuan 2002[467]	Not available in English language
Silverfield 2002[468]	Not guideline condition (other pain conditions). Not review population. Inappropriate comparison (compared strong opioids and paracetamol to placebo)
Singh 2006[469]	Inappropriate comparison (compared different types of non-steroidal anti-inflammatory drugs)
Singh 2012[470]	Incorrect interventions (included diacerein which is not licensed for use in the United Kingdom)
Skljarevski 2010[471]	Not review population (chronic low back pain)
Skljarevski 2010[472]	Abstract only
Smith 2016[474]	Systematic review; references checked (inadequate quality assessment)
Smith 2018[473]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Solomon 1974[475]	No usable outcomes (no standard deviation reported and no way to calculate this from the information available)
Song 2016[476]	Systematic review; references checked (inadequate quality assessment)
Song 2016[477]	Systematic review is not relevant to review question or unclear PICO (included moxibustion which is not included in the protocol)
Sowers 2003[478]	Abstract only
Sowers 2005[479]	Inappropriate comparison (compares different types of non-steroidal anti-inflammatory drugs)
Stengaard-pedersen 2004[481]	Inappropriate comparison (compares different doses of an non-steroidal anti-inflammatory drugs)
Stewart 2018[482]	Incorrect interventions (included glucosamine and exercise therapy which is not included in the protocol)
Strand 2011[484]	Inappropriate comparison (compares different regimens of an non-steroidal anti-inflammatory drugs)
Strand 2015[483]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Stricker 2008[485]	Incorrect interventions (included rofecoxib and lumiracoxib which is not licensed for use in the United Kingdom)

Study	Exclusion reason
Suarez-otero 2002[486]	Incorrect interventions (compared an non-steroidal anti-inflammatory drugs and bile acid sequestrant to another non-steroidal anti-inflammatory drugs)
Sullivan 2009[487]	Incorrect study design (non-randomised)
Sullivan 2009[488]	Incorrect study design (non-randomised)
Sun, 2020[489]	Wrong comparison (glucosamine plus non-steroidal anti-inflammatory drugs versus non-steroidal anti-inflammatory drugs only)
Svensson 2006[490]	Secondary analysis only
Tascioglu 2004[492]	Not available in English language
Thie 2001[494]	Dose of glucosamine is below the licensed dose (1178 mg/day)
Tian 2018[495]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Tindall 2002[496]	Inappropriate comparison (compared drug response for people with hip and knee osteoarthritis and rheumatoid arthritis)
Toupin 2019[498]	Cochrane review - Wrong intervention (includes tramadol combined with paracetamol or non-steroidal anti-inflammatory drugs), different outcomes, different hierarchy of outcomes
Tosun 2010[497]	Incorrect interventions (included transdermal non-steroidal anti-inflammatory drugs which are not included in the protocol)
Towheed 2005[499]	Systematic review is not relevant to review question or unclear PICO (Cochrane review, included different doses of glucosamine)
Towheed 2006[500]	Systematic review is not relevant to review question or unclear PICO (Cochrane review, included spinal osteoarthritis)
Trc 2011[501]	Incorrect interventions (included enzymatic hydrolysed collagen which was not included in the protocol)
Trellu 2015[502]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Trueba davalillo 2015[503]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Tucker 2003[504]	Inappropriate comparison (compared an non-steroidal anti-inflammatory drugs to manual therapy)
Tuzun 1995[505]	Not available in English language
Usha 2004[507]	Inappropriate comparison (included methylsulfonamide and glucosamine compared to glucosamine alone and sulphonamidenamide alone)
Vajranetra 1984[508]	Incorrect study design
Valtonen 1981[509]	Incorrect interventions (included diazepam and non-steroidal anti-inflammatory drugs which was not not included in the protocol)
Van akkeren 1991[510]	Not available in English language
Van den driest 2017[511]	Protocol only
Van haselen 2000[512]	Incorrect interventions (included topical homeopathic agents)
Van middelkoop 2013[514]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Van middelkoop 2016[513]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Vannabouathong 2018[515]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Varadi 2013[516]	Incorrect interventions (included transdermal non-steroidal anti-inflammatory drugs which were not included in the protocol)

Study	Exclusion reason
Vlok 1987[517]	Inappropriate comparison (compared weak opioids, non-steroidal anti-inflammatory drugs and paracetamol to non-steroidal anti-inflammatory drugs alone)
Vorsanger 2008[519]	Not guideline condition (other pain conditions). Not review population
Vorsanger 2010[518]	Unclear population (for example, the proportion of participants with an osteoarthritis diagnosis not stated). Inappropriate comparison (compared two strong opioids)
Waikakul 1997[520]	Inappropriate comparison (compared two non-steroidal anti-inflammatory drugs)
Wallace 1994[521]	Inappropriate comparison (compared non-steroidal anti-inflammatory drugs and weak opioids to non-steroidal anti-inflammatory drugs alone)
Wang 2015[524]	Systematic review is not relevant to review question or unclear PICO (included intra-articular agents)
Wang 2015[522]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Wang 2018[523]	Protocol only
Wangroongsub 2010[525]	Inappropriate comparison (compares two different glucosamine formulations)
Watson 2000[528]	Incorrect interventions (included rofecoxib which is not licensed for use in the United Kingdom)
Watson 2001[527]	No usable outcomes (does not report outcomes included in the protocol)
Watson 2004[529]	Incorrect interventions (included rofecoxib which is not licensed for use in the United Kingdom). People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, hemochromatosis, haemophilic arthropathy, diseases of childhood that may predispose to osteoarthritis and malignancy)
Watson 2004[526]	Systematic review; references checked (inadequate quality assessment)
Weaver 1995[530]	No usable outcomes (reported adverse events that could not be categorised into the protocol adverse events outcomes without making the number of participants who had any events in that category unclear)
Weaver 2006[531]	Incorrect interventions (included rofecoxib which is not licensed for use in the United Kingdom)
Wegman 2003[532]	No usable outcomes (no validated scales reported for outcomes included in the protocol)
Wei 1995[533]	Not available in English language
Wein 1998[534]	Abstract only
Welsch, 2020[535]	Systematic review, references checked (insufficient quality assessment)
Whelton 2001[537]	Inappropriate comparison (compared two non-steroidal anti-inflammatory drugs)
Whelton 2002[536]	Inappropriate comparison (compared two non-steroidal anti-inflammatory drugs)
White 2004[538]	Not review population (included people with rheumatoid arthritis)

Study	Exclusion reason
Widrig 2007[539]	Incorrect interventions (included arnica which is not included in the protocol)
Wild 2010[540]	Unclear population (for example, the proportion of participants with an osteoarthritis diagnosis not stated). Inappropriate comparison (compared two strong opioids)
Wilder-smith 2001[541]	Inappropriate comparison (compare non-steroidal anti-inflammatory drugs and strong opioids with non-steroidal anti-inflammatory drugs and weak opioids)
Wilkens 2010[542]	Incorrect stratum (low back pain and spinal osteoarthritis)
Williams 1983[543]	Incorrect interventions (included benoxaprofen which is not licensed for use in the United Kingdom)
Williamson 2014[544]	Post-hoc analysis (analysis of a previous study of people with osteoarthritis knee pain and chronic low back pain)
Wise 2010[545]	Abstract only
Witteveen 2015[546]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Wluka 2021[547]	Protocol only
Woitzek 2012[548]	Not available in English language
Wojtulewski 1974[549]	Incorrect interventions (included fenoprofen and phenylbutazone which are not licensed for use in the United Kingdom)
Wolff 2021[550]	Systematic review; references checked
Woolf 1978[551]	Inappropriate comparison (compared two non-steroidal anti-inflammatory drugs)
Wu 2017[552]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Xiao 2020[553]	Narrative review only
Xing 2017[554]	Incorrect interventions (included intra-articular pharmacological agents, which are considered in a different review question)
Xu 2016[555]	Systematic review; references checked (inadequate quality assessment)
Yaligod 2014[556]	Inappropriate comparison (compared different formulations of paracetamol)
Yamamoto 1979[557]	Not available in English language
Yataba 2017[559]	Incorrect interventions (included transdermal non-steroidal anti-inflammatory drugs which are not included in the protocol)
Yataba 2017[558]	Incorrect interventions (included transdermal non-steroidal anti-inflammatory drugs which are not included in the protocol)
Yelland 2007[560]	Incorrect stratum (included people with spinal osteoarthritis)
Yeomans 2018[561]	Inappropriate comparison (compared multiple non-steroidal anti-inflammatory drugs)
Yocum 2001[562]	Abstract only
Yoo 2014[563]	Inappropriate comparison (compared two non-steroidal anti-inflammatory drugs)
Yoon 2017[564]	Not review population (multiple pain conditions)
Yu 2018[565]	Inappropriate comparison (compared two non-steroidal anti-inflammatory drugs when both arms were given intra-articular injections)
Yue 2018[566]	Insufficient duration of treatment (<1 week)
Yuenyongviwat 2019[567]	Inappropriate comparison (glucosamine compared to usual care)

Study	Exclusion reason
Zacher 2001[568]	Not available in English language
Zacher 2003[569]	Post-hoc analysis
Zammit 2010[570]	Systematic review is not relevant to review question or unclear PICO (Cochrane review; included a range of different interventions for toe osteoarthritis that were not relevant to this review)
Zeng 2015[571]	Systematic review; references checked (inadequate quality assessment)
Zeng 2015[572]	Systematic review; references checked (inadequate quality assessment)
Zeng 2018[573]	Systematic review; references checked (inadequate quality assessment)
Zhang 2007[576]	Not available in English language
Zhang 2012[575]	Not available in English language
Zhao 1999[579]	No usable outcomes
Zhao 2016[578]	Systematic review is not relevant to review question or unclear PICO (intra-articular injections)
Zhao 2019[577]	Incorrect interventions (included loxoprofen which is not licensed for use in the United Kingdom)
Zheng 2006[580]	Not available in English Language
Zhu 2018[581]	Systematic review; references checked (inadequate quality assessment)
Zhu 2018[582]	Systematic review; references checked (inadequate quality assessment)
Zoppi 1995[167]	No usable outcomes (reported adverse events that could not be categorised into the protocol adverse events outcomes without making the number of participants who had any events in that category unclear)

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2005 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 27: Studies excluded from the health economic review

Reference	Reason for exclusion
Brereton 2014 [65]	This study was assessed as partially applicable (Swedish setting may not reflect current NHS context); however, given that a more applicable UK analysis[298] was available based on the same model this study was selectively excluded.
Bruyere 2009 [76]	Excluded as rated not applicable. The study intervention was not relevant to the review.
Bruyere 2021[73]	Selectively excluded (Germany) as there are UK-based cost utility analyses included.
De Lossada 2014[122]	Selectively excluded (Spain) as there are UK-based cost utility analyses included.
Leisewitz 2014[305]	Selectively excluded (Chile) as there are UK-based cost utility analyses included.

Reference	Reason for exclusion
Maetzel 2003 [329]	Excluded as rated not applicable. Canadian resource use and costs from before 2005 judged unlikely to be applicable to current UK NHS context.
McKell 1994 [343]	Excluded as rated not applicable. UK resource use and costs from before 2005 judged unlikely to be applicable to current UK NHS context.
Peacock 1993 [390]	Excluded as rated not applicable. UK resource use and costs from before 2005 judged unlikely to be applicable to current UK NHS context.
Schaefer 2005 [443]	Excluded as rated not applicable. US perspective judged unlikely to be applicable to current UK NHS context.
Segal 2004 [455]	Excluded as rated not applicable. Australian resource use and costs from before 2005 judged unlikely to be applicable to current UK NHS context.
Spiegel 2003 [480]	Excluded as rated not applicable. US resource use and costs from before 2005 judged unlikely to be applicable to current UK NHS context.
Tavakoli 2003 [493]	Excluded as rated not applicable. UK resource use and costs from before 2005 judged unlikely to be applicable to current UK NHS context.

Appendix J – Research recommendations – full details

J.1.1 Research recommendation

What is the clinical and cost-effectiveness of antiepileptics and antidepressants (other than duloxetine) for people with osteoarthritis?

J.1.2 Why this is important

Antiepileptic drugs and antidepressants are used by people with osteoarthritis. However, the evidence for them was limited. Evidence for antiepileptic drugs was limited to two trials that had small sample sizes and so the effects were overall unclear. Evidence for antidepressants was mostly limited to duloxetine, which would not be the antidepressant drug of choice used by most people in the United Kingdom. Therefore, in order to support their continued use, further research is required to ensure their efficacy is present and to understand the potential harms from their use.

J.1.3 Rationale for research recommendation

Importance to 'patients' or the population	Antiepileptic drugs and antidepressants are drugs that aim to reduce pain in a different method to the other oral medicines investigated in this review, meaning that they could be more effective for some people with osteoarthritis. Antidepressants if used at a higher dose may help manage symptoms of depression, which may reduce pain experienced. However, the doses commonly used for managing pain alone are generally too low to reach this effect.
Relevance to NICE guidance	There was insufficient evidence in this guideline to produce recommendations supporting the use of these medicines. In general, there are very few effective treatments for osteoarthritis that have been identified in this guideline. Therefore, further work that could show the people in whom treatments are effective would be of great benefit. Therefore, further research would allow future work to be clearer regarding their use.
Relevance to the NHS	The use of these medicines, while the cost is variable (and these drugs are generally generic and so should not be particularly expensive), may have an important cost implication for the NHS. Therefore, a further understanding of their cost-effectiveness may be important to allow decision making regarding their use to be considered in the future.
National priorities	This is not a national priority area.
Current evidence base	Currently there is very limited evidence with small sample sizes for the use of antiepileptic drugs. There is a significant number of studies investigating the use of duloxetine in the short term. However, there is limited information investigating the use of other antidepressants that may be used more commonly in the United Kingdom, such as amitriptyline.

Equality considerations	Research should consider older people in the trials (including people above the age of 75 years) to better reflect the population of people with osteoarthritis. People with comorbidities should also be considered to better reflect the population of people with osteoarthritis. The committee noted that the research identified in this review does not appear to represent the diverse population of people with osteoarthritis. They agreed that any further research should be representative of the population, including people from different family backgrounds, and socioeconomic backgrounds, disabled people, and people of different ages and genders. Future work should be done to consider the different experiences of people from diverse communities to ensure that the approach taken can be made equitable for everyone.

J.1.4 Modified PICO table

Population	Inclusion: • Adults (age ≥16 years) with osteoarthritis affecting any joint Exclusion: • Children (age <16 years) • People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, hemochromatosis, haemophilic arthropathy, diseases of childhood that may predispose to osteoarthritis, and malignancy). • Studies with an unclear population (e,g, proportion of participants with osteoarthritis unclear) • Spinal osteoarthritis
Intervention	Antidepressants (including tricyclic antidepressants) Anti-epileptic drugs (including gabapentin and pregabalin)
Comparator	Placebo
Outcome	Stratify by ≤/>3 months (longest time-point in each): • Health-related quality of life [validated patient-reported outcomes, continuous data prioritised] • Pain [validated patient-reported outcomes, continuous data prioritised] • Physical function [validated patient-reported outcomes, continuous data prioritised]

	• Psychological distress [validated patient-reported outcomes, continuous data prioritised] • Osteoarthritis flares [dichotomous data] • Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events • Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events • Serious adverse events 2: Cardiovascular adverse events • Serious adverse events 3: Hepatorenal adverse events • Serious adverse events 4: Central nervous system adverse events
Study design	Randomised control trial
Timeframe	Long term (at least 1 year)
Additional information	Adequately powered high quality randomised controlled trials Trials with sufficient blinding, adequate randomisation methods and allocation concealment. Subgroup analyses: • Presence of multimorbidity (high versus low morbidity score) • Age (≤/> 75 years) • Site of osteoarthritis ○ Hip ○ Knee ○ Ankle ○ Foot ○ Toe ○ Shoulder ○ Elbow ○ Wrist ○ Hand ○ Thumb ○ Finger ○ Temporomandibular joint (TMJ) ○ Multisite

J.2 Research recommendation

What is the clinical and cost-effectiveness of weak opioids for people with osteoarthritis?

J.2.1 Why this is important

Weak opioids are used for people with osteoarthritis and may be a more used treatment strategy for people who cannot tolerate non-steroidal anti-inflammatory drugs (especially in older people). However, the evidence for them was limited to one small trial making the effects unclear. Therefore, in order to support their continued use, further research is

required to ensure their efficacy is present and to understand the potential harms from their use.

J.2.2 Rationale for research recommendation

Importance to 'patients' or the population	Weak opioids are widely used to manage osteoarthritis symptoms and other conditions causing pain and so being able to understand their beneficial effects balanced against the potential harms would be important. They may be used by people who are not able to tolerate other treatments, such as non-steroidal anti-inflammatory drugs.
Relevance to NICE guidance	There was insufficient evidence in this guideline to produce recommendations supporting the use of these medicines. Given that the recommended pharmacological treatments for this guideline are topical treatments that may not penetrate the joint in all cases, non-steroidal anti-inflammatory drugs, which may not be tolerable for all people due to potential gastrointestinal, cardiovascular and hepatorenal adverse effects and transdermal opioids which could also have increased adverse effects and are not suitable to all, weak opioids may be used as an alternative treatment by prescribers as a strong recommendation could not be made regarding their use based on limited evidence. In general, there are very few effective treatments for osteoarthritis that have been identified in this guideline. Therefore, further work that could show the people in whom treatments are effective would be of great benefit.
Relevance to the NHS	Although the cost of prescribing weak opioids is likely inexpensive, the widespread use of these medicines may have an important cost implication for the NHS (directly or through the management of concurrent adverse events, such as constipation). Therefore, a further understanding of their cost-effectiveness may be important to allow decision making regarding their use to be considered in the future.
National priorities	Reducing opioid usage is a national priority area (NHS National Patient Safety Improvement Programmes).
Current evidence base	Currently there is very limited evidence with small sample sizes for the use of weak opioids. Designing studies is difficult for this population, as you are unlikely to find a drug naïve population that has not received weak opioids previously.
Equality considerations	Research should consider older people in the trials (including people above the age of 75 years) to better reflect the population of people with osteoarthritis. This is particularly important for this question as older people may not be able to take oral non-steroidal anti-inflammatory drugs and so low opioids may be used more readily. People with comorbidities should also be

	considered to better reflect the population of people with osteoarthritis. The committee noted that the research identified in this review does not appear to represent the diverse population of people with osteoarthritis. They agreed that any further research should be representative of the population, including people from different family backgrounds, and socioeconomic backgrounds, disabled people, and people of different ages and genders. Future work should be done to consider the different experiences of people from diverse communities to ensure that the approach taken can be made equitable for everyone.

J.2.3 Modified PICO table

Population	Inclusion: • Adults (age ≥16 years) with osteoarthritis affecting any joint Exclusion: • Children (age <16 years) • People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, hemochromatosis, haemophilic arthropathy, diseases of childhood that may predispose to osteoarthritis, and malignancy). • Studies with an unclear population (e,g, proportion of participants with osteoarthritis unclear) • Spinal osteoarthritis
Intervention	Weak opioids (including codeine and dihydrocodeine)
Comparator	Placebo
Outcome	Stratify by ≤/>3 months (longest time-point in each): • Health-related quality of life [validated patient-reported outcomes, continuous data prioritised] • Pain [validated patient-reported outcomes, continuous data prioritised] • Physical function [validated patient-reported outcomes, continuous data prioritised] • Psychological distress [validated patient-reported outcomes, continuous data prioritised] • Osteoarthritis flares [dichotomous data] • Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events

	• Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events • Serious adverse events 2: Cardiovascular adverse events • Serious adverse events 3: Hepatorenal adverse events • Serious adverse events 4: Central nervous system adverse events
Study design	Randomised control trial
Timeframe	Long term (at least 1 year)

Additional information	Adequately powered high quality randomised controlled trials
	Trials with sufficient blinding, adequate randomisation methods and allocation concealment.
	
	Subgroup analyses:
	• Presence of multimorbidity (high versus low morbidity score)
	• Age (≤/> 75 years)
	• Site of osteoarthritis
	  ○ Hip
	  ○ Knee
	  ○ Ankle
	  ○ Foot
	  ○ Toe
	  ○ Shoulder
	  ○ Elbow
	  ○ Wrist
	  ○ Hand
	  ○ Thumb
	  ○ Finger
	  ○ Temporomandibular joint (TMJ)
	  ○ Multisite

J.3 Research recommendation

What is the clinical and cost-effectiveness of topical local anaesthetics for people with osteoarthritis?

J.3.1 Why this is important

Topical local anaesthetics are a potential therapy for osteoarthritis that may be used for people who cannot tolerate other medicines (such as non-steroidal anti-inflammatory drugs and opioids). However, no studies were identified in this review investigating the efficacy of the treatment. Given this, further research is required to ensure that this is a safe and effective treatment for people with osteoarthritis.

J.3.2 Rationale for research recommendation

Importance to 'patients' or the population	Topical local anaesthetics are a possible treatment for people who cannot tolerate other treatments that could provide benefit. However, their efficacy for osteoarthritis is not understood and so further research to give information about this would be beneficial. As topical treatments are generally well tolerated then this may be a welcome option if effective.
Relevance to NICE guidance	There was no evidence for this medicine identified in this review which meant that no recommendations could be made discussing it. Therefore, further research would allow future guidance to make a recommendation regarding this medicine.
Relevance to the NHS	Local anaesthetic patches could lead have a significant cost and so additional information about the effectiveness, including cost-effectiveness, would be important to inform their use in the NHS.
National priorities	This is not a national priority area.
Current evidence base	Currently there is no evidence identified in this guideline regarding the use of local anaesthetic patches for people with osteoarthritis. Therefore, new research would allow this medicine to be investigated.
Equality considerations	Research should consider older people in the trials (including people above the age of 75 years) to better reflect the population of people with osteoarthritis. People with comorbidities should also be considered to better reflect the population of people with osteoarthritis. This therapy would likely to be used by people who cannot tolerate or have contraindications for non-steroidal anti-inflammatory drugs and so involving these two groups would be important. The committee noted that the research identified in this review does not appear to represent the diverse population of people with osteoarthritis. They agreed that any further research should be representative of the population, including people from different family backgrounds, and socioeconomic backgrounds, disabled people, and people of different ages and genders. Future work should be done to consider the different experiences of people from diverse communities to ensure that the approach taken can be made equitable for everyone.

J.3.3 Modified PICO table

Population	Inclusion:

	• Adults (age ≥16 years) with osteoarthritis affecting any joint Exclusion: • Children (age <16 years) • People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, hemochromatosis, haemophilic arthropathy, diseases of childhood that may predispose to osteoarthritis, and malignancy). • Studies with an unclear population (e,g, proportion of participants with osteoarthritis unclear) • Spinal osteoarthritis
Intervention	Topical local anaesthetic patches
Comparator	Placebo
Outcome	Stratify by ≤/>3 months (longest time-point in each): • Health-related quality of life [validated patient-reported outcomes, continuous data prioritised] • Pain [validated patient-reported outcomes, continuous data prioritised] • Physical function [validated patient-reported outcomes, continuous data prioritised] • Psychological distress [validated patient-reported outcomes, continuous data prioritised] • Osteoarthritis flares [dichotomous data] • Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events • Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events • Serious adverse events 2: Cardiovascular adverse events • Serious adverse events 3: Hepatorenal adverse events • Serious adverse events 4: Central nervous system adverse events
Study design	Randomised control trial
Timeframe	Long term (at least 1 year)
Additional information	Adequately powered high quality randomised controlled trials Trials with sufficient blinding, adequate randomisation methods and allocation concealment. Subgroup analyses: • Presence of multimorbidity (high versus low morbidity score)

	• Age (≤/> 75 years)
	• Site of osteoarthritis
	  ○ Hip
	  ○ Knee
	  ○ Ankle
	  ○ Foot
	  ○ Toe
	  ○ Shoulder
	  ○ Elbow
	  ○ Wrist
	  ○ Hand
	  ○ Thumb
	  ○ Finger
	  ○ Temporomandibular joint (TMJ)
	  ○ Multisite

J.4 Research recommendation

What is the clinical and cost effectiveness of topical non-steroidal anti-inflammatory drugs and topical capsaicin for osteoarthritis affected joints other than the knee?

J.4.1 Why this is important

Topical non-steroidal anti-inflammatory drugs were found to be clinically and cost-effective and safe treatments for people with knee osteoarthritis. However, there was limited evidence identified for people with hand osteoarthritis and no evidence for other joints affected by osteoarthritis. It is unclear about whether local topical medicines would be effective for joints that are deeper under the skin (for example: the hip). The committee made a recommendation to consider using topical non-steroidal anti-inflammatory drugs for non-knee joint sites. Further research to ensure their efficacy would be required before making strong recommendations. Meanwhile, there was very limited evidence supporting the efficacy of topical capsaicin. Therefore, further research is required to show the effect of topical capsaicin.

J.4.2 Rationale for research recommendation

Importance to 'patients' or the population	Topical non-steroidal anti-inflammatory drugs have been shown to be effective and safe for people with knee osteoarthritis. Limited evidence has indicated possible benefits of topical capsaicin for people with knee and hand osteoarthritis. The safety of the preparations makes them preferable to oral non-steroidal anti-inflammatory drugs. Given then, if evidence indicates that they are effective for joint sites where they have been believed to be ineffective, then this could provide better support for people with osteoarthritis.
Relevance to NICE guidance	In this guideline, topical non-steroidal anti-inflammatory drugs were recommended to be offered for people with knee osteoarthritis, while only to be considered for other joint sites due to a lack of evidence. Topical capsaicin was only

	recommended to be considered due to a limited amount of evidence investigating its use. If additional research is conducted then this will allow stronger recommendations to be made in the future.
Relevance to the NHS	Topical non-steroidal anti-inflammatory drugs have been shown to be the most cost-effective medicine out of those included in the economic model for this question. Given this, there could be additional savings if topical non-steroidal anti-inflammatory drugs are as effective for other joint sites as people will be able to receive this treatment over others where there may be safety concerns. However, they may be more expensive treatments than oral formulations and so their efficacy for other joint sites must be confirmed to be certain of this. There is no cost-effectiveness evidence for topical capsaicin. Therefore, gaining an understanding of their cost-effectiveness would be important to ensure that they are appropriate for use in the NHS.
National priorities	This is not a national priority area.
Current evidence base	Evidence for topical non-steroidal anti-inflammatory drugs for the knee have shown the medicine to be clinically and cost-effective in the short term (≤3 months). Currently there is no evidence regarding the use of topical non-steroidal anti-inflammatory drugs for joint sites other than the knee. There is limited evidence for the effectiveness of topical capsaicin for the knee and hand. Therefore, additional evidence for this intervention would be important.
Equality considerations	Research should consider older people in the trials (including people above the age of 75 years) to better reflect the population of people with osteoarthritis. People with comorbidities should also be considered to better reflect the population of people with osteoarthritis. The committee noted that the research identified in this review does not appear to represent the diverse population of people with osteoarthritis. They agreed that any further research should be representative of the population, including people from different family backgrounds, and socioeconomic backgrounds, disabled people, and people of different ages and genders. Future work should be done to consider the different experiences of people from diverse communities to ensure that the approach taken can be made equitable for everyone.

J.4.3 Modified PICO table

Population	Inclusion: • Adults (age ≥16 years) with osteoarthritis affecting any joint (apart from people where

	the joint they have the most symptoms from are the knee joints) Exclusion: • Children (age <16 years) • People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, hemochromatosis, haemophilic arthropathy, diseases of childhood that may predispose to osteoarthritis, and malignancy). • Studies with an unclear population (e,g, proportion of participants with osteoarthritis unclear) • Spinal osteoarthritis • Knee osteoarthritis
Intervention	Topical non-steroidal anti-inflammatory drugs Topical capsaicin
Comparator	Placebo
Outcome	Stratify by ≤/>3 months (longest time-point in each): • Health-related quality of life [validated patient-reported outcomes, continuous data prioritised] • Pain [validated patient-reported outcomes, continuous data prioritised] • Physical function [validated patient-reported outcomes, continuous data prioritised] • Psychological distress [validated patient-reported outcomes, continuous data prioritised] • Osteoarthritis flares [dichotomous data] • Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events • Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events • Serious adverse events 2: Cardiovascular adverse events • Serious adverse events 3: Hepatorenal adverse events • Serious adverse events 4: Central nervous system adverse events
Study design	Randomised control trial
Timeframe	Short term (3 months)
Additional information	Adequately powered high quality randomised controlled trials Trials with sufficient blinding, adequate randomisation methods and allocation concealment. Subgroup analyses:

	• Presence of multimorbidity (high versus low morbidity score)
	• Age (≤/> 75 years)
	• Site of osteoarthritis
	  ○ Hip
	  ○ Ankle
	  ○ Foot
	  ○ Toe
	  ○ Shoulder
	  ○ Elbow
	  ○ Wrist
	  ○ Hand
	  ○ Thumb
	  ○ Finger
	  ○ Temporomandibular joint (TMJ)
	  ○ Multisite