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Supporting Information

Supplementary methods and results

This appendix was part of the submitted manuscript and has been peer reviewed.
It is posted as supplied by the authors.

Appendix to: Abdel Shaheed C, Awal W, Zhang G, et al. Efficacy, safety, and dose-dependence of the analgesic effects of opioid therapy for people with osteoarthritis: systematic review and meta-analysis. *Med J Aust* 2022; doi: 10.5694/mja2.51392.

Contents

Table 1. Search strategy (OVID databases)

1	Randomized controlled trial/ OR Controlled clinical trial/ OR Random$.ti,ab. OR randomization/ OR placebo.ti,ab. OR ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. OR double blind procedure (keyword) OR parallel group$1.ti,ab. OR (crossover or cross over).ti,ab. OR ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. OR (assigned or allocated).ti,ab. OR (controlled adj7 (study or design or trial)).ti,ab. OR trial.ti.
2	ANIMAL/ not HUMAN/
3	1 NOT 2
4	Opioid.mp OR exp opioid analgesic OR oxycodone OR oxymorphone OR tramadol OR codeine OR buprenorphine OR fentanyl OR tapentadol OR hydrocodone OR hydromorphone OR pethidine OR Meperidine OR morphine OR pentazocine OR Alfentanil OR Sufentanil OR Remifentanil OR methadone OR dihydrocodeine OR Nicomorphine OR N01AH OR N02A
5	exp osteoarthritis OR (osteoarthriti* or osteo-arthriti* or osteoarthritic OR osteoarthros*).ti,ab. OR (degenerative adj2 arthritis).ti,ab. OR coxarthrosis.ti,ab
6	3 and 4 and 5

Table 2. Definitions of quality of evidence ratings

Quality of evidence	Definition
High	Future research very unlikely to change our confidence in the effect estimate
Moderate	Future research likely to have an important impact on our confidence in the effect estimate and may change the estimate
Low	Future research is very likely to have an important impact on our confidence in the effect estimate and is likely to change the estimate
Very low	The effect estimate is very uncertain

Adapted from Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336: 924-926.

Table 3. Characteristics of the trials included in our systematic review

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
Quiding 1992 [18]	27 outpatients 22 F 4 M	Outpatients with persistent pain due to coxarthrosis (hip osteoarthritis) awaiting hip surgery	53 (range 32-70)	Norway	Paracetamol available as rescue analgesic	Ibuprofen 200 mg + codeine 30 mg 6 doses over 24 hours	Placebo	24 hours	0, 8, 12, 16, 20, 24 hours	VAS 0-100	Not reported
Roth 1998 [19]	42 randomised, 41 received treatment, 11 M, 30 F	Aged ≥40 with breakthrough osteoarthritis pain for 2-5 days before study, radiographically confirmed osteoarthritis made ≥1 year ago, stable NSAID dose for ≥30 days	66.5 (NS)	Single centre - Arizona, United States	Pre-study NSAIDs at a stable dose	Tramadol IR 50-100mg every 4-6 hours (n=21)	Placebo (n=21)	24 hour open label phase, treatment phase was 13 days or when patient had insufficient pain relief for 24h (median = 5.2 days)	Day 13 or at discontinuation	Pain (Likert, 0-3), adverse events	Ortho-McNeil Pharmaceutical
Caldwell 1999 [20]	107 randomised after titration and received treatment, 40 M, 67 F	Moderate to severe osteoarthritis pain despite regular NSAIDs use for ≥1 month, osteoarthritis confirmed by radiographic and clinical criteria	57 (NS)	9 sites in United States	Continued NSAIDs at a stable pre-study dosage	Oxycodone CR 10mg (n=34) twice daily, Oxycodone IR 5mg + paracetamol 325mg four times daily (n=37)	Placebo (n=36)	30 days titration, 30 days treatment	Week 2 and 4	Pain (Likert, 0-3), adverse events	Purdue

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
Peloso 2000 [21]	103 patients, 39 M, 64 F, 47.6% (n=49) hip osteoarthritis, 91.3% (n=94) knee osteoarthritis	Aged >35 with primary osteoarthritis, required paracetamol, anti-inflammatory agents or opioids for ≥3 months prior to study, grade II or higher OA severity on radiographs (joint space narrowing and osteophytes), increase in pain and Likert scale ≥2 after washout period	62.2 (10.4)	Multi-centre, 4 Canadian sites	Paracetamol 650mg up to 3 times daily for pain not controlled by codeine or placebo	Codeine CR 100-200mg every 12 hours (n=51)	Placebo (n=52)	2-7 day washout period, 4 weeks treatment	Weekly	Pain (VAS, 0-100), WOMAC (except composite score), adverse events	Unclear; Purdue authors

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
Roth 2000 [22]	133 randomised and received treatment, 35 M, 98 F, 45.9% (n=61) spine osteoarthritis, 30.8% (n=41) knee osteoarthritis, 23.3% (n=31) other osteoarthritis, 65.4% (n=87) continued taking NSAIDs throughout study, 60.9% (n=81) had been taking opioids before study and discontinued them	Osteoarthritis as defined by clinical and radiographic criteria, pain for ≥1 month, moderate or severe pain on baseline	62.3 (13.2)	Multi-centre, 7 rheumatology clinics in United States	Patients taking NSAIDs at a stable dose for ≥1 month could continue it at a stable dose, other analgesics were prohibited	Oxycodone CR 10mg every 12 hours (n=44), oxycodone CR 20mg every 12 hours (n=44)	Placebo (n=45)	2 weeks	Baseline, week 1, week 2	Pain (categorical scale, 0-4), adverse events	Purdue
Fleischmann 2001 [23]	129 randomised and received treatment, 49 M, 80 F	Aged 35-75 with knee osteoarthritis for ≥1 year confirmed by osteophytes on knee radiographs taken within 1 year of enrolment, used NSAIDs for ≥3 months prior to enrolment, pain intensity ≥50 after washout period	62.5 (9.1)	Multi-centre, unspecified locations	Discontinued all pain medications during washout. Physiotherapy initiated before the study allowed to continue.	Tramadol 200-400mg IR (in 50 mg increments) (n=63)	Placebo (n=66)	10 day screening and washout, 13 week treatment	Day 0, 14, 28, 56, 91	Pain (Likert scale, 0-4), WOMAC, adverse events	Ortho-McNeil Pharmaceutical

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
Caldwell 2002 [24]	295 randomised and received treatment, 111 M, 184 F	Aged >40 with hip and/or knee osteoarthritis, Grade II-IV radiographic evidence of osteoarthritis, VAS pain ≥40mm, prior suboptimal response to NSAID or paracetamol, or had previously received intermittent opioids	62.4 (10.4)	Multi-centre, locations unspecified	Paracetamol up to 2g/day for up to 3 consecutive days for non-osteoarthritis pain (stopped 24 hours prior to outcome assessment), aspirin up to 325mg/day for cardiovascular prophylaxis, inhaled and topical steroids for respiratory/dermatological disorders, topical analgesics and physical therapy for treatment of osteoarthritis allowed	Morphine sulfate ER (Avinza) 30mg mane (n=73), Avinza 30mg in the evening (n=73), morphine sulfate CR (MS Contin) 15mg BD (n=76)	Placebo (n=73)	≤7 day washout, 4 week treatment	At baseline and weekly thereafter	Pain (VAS, 0-100), WOMAC (except composite score), adverse events	Unclear. MS Contin Purdue drug

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
Silverfield 2002 [25]	308 randomised and received treatment, 87 M, 221 F, 77.9% (n=240) knee osteoarthritis, 22.1% (n=68) hip osteoarthritis	Aged 35-75 with hip and/or knee osteoarthritis for ≥1 year, had been taking NSAID or COX2 inhibitor at a stable dose for at least 30 days before the study, had been experiencing osteoarthritis flare for 2-5 days requiring additional analgesia or increased NSAID dose, pain VAS ≥50mm and ≥2 on 4-point scale, excluded if received tramadol within 30 days of study entry or received any supplemental pain meds within <5 half-lives of the medication	60.1 (9.87)	Multi-centre, 30 centres	Patients continued their NSAID/COX2 inhibitor therapy at a stable dose	Tramadol IR + parcaetamol 37.5mg/325mg QID (n=102), tramadol IR + paracetamol 75mg/650mg QID (n=95)	Placebo (n=111)	10 days	End of each day	Pain (categorical scale, 0-4), WOMAC, adverse events	Ortho-McNeil Pharmaceutical

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
Babul 2004 [26]	246 randomised and received treatment, 95 M, 151 F	Aged ≥18 with knee osteoarthritis, ACR Class I-III, VAS ≥40, analgesia for at least 75 of 90 days prior to study	61.3 (10.1)	Multicentre, locations unspecified	Paracetamol up to 2000mg per day for reasons other than for chronic pain, for no more than 3 consecutive days. Cannot consume within 24 hours of outcome assessment. Glucosamine and chondroitin were permitted provided the patient was on stable doses for a minimum of 2 months prior to randomisation and agreed to continue on the same dose for the duration of the study. NSAIDs and other analgesia not allowed	Tramadol ER OD 100-400mg oral (n=124)	Placebo (n=122)	2-7 day washout, 12 week treatment period	Week 1, 2, 4, 8, 12	Pain (VAS, 0-100), WOMAC, adverse events	Unclear
Emkey 2004 [27]	307 randomised, 306 received treatment, 97 M, 209 F, 77.5% (n=237) knee osteoarthritis, 22.5% (n=69) hip osteoarthritis	Hip and/or knee osteoarthritis for ≥1 year, VAS ≥50 despite treatment with stable dose of celecoxib or rofecoxib, osteophytes on radiograph within last 2 years, excluded if received tramadol within last 30 days	61.0 (8.99)	Multi-centre, 28 sites, location unspecified	Add-on study for patients with inadequate pain relief despite taking celecoxib (≥200 mg/day) or rofecoxib (≥25 mg/day) for ≥2 weeks. If subject could not tolerate 25mg/day of rofecoxib, they were included if they have been taking rofecoxib 12.5mg/day for at least 5 days.	Tramadol IR 37.5 mg + paracetamol 325 mg (up to 8 tablets/day) (n=153)	Placebo (n=153)	3 week screening, washout, 13 week treatment period	Unspecified, only baseline and final values reported	Pain (VAS, 0-100), WOMAC, SF-36, adverse events	Ortho-McNeil Pharmaceutical

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
Malonne 2004 [28]	231 randomised, 230 received treatment, 63 M, 167 F, 68.3% (n=157) knee osteoarthritis, 31.7% (n=73) hip osteoarthritis	Aged 45-80 with hip and/or knee OA defined by EULAR criteria, VAS ≥35, ≥4/20 on Lequesne functional discomfort index, symptoms ≥6 months, requires analgesia for ≥1 months, excluded if had NSAIDs within 48 hours	66.7 (8.2)	Multi-centre, locations unspecified	Paracetamol up to 2g/day allowed in the second week of the study as rescue analgesia for uncontrolled pain	Tramadol SR 200mg once daily (n=111)	Placebo (n=119)	1 week screening, 2 weeks treatment	Day 0, 7, 14	Pain (VAS, 0-100), adverse events	No
Chindalore 2005 [29]	362 randomised, 360 received treatment, 251 F, 111 M	Aged 18-70 with hip and/or knee osteoarthritis for ≥3 months, moderate to severe pain in hip or knee while taking ≥1 oral analgesic medication in the previous month, NRS ≥5, NRS ≥5 during last 2 days of 4-7 day washout period, no opioid use equivalent to >20mg oxycodone for ≥2 days within past 4 weeks or opioids within past 72 hours	54.3 (NS)	Multicentre, 37 sites	Aspirin ≤325mg for cardiovascular disease prophylaxis	Oxycodone IR 2.5-10mg QID (n=102), oxycodone IR 2·5-10mg + naltrexone 0.001mg QID (n=104), oxycodone IR 5-20mg + naltrexone 0.001mg BD (n=103)	Placebo (n=51)	4-7 day washout, 3 week treatment	Beginning of week 2 and 3, end of week 3, 1 week post-treatment	Pain (NRS, 0-10), WOMAC, SF-36, adverse events	Pain Therapeutics

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
Markenson 2005 [30]	109 randomised, 107 received medications, 29 M, 78 F, 17.8% (n=19) hip osteoarthritis, 30.8% (n=33) knee osteoarthritis, 44.9% (n=48) spine osteoarthritis, 8.4% (n=9) other osteoarthritis	Osteoarthritis defined by ACR criteria, pain ≥1 month prior to study or after discontinuation of opioids, NRS ≥5 during the week prior to the study, had been taking NSAIDs or paracetamol for at least 2 weeks prior to study OR were not tolerant to NSAIDs OR were taking opioids equivalent to ≤60mg oxycodone per day	63·0 (NS)	Multi-centre, 9 centres from the United States	Patients were permitted to continue their stable NSAID (or paracetamol) regimen during the study; the dose could be decreased but could not be increased. Opioids were to be discontinued.	Oxycodone CR 10-60mg every 12 hours (n=56)	Placebo (n=51)	≤15 day titration period, 90 day treatment	After titration period or day 15 (whichever first), days 30, 45, 60, 90	Pain (NRS, 0-10), WOMAC, patient generated index (PGI), adverse events	Purdue
Matsumoto 2005 [31]	491 randomised, 489 received treatment, 192 M, 297 F	Aged >40 with hip and/or knee osteoarthritis, radiographic evidence of osteoarthritis ≥ grade 2 on Kellgren-Lawrence scale, must have taken analgesia for osteoarthritis at least 75 to 90 days before screening with a suboptimal response, VAS ≥40 after washout	62.3 (10.8)	Multi-centre, locations unspecified	Nil	Oxymorphone ER 40mg every 12 hours (n=121), oxymorphone ER 20mg every 12 hours (n=119), oxycodone CR 20mg every 12 hours (n=125)	Placebo (n=124)	2-7 day washout period, 4 weeks treatment	End of each week	Pain (VAS, 0-100), WOMAC, SF-36, adverse events	Endo Pharmaceuticals

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
Gana 2006 [32]	1020 randomised, 1011 patients received treatment, 380 M, 631 F, 74.0% (n=748) knee osteoarthritis, 26.0% (n=263) hip osteoarthritis	Aged 18-74 with hip and/or knee osteoarthritis, radiographically confirmed ACR class I-III, took NSAID/COX2 inhibitor/opioid for at least 75 out of 90 days prior to enrolment, VAS ≥40 after washout	58.2 (10.0)	Multi-centre, United States	Paracetamol up to 2g/day for up to 3 consecutive days for non-osteoarthritis pain (stopped 48 hours prior to outcome assessment and during washout)	Tramadol ER 100mg (n=203, n=202 began treatment), 200mg (n=203, n=201 began treatment), 300mg (n=204, n=201 began treatment), 400mg (n=205, n=202 began treatment)	Placebo (n=205)	2-7 day washout, 12 week treatment	At baseline and weeks 1, 2, 3, 6, 9, 12, 13	Pain (VAS, 0-10), WOMAC, SF-36, adverse events	Biopharmatech Consulting,
Kivitz 2006 [33]	370 randomised and received treatment, 146 M, 224 F, 80.3% (n=297) knee osteoarthritis, 19.7% (n=73) hip osteoarthritis, ~70% opioid naïve	Aged ≥18 with hip and/or knee osteoarthritis, symptoms and signs of osteoarthritis, radiographic Kellgren-Lawrence grade II-IV, must have regularly taken paracetamol, NSAIDs or opioids for 90 days before screening, VAS ≥40	61.8 (11.3)	Multi-centre, locations unspecified	Aspirin ≤325mg for cardiovascular disease prophylaxis	Oxymorphone ER 10mg every 12 hours (n=95), oxymorphone ER 40mg every 12 hours (n=93), oxymorphone ER 50mg every 12 hours (n=91)	Placebo (n=91)	2-7 day washout, 2 weeks treatment	End of each week	Pain (VAS, 0-100), WOMAC, SF-36, adverse events	Endo Pharmaceuticals

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
Langford 2006 [34]	416 randomised, 399 received treatment, 134 M, 265 F, 52.9% (n=211) knee osteoarthritis, 47.1% (n=88) hip osteoarthritis	Aged ≥40 with hip and/or knee osteoarthritis, meets ACR criteria for osteoarthritis, requires joint replacement, radiographic evidence of osteoarthritis, joint pain for ≥3 months and at least 20 days per month, pain not adequately controlled by weak opioids +/- paracetamol, VAS ≥50 on first and last day or run-in phase and mean VAS ≥50 for entire 7-day run-in phase, excluded if received strong opioid for 4 weeks before study	66 (9.9)	Multi-centre in Canada, Czech Republic, Hungary, Poland, Slovakia, United Kingdom	Stable dose of NSAIDs/COX2 inhibitors or steroids. Opioids were ceased. Paracetamol up to 4g/day, metoclopramide 10mg tablets and laxatives were permitted	Transdermal fentanyl 25-100μg/hour, replaced every 72 hours (n=202)	Placebo patch (n=197)	1 week run-in phase, 6 week treatment, then patches withdrawn at rate of 1 patch every 3 days	Day 1, 15, 29, 43, and 3 days after last patch is removed	Pain (VAS, 0-100), WOMAC, SF-36, adverse events	Janssen-Cilag

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
NCT00313846 2006 [35]	327 randomised, 326 received treatment, 107 M, 219 F	Aged 40-75, clinical diagnosis of hip and/or knee osteoarthritis for ≥1 year, moderate to severe pain 14 days prior to enrolment, excludes patients taking daily opioids or >2500mg paracetamol regularly	60.8 (9.45)	44 sites in United States	Supplemental paracetamol	Buprenorphine transdermal patch 5, 10 or 20 µg/hour changed every 7 days (n=164)	Placebo (n=162)	4 weeks	Unspecified	Pain (NRS, 0-10), adverse events	Yes Purdue
NCT00531427 2007 [36]	570 randomised, 567 analysed, 211 M, 356 F	Aged ≥40 with knee osteoarthritis for ≥1 year, treated with opioids <5mg oxycodone equivalent per day in last 14 days, osteoarthritis knee pain not adequately controlled with non-opioid therapy	59.1 (9.75)	87 sites in United States	Rescue analgesia (immediate-release oxycodone for the first 6 days post-randomization and paracetamol or ibuprofen for the remainder of the double-blind phase)	Buprenorphine transdermal patches (BTDS) 10 or 20 µg/hour applied for 7 days (n=282)	Placebo patch applied for 7 days (n=285)	12 weeks	Weeks 1, 2, 4, 6, 8, 10, 12	24-hr pain (NRS, 0-10), rescue analgesia	Purdue
Burch 2007 [37]	646 randomised, 645 received treatment, 238 M, 408 F	Aged 40-80 with knee osteoarthritis, NRS ≥4, taking NSAIDS/COX2 inhibitor/tramadol for osteoarthritis for 30 days prior to enrolment	63 (9)	108 outpatient clinics in United States, Canada, France, Romania	Allowed short-acting analgesics for non-osteoarthritis pain for up to 3 consecutive days but not 3 days before outcome assessment	Tramadol ER 100-300mg once daily (increased by increments of 100mg, final dose of 200 or 300mg) (n=432)	Placebo (n=214)	Titration, 5 day washout, 12 week maintenance period	Week 3, 6, 9, 12	Pain (NRS, 0-10), adverse events	Labopharm

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
Fishman 2007 (NCT00852917) [38]	552 patients, 208 M, 344 F	Aged 40-75 with knee osteoarthritis defined by ACR criteria, CRP <8µg/mL or ESR <40mm/hr, total WOMAC pain subscale score >150mm at baseline	61.3 (9.3)	Multi-centre, unspecified locations	Short acting analgesics for acute pain other than OA pain allowed for 3 days, but must be ceased 3 days before study visit	Tramadol ER 100mg (n=106), Tramadol 200mg (n=111), Tramadol 300mg (n=108) OD	Placebo (n=227)	12 weeks	Week 0, 3, 6, 12	Pain (VAS, 0-100), WOMAC percent change, adverse events	Yes
Hartrick 2009 [39]	666 patients, 659 included in analysis, 335 M	Patient 18-80 years old who were candidates for primary joint replacement surgery as a result of degenerative joint disease	61.2 (9.83)	United States of America	Patients who required rescue drug beyond study medication were withdrawn	Tapentadol IR 50 mg OR Tapentadol IR 75 mg OR oxycodone HCI IR 10 mg	Placebo	10 day double blind treatment period (days 1-10)	Follow up period of 5 days (Days 11 to 15)	Adverse events	Johnson and Johnson Pharmaceuticals
NCT00832416 2009 [40]	565 participants 341 F 224 M	Aged 40-75 with moderate to severe knee osteoarthritis based on ACR classification	60.4 (9.3)	Official site not provided	Not reported	Tramadol ER 100mg, 200 mg or 300mg once a day	Placebo	12 weeks	Week 12	WOMAC Pain, WOMAC physical function (change from baseline) VAS 0-100	Labopharm

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
NCT00979953 2009 [41]	408 randomised and received treatment, 168 M, 240 F	Aged 18-75 with knee osteoarthritis defined by ACR criteria confirmed on radiographs from the last year, osteophytes on radiographs, average weekly pain score NRS ≥4, discontinue NSAIDs if not taken regularly for ≥4 weeks before screening, at least 1 of the following: (1) be more than 50 years old, (2) have morning stiffness for less than 30 minutes, or (3) have crepitus on active motion	57.0 (8.34)	Multi-centre, 11 sites in United States	NSAIDs taken at a stable dose for ≥4 weeks before screening	Oxycodone CR (n=104), ADL5859 (n=101), ADL5747 (n=99)	Placebo (n=104)	2 weeks	Daily	Pain (NRS, 0-10)	Cubist Pharmaceuticals
Afilalo 2010 [42]	1030 randomised, 1023 received treatment, 405 M, 618 F	Aged ≥40 with knee osteoarthritis, ACR class I-III, pain in index joint for ≥3 months requiring analgesia, NRS ≥5 three days before randomisation	58.3 (9.9)	87 US sites, 15 Canadian sites, 6 New Zealand sites, 4 Australian sites	Only paracetamol ≤1000mg/day for maximum of 3 consecutive days for pain unrelated to index joint osteoarthritis	Tapentadol ER 100-250mg BD (n=346, n=344 began treatment) or oxycodone CR 20-50mg BD (n=345, n=342 began treatment)	Placebo (n=339)	3-7 day washout, 3 week titration, 12 week maintenance, 10-14 day follow-up for TEAEs	Week 1, 2, 3 of titration period and week 1, 2, 3, 5, 7, 9, 11, 12	Pain (NRS, 0-10), WOMAC, EQ-5D, SF-36, AEs	Johnson and Johnson. Purdue make Oxycontin

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
Breivik 2010 [43]	199 randomised and received treatment, 63 M, 136 F, 73 (36.7%) hip OA, 126 (63.3%) knee OA	Aged >40 with hip and/or knee osteoarthritis, satisfied ACR criteria for OA, Grade II-IV radiographic Kellgren and Lawrence scale, was taking NSAIDs for at least one month prior to screening at a stable frequency/dose but still experienced at least moderate pain on walking, must discontinue intermittent or short term weak opioids, excluded if using strong opioids or regular weak opioids	62.9 (9.4)	19 centres in Denmark, Sweden, Norway, Finland	NSAID/COX2 inhibitor, aspirin for CV prophylaxis, paracetamol 0.5 g 4-6 hourly (max 4 g/day) for rescue analgesia	Buprenorphine 5, 10 or 20μg/h (n=100), worn for 7 days	Placebo patch (n=99)	Screening + 24 weeks	Weekly for first two weeks, biweekly thereafter	Pain on movement (NRS, 0-10), WOMAC, EuroQol, rescue analgesia, adverse events	Cyncron Norpharma A/S, Slotsmarken 15, DK-2970 Hørsholm, Denmark. Purdue make the patches

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
Katz 2010 [44]	344 randomised and received treatment, 143 M, 201 F, 22.4% (n=77) hip osteoarthritis, 77.6% (n=267) knee osteoarthritis, 73.8% (n=254) opioid naïve, 24.4% (n=84) opioid experienced	Aged ≥21 with hip and/or knee osteoarthritis, ACR class I-III, required treatment within last 90 days for joint pain, unable to control joint pain with non-opioid analgesia or opioid analgesia equivalent to ≤40mg/day of oral morphine, NRS ≥5 following cessation of previous medications, BPI decreased by ≥2 during titration phase (i.e. enrichment study)	54.4 (12.27)	Multi-centre, 81 sites in United States	Rescue medication with paracetamol (≤500mg every 6 hours), aspirin ≤325mg for cardiovascular disease prophylaxis	Morphine sulfate and naltrexone hydrochloride ER 20-160mg (n=171)	Placebo (n=173)	≤14 days screening and washout, ≤45 days titration period, 12 week maintenance	Week 0, 1, 2, 4, 6, 8, 10, 12	Pain (NRS, 0-10), WOMAC, adverse events	King Pharmaceuticals
Munera 2010 [45]	315 randomised and received treatment, 103 M, 212 F, 45.1% (n=142) hip osteoarthritis, 54.9% (n=173) knee osteoarthritis	Aged ≥18 with hip and/or knee osteoarthritis, radiological evidence of osteoarthritis, opioids (≤90 MME) in the previous year or osteoarthritis inadequately controlled by opioids, NRS ≥7 during run-in phase where patients received ibuprofen 1600mg/day	61·0 (12.6)	25 sites in United States	Aspirin as an anti-thrombotic ≤325mg/day	Buprenorphine transdermal patch 5-20 µg/hour (n=152), worn for 7 days	Placebo patch (n=163)	1 week run-in, 3 weeks titration, 1 week maintenance	Weekly	Pain (NRS, 0-10), adverse events	Purdue

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
DeLemos 2011 [46]	1011 randomised, 1001 received treatment, 369 M, 632 F, 74.0% (n=741) with knee osteoarthritis, 26.0% (n=260) with hip osteoarthritis	Aged >18 with hip and/or knee osteoarthritis, radiological ACR Class I-III criteria met, VAS ≥40 (at screening and after washout), required analgesia for at least 75 of 90 days preceding screening visit	60.0 (10.9)	Multicentre, United States	Must discontinue all analgesics except aspirin <325 mg for cardiovascular prophylaxis. Paracetamol up to 2 g/day was allowed for non-osteoarthritis pain for up to 3 consecutive days (must be avoided during washout period and within 48 hours of outcome assessment)	Tramadol ER 100mg (n=201), 200mg (n=199), 300mg (n=199), celecoxib 200mg (n=202)	Placebo (n=200)	2-7 day washout, 12 weeks	At baseline, Week 1, 2, 3, 6, 9, 12	Pain (VAS, 0-100), WOMAC, SF-36, Adverse events	Ortho-McNeil Janssen Scientific Affairs, Biopharmatech Consulting Inc, Biovail Corporation, Mississauga, Canada.
Friedman 2011 [47]	558 patients (40-75 years); 70% female.	Patients with knee and or hip OA diagnosed using the ACR criteria.	Mean age 58 years	61 United States clinics	-	Oxycodone CR 20 mg twice daily over 12 week double blind period following open label run-in phase	Placebo	12 weeks	12 weeks	Adverse events	Pain Therapeutics
Vojtassak 2011 [48]	288 randomised, 287 received treatment, 80 M, 207 F, 74.0% (n=213) knee osteoarthritis, 25.7% (n=74) hip osteoarthritis	Aged ≥40 years with hip and/or knee osteoarthritis defined by ACR criteria, osteoarthritis >3 months, BPI ≥5, not adequately controlled by NSAIDs or paracetamol, patients that took strong opioids in the 4 weeks before the study were excluded but use of weak opioids for ≤10 days was allowed	65 (10.2)	18 sites in Czech Republic, Romania, Slovakia, United Kingdom	Subjects taking NSAIDs or paracetamol remaining on a stable dose, paracetamol as rescue analgesia (≤4g/day until day 8 and then ≤2g/day for rest of study)	OROS hydromorphone ER 4-32mg (n=139)	Placebo (n=149)	1 week screening, 4 weeks titration, 12 weeks maintenance	Week 1, 2, 3, 4 of titration, Week 4, 8, 12 of maintenance	Pain (NRS, 0-10), WOMAC, SF-36, adverse events	Janssen Cilag

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
Rauck 2013 [49]	990 randomised, 981 received treatment, 354 M, 627 F, 23.5% (n=231) hip osteoarthritis, 76.5% (n=750) knee osteoarthritis	Aged ≥21 with hip and/or knee osteoarthritis, functional class I-III, NRS ≥5, unable to consistently control pain with non-opioid medications or received opioids,	59.7 (10.8)	Multi-centre, locations unspecified	Paracetamol (≤2000mg/day) was permitted as supplemental analgesia (not permitted within 6 hours of outcome assessments)	OROS hydromorphone ER 8mg (n=319), OROS hydromorphone ER 16mg (n=330)	Placebo (n=332)	≤2 week washout period, ≤16 day titration phase, 12 week maintenance period, ≤1 week taper	Weeks 1, 2, 3, 4, 6, 8, 10, 12	Pain (NRS, 0-10), WOMAC, adverse events	Mallinckrodt Inc a Covidien company
Spierings 2013 [50]	301 randomised, 299 received treatment, 108 M, 199 F, 80.9% (n=242) knee osteoarthritis, 19.1% (n=57) hip osteoarthritis	Hip and/or knee osteoarthritis with Kellgren-Lawrence grade ≥2; WOMAC pain score ≥4/10 at screening, ≥5 at baseline, and an increase ≥1 after washout period; WOMAC physical function score ≥4; PGA of fair, poor or very poor at baseline; regular use of analgesics other than paracetamol for osteoarthritis pain >4 days per week for the last month before screening; used non-opioids or opioids up to 90mg/day in morphine equivalents but was not adequate or tolerated	57.4 (9.6)	Multi-center, 112 locations in United States, Austria, Denmark, Germany, Poland, Spain, Sweden	Rescue medication with paracetamol (≤3000mg per day) but ceased 48hrs before each study visit	Oxycodone CR 10-40mg q12h (n=158), Tanezumab 5mg (n=161), tanezumab 10mg (n=150)	Placebo (n=141)	≤30 days screening, 2-27 days washout, 16 week treatment period	Week 2, 4, 8, 12, 16	WOMAC, adverse events	Pfizer

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
Mayorga 2016 [51]	196 randomised and received treatment, 48 M, 50 F	Aged 40-80 years with knee osteoarthritis, ACR radiographic evidence of osteoarthritis (Kellgren-Lawrence grade ≥2), NRS ≥5 average over 3 days before randomisation, stable dose of NSAIDs or opioids (≤40 MME/day) for minimum of 5 days/week for 4 weeks before screening	60.1 (9.0)	7 sites in Canada, 33 sites in United States of America	Paracetamol up to 3g/day during week 1 and 2 of titration of phase and 1g/day for the rest of the study, no other meds	Oxycodone CR 20-50mg BD (n=50)	Placebo (n=48)	2 week screening, 1 week washout, 4 weeks titration, 12 weeks maintenance	Weeks 2, 4, 8, 12, 16	Pain (NRS, 0-10), WOMAC, adverse events, rescue analgesia	Janssen Research & Development
Tominaga 2016 [52]	91 randomised and received treatment, 29 M, 62 F, 44% (n=40) knee osteoarthritis, 56% (n=51) with LBP	Aged ≥20 years with low back pain (LBP) or knee osteoarthritis last ≥12 weeks prior to study, inadequate analgesia with non-opioid medications, NRS ≥5, must be opioid naïve, excluded if used intra- or post-operative opioids for acute pain in last 30 days	65.1 (15.0)	Multi-centre, 18 study sites in Japan	Previous non-opioid analgesics could be continued throughout the study	Tapentadol ER 25-250mg BD (n=60)	Placebo (n=31)	1 week screening, 6 weeks titration, 6 weeks maintenance, 1 week follow-up	Weekly	Pain (NRS, 0-10), WOMAC, adverse events	Janssen Research & Development,

Study	Participant details	Inclusion criteria	Mean age (SD)	Setting	Concomitant medications	Intervention and sample size	Comparison and sample size	Length of treatment	Follow up period	Eligible outcome measures	Industry funding
Serrie 2017 [53]	990 randomised, 987 received treatment, 280 M, 707 F	Aged ≥40 with knee osteoarthritis, ACR class I-III, pain required analgesia for ≥3 months (if opioids, must be ≤160mg morphine equivalent dose), dissatisfaction with analgesic treatment, NRS ≥5 during last 3 days prior to randomisation	62.1 (9.3)	Multi-centre, 79 sites in 12 European countries	Aspirin ≤325mg/day for CV prophylaxis, paracetamol up to 1000mg/day for no more than 3 consecutive days for reasons other than osteoarthritis-related chronic pain	Tapentadol PR 100-250mg BD (n=319), oxycodone CR 20-50mg BD (n=331)	Placebo (n=337)	≤14 days screening, 3-7 days washout, 3 weeks titration, 12 weeks maintenance, 14 days follow-up	Weekly for first 3 weeks, every second week thereafter	Pain (NRS, 0-10), WOMAC, EQ-5D, SF-36, adverse events	Johnson & Johnson

ACR=American College of Rheumatology; OD=once daily; ER=extended release; CR=controlled release; IR=immediate release; M=Male F=Female; HCl=hydrochloride. NS=Not Specified; NSAID=Non-steroidal anti-inflammatory drug; VAS=Visual analogue scale; EULAR=European league against rheumatism; BPI=brief pain inventory; NRS=numerical rating scale; PGA=patient global assessment; mm=millimetre; BD=twice a day; QID=four times a day; COX=cyclooxygenase; WOMAC=Western Ontario and McMaster Universities Arthritis Index; SF-36=Short Form (36) Health Survey; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; EuroQol=European Quality of Life Scale; MME=morphine milligram equivalent; TEAs=treatment emergent adverse events; OROS=osmotic release oral system; EQ-5D; European Quality of Life Five Dimension.

Table 4. List of excluded studies and reasons for exclusion

Reason	Study
Ineligible comparison (8)	• Biondi D, Xiang J, Vorsanger G, et al. Tapentadol extended release (ER) versus oxycodone controlled release (CR) for management of chronic low back or osteoarthritis pain: Influence of prior opioid experience on study discontinuations due to constipation, nausea, or vomiting. *J Pain* 2010;1:S42. • Biondi DM, Xiang J, Etropolski M, et al. Tolerability and efficacy of tapentadol extended release in elderly patients >= 75 years of age with chronic osteoarthritis knee or low back pain. *J Opioid Manag* 2015;11:393-403. • Conaghan PG, O'Brien CM, Wilson M, et al. Transdermal buprenorphine plus oral paracetamol vs an oral codeine-paracetamol combination for osteoarthritis of hip and/or knee: a randomised trial. *Osteoarthritis Cartilage* 2011;19:930-938. • de Craen AJ, Di Giulio G, Lampe-Schoenmaeckers JE, et al. Analgesic efficacy and safety of paracetamol-codeine combinations versus paracetamol alone: a systematic review. *BMJ* 1996;313:321-325. • Kjaersgaard-Andersen P, Nafei A, Skov O, et al. Codeine plus paracetamol versus paracetamol in longer-term treatment of chronic pain due to osteoarthritis of the hip. A randomised, double-blind, multi-centre study. *Pain* 1990;43:309-318. • Kroner K, Hansen TB, Harving S, et al. Individually dosed codeine plus paracetamol versus paracetamol in long-term treatment of chronic pain due to arthrosis of the hip - A randomised, double blind, multicenter study. *Acta Orthopaedica Scandinavica, Supplement* 1991;62:43. • Lloyd RS, Costello F, Eves MJ, et al. The efficacy and tolerability of controlled-release dihydrocodeine tablets and combination dextropropoxyphene/paracetamol tablets in patients with severe osteoarthritis of the hips. *Curr Med Res Opin* 1992;13:37-48. • Rauschkolb C, Lange B, Kuperwasser B, et al. Tapentadol extended release for the relief of chronic osteoarthritis knee pain: Results from the EuroQol-5 dimension (EQ-5D) and Western Ontario and Macmaster Universities osteoarthritis index (WOMAC) questionnaires. *Osteoarthr Cartil* 2009;1:S179.
Ineligible outcome (3)	• Friedmann N, Klutzaritz V, Webster L. Efficacy and safety of an extended-release oxycodone (Remoxy) formulation in patients with moderate to severe osteoarthritic pain. *J Opioid Manag* 2011;7:193-202. • Hale M, Upmalis D, Okamoto A, et al. Tolerability of tapentadol immediate release in patients with lower back pain or osteoarthritis of the hip or knee over 90 days: a randomized, double-blind study. *Curr Med Res Opin* 2009;25:1095-1104. • Malonne H, Coffiner M, Fontaine D, et al. Long-term tolerability of tramadol LP, a new once-daily formulation, in patients with osteoarthritis or low back pain. *J Clin Pharm Ther* 2005;30:113-120.

Reason	Study
Ineligible or mixed population (8)	• Buynak R, Rappaport SA, Rod K, et al. Long-term safety and efficacy of tapentadol extended release following up to 2 years of treatment in patients with moderate to severe, chronic pain: results of an open-label extension trial. *Clin ther* 2015;37:2420. • Hale M, D'Andrea D, Yang R, et al. Efficacy and tolerability of hydrocodone extended-release tablets for the treatment of moderate to severe pain in opioid-treated patients with osteoarthritis or low back pain. *J Pain* 2012;1:S84. • Hale ME, Laudadio C, Yang R, et al. Efficacy and tolerability of a hydrocodone extended-release tablet formulated with abuse-deterrence technology for the treatment of moderate-to-severe chronic pain in patients with osteoarthritis or low back pain. *J Pain Res* 2015;8:623-636. • Leng X, Li Z, Lv H, et al. Effectiveness and safety of transdermal buprenorphine versus sustained-release tramadol in patients with moderate to severe musculoskeletal pain: An 8-week, randomized, double-blind, double-dummy, multicenter, active-controlled, noninferiority Study. *Clin J Pain* 2015;31:612-620. • Matsushita T, Hasebe M, Nishimura A. Phase III clinical study of tramadol hydrochloride/acetaminophen combination tablet in patients with chronic osteoarthritis pain or chronic low back pain - A randomized withdrawal, double-blind, parallel group, placebo-controlled study. *Osteoporosis Int* 2012;2:S85. • National Institute of Health. US national library of medicine. NCT01240863. Study to evaluate the efficacy and safety of hydrocodone bitartrate extended-release tablets (CEP-33237) for relief of moderate to severe pain in patients with osteoarthritis or low back pain who require opioid treatment for an extended period of time. Available from: https://clinicaltrials.gov/ct2/show/NCT01240863 • Stein A, Yassouridis A, Szopko C, Helmke K, Stein C. Intraarticular morphine versus dexamethasone in chronic arthritis. *Pain* 1999;83:525. • Zheng Y, Kostenbader K, Barrett T, et al. Tolerability of biphasic-release hydrocodone bitartrate/acetaminophen tablets (MNK-155): a phase III, multicenter, open-label study in patients with osteoarthritis or chronic low back pain. *Clin ther* 2015;37:1235.
Other (5)	• Aazami H, Glover RM, Kivitz AJ, et al. Actual-use study of CL-108 for the treatment of flares of osteoarthritis of the knee or hip. *Postgrad Med* 2016;128:S2:79. No results posted. • National Institute of Health. US national library of medicine. NCT0023636. A study of the effect on pain control of treatment with fentanyl, administered through the skin, compared with placebo in patients with osteoarthritis. 2005. No results posted. • National Institute of Health. US national library of medicine. NCT01643759. Norspan transdermal patches study in osteoarthritis patients. 2011 No results posted. • Schnitzer TJ, Easton R, Pang S, et al. Efficacy and safety of subcutaneous tanezumab for the treatment of osteoarthritis of the hip or knee. *Br J Pain* 2019;13:7. • Thorne C, Beaulieu AD, Callaghan DJ, et al. A randomized, double-blind, crossover comparison of the efficacy and safety of oral controlled-release tramadol and placebo in patients with painful osteoarthritis. *Pain Res Manag* 2008;13:93-102. Inconsistencies in results led to exclusion.

Reason	Study
Ineligible control group (3)	• Choi CB, Song JS, Kang YM et al. A 2-week, multicenter, randomized, double-blind, double-dummy, add-on study of the effects of titration on tolerability of tramadol/acetaminophen combination tablet in Korean adults with knee osteoarthritis pain. *Clin ther* 2007;29:1381. • Hale M, Tudor IC, Khanna S, Thipphawong J. Efficacy and tolerability of once-daily OROS hydromorphone and twice-daily extended-release oxycodone in patients with chronic, moderate to severe osteoarthritis pain: results of a 6-week, randomized, open-label, noninferiority analysis. *Clin ther* 2007;29:874. • Likar R, Schafer M, Paulak F et al. Intraarticular morphine analgesia in chronic pain patients with osteoarthritis. *Anesth analg* 1997;84:1313.
Subset or post-hoc analysis of other trial (5)	• Kean WF, Bouchard S, Roderich Gossen E. Women with pain due to osteoarthritis: the efficacy and safety of a once-daily formulation of tramadol. *Pain Med* 2009;10:1001-11. (Overlapping data with NCT00852917 and did not include VAS pain intensity scores). • Kosinski M, Janagap C, Gajria K, Schein J, Freedman J. Pain relief and pain-related sleep disturbance with extended-release tramadol in patients with osteoarthritis. *Curr Med Res Opin* 2007;23:1615-1626. (Overlapping data with Gana et al [32]). • Rosenthal NR, Silverfield JC, Wu SC, Jordan D, Kamin M. Tramadol/acetaminophen combination tablets for the treatment of pain associated with osteoarthritis flare in an elderly population. J Amer Geriatr Soc 2004;52:374-380. (Subset Analysis of Silverfield et al [25]). • Vorsanger G, Xiang J, Jordan D, Farrell J. Post hoc analysis of a randomized, double-blind, placebo-controlled efficacy and tolerability study of tramadol extended release for the treatment of osteoarthritis pain in geriatric patients. *Clin Ther* 2007;29 Suppl:2520-35. (Subset analysis of Gana et al [32]). • Zautra AJ, Smith BW. Impact of controlled-release oxycodone on efficacy beliefs and coping efforts among osteoarthritis patients with moderate to severe pain. *Clin J Pain* 2005;21:471-477. (Overlapping data with Markenson et al [30]).

Reason	Study
Clinical trial with corresponding peer-reviewed article (6)	• National Institute of Health. US national library of medicine. A study to evaluate the efficacy and safety of CG5503 prolonged release (PR) in subjects with moderate to severe chronic pain due to osteoarthritis of the knee. Available from: https://clinicaltrials.gov/ct2/show/NCT00486811 Accessed December 18, 2019. (Overlapping data with Serrie et al [53]). • National Institute of Health. US national library of medicine. A four-arm study comparing the analgesic efficacy and safety of tramadol once a day 100, 200 and 300 mg versus placebo for the treatment of pain due to osteoarthritis of the knee. Available from: https://clinicaltrials.gov/show/NCT00832416 Accessed December 18, 2019 Overlapping data with NCT00852917 (Fishman et al. 2007 [38] chosen instead). • National Institute of Health. US national library of medicine. Placebo-controlled trial with OROS hydromorphone hydrochloride to treat patients with moderate to severe pain induced by osteoarthritis of the hip or the knee. Available from: https://clinicaltrials.gov/ct2/show/NCT00980798 Accessed December 18, 2019. (Overlapping data with Vojtassak et al [48]). • National Institute of Health. US national library of medicine. Placebo-controlled trial with OROS hydromorphone hydrochloride to treat patients with moderate to severe pain induced by osteoarthritis of the hip or the knee. Available from: https://clinicaltrials.gov/ct2/show/NCT01124604 Accessed December 18, 2019. (Overlapping data with Tominaga et al [52]). • National Institute of Health. US national library of medicine. A phase 3 randomized, double-blind, placebo- and oxycodone-controlled, multicenter study of the efficacy and safety of tanezumab in patients with osteoarthritis of the knee or hip. Available from: http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2009-013329-41-SE Accessed December 18, 2019. (Data overlap with Spierings et al [50]). • National Institute of Health. US national library of medicine. Tapentadol (CG5503). Available from: https://clinicaltrials.gov/ct2/show/NCT00421928 Accessed December 18, 2019. (Overlapping data with Afilalo et al [42]).

Table 5. Withdrawals and reasons for withdrawal during the trial phases of clinical trials

Study	Group	Number randomised	Lost to follow up	Proportion discontinued	Adverse events	Proportion discontinued	Lack of efficacy	Proportion discontinued	Other (e.g. protocol violation or choice)	Proportion discontinued	Total discontinued	Proportion discontinued
Quiding 1992 [18]	Not reported	-	-	-	-	-	-	-	-	-	-	-
Roth 1998 [19]	Placebo	21	0	0	5	24%	8	38%	0	0	13	62%
Roth 1998 [19]	Tramadol	21	0	0	1	5%	3	14%	1	5%	5	24%
Caldwell 1999a [20]	Oxycodone	34	0	0	3	9%	3	9%	1	3%	7	21%
Caldwell 1999b [20]	Oxycodone + acetaminophen	37	0	0	5	14%	4	11%	2	5%	11	30%
Caldwell 1999 [20]	Placebo	36	0	0	3	8%	13	36%	2	6%	18	50%
Peloso 2000 [21]	Codeine	51	0	0	15	29%	1	2%	4	8%	20	39%
Peloso 2000 [21]	Placebo	52	0	0	4	8%	5	10%	8	15%	17	33%
Roth 2000 [22]	Placebo	45	0	0	2	4%	22	49%	3	7%	27	60%
Roth 2000a [22]	Oxycodone 10 mg	44	0	0	12	27%	12	27%	0	0	24	55%
Roth 2000b [22]	Oxycodone 20 mg	44	0	0	14	32%	5	11%	0	0	19	43%
Fleischmann 2001 [23]	Tramadol	63	0	0	0	0	0	0	43 (unspecified)	68%	43	68%
Fleischmann 2001 [23]	Placebo	66	0	0	0	0	0	0	49 (unspecified)	74%	49	74%
Caldwell 2002a [24]	Avinza (morphine sulfate) (morning dose)	73	0	0	17	23%	9	12%	1	1%	27	37%

Study	Group	Number randomised	Lost to follow up	Proportion discontinued	Adverse events	Proportion discontinued	Lack of efficacy	Proportion discontinued	Other (e.g. protocol violation or choice)	Proportion discontinued	Total discontinued	Proportion discontinued
Caldwell 2002b [24]	Avinza (morphine sulfate) (afternoon dose)	73	0	0	18	25%	12	16%	3	4%	33	45%
Caldwell 2002c [24]	MS Contin (morphine sulfate CR)	76	0	0	18	24%	8	11%	2	3%	28	37%
Caldwell 2002 [24]	Placebo	73	0	0	5	7%	14	19%	4	5%	23	32%
Silverfield 2002a [25]	Tramadol/paracetamol 1 tab	102	0	0	10	10%	1	1%	1	1%	12	12%
Silverfield 2002b [25]	Tramadol/paracetamol 2 tab	95	0	0	15	16%	0	0	1	1%	16	17%
Silverfield 2002 [25]	Placebo	111	0	0	6	5%	0	0	0	0	6	5%
Babul 2004 [26]	Tramadol	124	0	0	33	27%	19	15%	11	9%	63	51%
Babul 2004 [26]	Placebo	122	0	0	9	7%	45	37%	5	4%	59	48%
Emkey 2004 [27]	Tramadol/paracetamol	153	0	0	20	13%	13	8%	8	5%	41	27%
Emkey 2004 [27]	Placebo	154	0	0	6	4%	26	17%	7	5%	39	25%
Malonne 2004 [28]	Tramadol 200 mg	111	-	-	24	22%	-	-	-	-	-	22%
Malonne 2004 [28]	Placebo	119	-	-	2	2%	-	-	-	-	-	2%
Chindalore 2005 [29]	Placebo	52	0	0	0	0	7	13%	3	6%	10	19%
Chindalore 2005 [29]	Oxycodone four times daily	103	0	0	29	28%	2	2%	1	1%	32	31%
Markenson 2005 [30]	Placebo	51	2	4%	2	4%	34	67%	0	0	38	75%

Study	Group	Number randomised	Lost to follow up	Proportion discontinued	Adverse events	Proportion discontinued	Lack of efficacy	Proportion discontinued	Other (e.g. protocol violation or choice)	Proportion discontinued	Total discontinued	Proportion discontinued
Markenson 2005 [30]	Oxycodone	56	1	2%	20	36%	9	16%	3	5%	33	59%
Matsumoto 2005a [31]	Oxymorphone 40mg	121	0	0	57	47%	9	7%	2	2%	68	56%
Matsumoto 2005b [31]	Oxymorphone 20mg	121	1	0.8%	46	38%	5	4%	6	5%	58	48%
Gana 2006 [32]	Placebo	205	0	0	21	10%	46	22%	23	11%	90	44%
Gana 2006a [32]	Tramadol 100mg	203	0	0	29	14%	31	15%	22	11%	82	40%
Gana 2006b [32]	Tramadol 200mg	203	0	0	40	20%	29	14%	16	8%	85	42%
Gana 2006c [32]	Tramadol 300mg	204	0	0	54	26%	18	9%	25	12%	97	48%
Gana 2006d [32]	Tramadol 400mg	205	0	0	60	29%	23	11%	16	8%	99	48%
Kivitz 2006a [33]	Oxymorphone 10mg	95	1	1%	24	25%	7	7%	2	2%	34	36%
Kivitz 2006b [33]	Oxymorphone 40mg	93	0	0	51	55%	5	5%	2	2%	58	62%
Langford 2006 [34]	Placebo	197	0	0	20	10%	64	32%	20	10%	104	52.8%
Langford 2006 [34]	Transdermal Fentanyl	202	1	0.5%	54	27%	15	7%	26	13%	96	48%
NCT00313846 2006 [35]	Transdermal Buprenorphine	164	-	-	8	5%	-	-	3	2%	11	7%
NCT00313846 2006 [35]	Placebo	162	-	-	1	1%	-	-	4	2%	5	3%
NCT00531427 2007 [36]	Transdermal Buprenorphine	282	4	1.4%	44	16%	14	5%	11	4%	73	26%
NCT00531427 2007 [36]	Placebo	285	3	1.0%	30	11%	39	14%	22	8%	94	33%

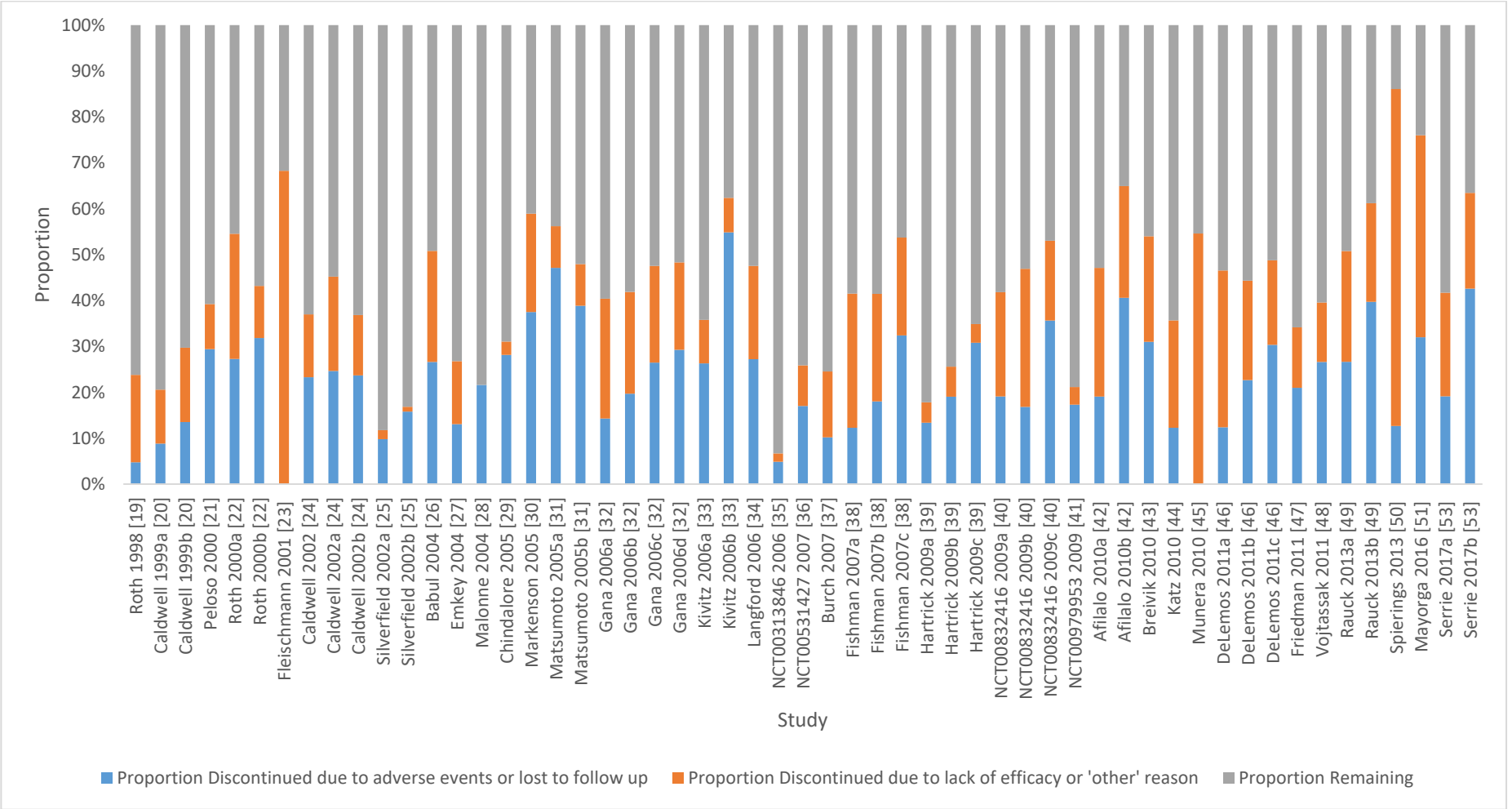
Study	Group	Number randomised	Lost to follow up	Proportion discontinued	Adverse events	Proportion discontinued	Lack of efficacy	Proportion discontinued	Other (e.g. protocol violation or choice)	Proportion discontinued	Total discontinued	Proportion discontinued
Burch 2007 [37]	Tramadol	432	0	0	44	10%	34	8%	28	6%	106	24.5%
Burch 2007 [37]	Placebo	214	0	0	11	5%	22	10%	16	7%	49	23%
Fishman 2007a [38]	Tramadol 100mg	106	0	0	13	12%	21	20%	10	9%	44	42%
Fishman 2007b [38]	Tramadol 200mg	111	0	0	20	18.%	11	10%	15	14%	46	41%
Fishman 2007c [38]	Tramadol 300mg	108	0	0	35	32%	11	10%	12	11%	58	54%
Fishman 2007 [38]	Placebo	227	0	0	17	7%	47	21%	29 (including 1 death)	13%	93	41%
Hartrick 2009a [39]	Tapentadol IR 50mg	157	0	0	21	13%	2	1%	5	3%	28	18%
Hartrick 2009b [39]	Tapentadol IR 75mg	168	1	0.6%	31	18%	2	1%	9	5%	43	26%
Hartrick 2009c [39]	Oxycodone IR 10mg	172	1	0.6%	52	30%	2	1%	5	3%	60	35%
Hartrick 2009 [39]	Placebo*	169	0	0	7	4%	6	4%	4	2%	17	10%
NCT00832416 2009a [40]	Tramadol 100mg	110	0	0	21	19%	17	15%	8 (including 1 death)	7%	46	42%
NCT00832416 2009b [40]	Tramadol 200 mg	113	0	0	19	17%	15	13%	19	17%	53	47%
NCT00832416 2009c [40]	Tramadol 300 mg	115	0	0	41	36%	13	11%	7	6%	61	53%
NCT00979953 2009 [41]	Oxycodone	104	1	1.0%	17	16%	0	0	4	4%	22	21%

Study	Group	Number randomised	Lost to follow up	Proportion discontinued	Adverse events	Proportion discontinued	Lack of efficacy	Proportion discontinued	Other (e.g. protocol violation or choice)	Proportion discontinued	Total discontinued	Proportion discontinued
NCT00979953 2009 [41]	Placebo	104	0	0	4	4%	0	0	3	3%	7	7%
Afilalo 2010 [42]	Placebo	339	3	0.9%	22	6%	35	10%	74	22%	134	39.5%
Afilalo 2010a [42]	Tapentadol	346	5	1.4%	61	17%	15	4%	82	24%	163	47.1%
Afilalo 2010b [42]	Oxycodone	345	0	0	140	41%	7	2%	77	22%	224	64.9%
Breivik 2010 [43]	Buprenorphine	100	0	0	31	31%	7	7%	16	16%	54	54%
Breivik 2010 [43]	Placebo	99	0	0	2	2%	12	12%	20	20%	34	34%
Katz 2010 [44]	Placebo	173	2	1.1%	13	8%	32	18%	28	16%	75	43%
Katz 2010 [44]	Morphine sulphate and Naltrexone	171	3	1.8%	18	11%	6	4%	34	20%	61	36%
Munera 2010 [45]	Placebo	163	-	-	-	-	-	-	77	47%	77	47%
Munera 2010 [45]	Transdermal Buprenorphine	152	-	-	-	-	-	-	83	55%	83	55%
DeLemos 2011 [46]	Placebo	202	0	0	15	7%	65	32%	17	8%	97	48%
DeLemos 2011a [46]	Tramadol 100mg	202	0	0	25	12%	51	25%	18	9%	94	47%
DeLemos 2011b [46]	Tramadol 200mg	203	0	0	46	23%	33	16%	11	5%	90	44%
DeLemos 2011c [46]	Tramadol 300mg	201	0	0	61	30%	22	11%	15	7%	98	49%
Friedman 2011 [47]	Oxycodone ER	205	0	0	43	21%	12	6%	15	7%	70	34%
Friedman 2011 [47]	Placebo	207	0	0	22	11%	38	18%	15	7%	75	36%
Vojtaššák 2011 [48]	Hydromorphone	139	1	0.7%	36	26%	5	4%	13	9%	55	40%
Vojtaššák 2011 [48]	Placebo	149	0	0	7	5%	16	11%	10	7%	33	22%

Study	Group	Number randomised	Lost to follow up	Proportion discontinued	Adverse events	Proportion discontinued	Lack of efficacy	Proportion discontinued	Other (e.g. protocol violation or choice)	Proportion discontinued	Total discontinued	Proportion discontinued
Rauck 2013 [49]	Placebo	332	2	0.6%	21	6%	83	25%	39	12%	145	43.7%
Rauck 2013a [49]	Hydromorphone 8mg	319	3	0.9%	82	26%	49	15%	28	9%	162	50.8%
Rauck 2013b [49]	Hydromorphone 16mg	330	4	1.2%	127	38.5%	30	9%	41	12%	202	61.2%
Spierings 2013 [50]	Placebo	141	2	1.4%	2	1%	10	7%	99	70%	113	80.1%
Spierings 2013 [50]	Oxycodone 10-40mg	158	4	2.5%	16	10%	12	8%	104	65.8%	136	86.1%
Mayorga 2016 [51]	Oxycodone	50	0	0	16	32%	3	6%	19	38%	38	76%
Mayorga 2016 [51]	Placebo	48	1	2.1%	2	4%	4	8%	15	31%	22	46%
Tominaga 2016 [52]		-	-	-	-	-	-	-	-	-	-	-
Serrie 2017 [53]	Placebo	337	0	0	28	8%	43	13%	45	13%	116	34.4%
Serrie 2017a [53]	Tapentadol	319	1	0.3%	60	19%	21	7%	51	16%	133	41.7%
Serrie 2017b [53]	Oxycodone	331	0	0	141	43%	12	4%	57	17%	210	63.4%

*Number randomised who took the trial drug; TDF=transdermal fentanyl, IR=immediate release; CR=controlled release; ER=extended release.

Figure 1. Proportion of participants in opioid treatment arms who dropped out during the trial phases



Note: Only the trials presented in Supplementary table 5 present eligible withdrawal data. See table 5 for corresponding drug regimens.

Table 6. Drug regimens and morphine milligram equivalent (MME) doses

Study	Drug	Daily dose (mg)	MME equivalent	CDC MME conversion factor
Roth 1998 [19]	Tramadol 100mg IR followed by 50mg 6 hourly for total 250mg	250	25	0.1
Caldwell 1999 [20]	Oxycodone CR 10mg (up to a maximum of ~ 4 doses)	40	60	1.5
Caldwell 1999 [20]	Oxycodone IR 5mg + paracetamol 325mg (up to a maximum of 12 doses)	40	60	1.5
Peloso 2000 [21]	Codeine 159mg 12 hourly	318	47.7	0.15
Roth 2000 [22]	Oxycodone CR 20mg bd	40	60	1.5
Roth 2000 [22]	Oxycodone CR 10mg bd	20	30	1.5
Fleischmann 2001 [23]	Tramadol ER	300	30	0.1
Caldwell 2002 [24]	Avinza (Morphine) 30mg daily	30	30	1
Caldwell 2002 [24]	Ms Contin 15 mg twice daily (Morphine sulfate)	30	30	1
Silverfield 2002 [25]	Tramadol IR + paracetamol	225	22.5	0.1 (tramadol)
Babul 2004 [26]	Tramadol ER 100-400mg daily	276 mg	27.6	0.1
Emkey 2004 [27]	Tramadol + paracetamol	154	15.4	0.1
Malonne 2004 [28]	Tramadol ER	200	20	0.1
Chindalore 2005 [29]	Oxycontin (oxycodone) all regimens	28.75	43.13	1.5
Markenson 2005 [30]	Oxycodone CR 10-60mg daily	57+44 / 2 =50.5	75.75	1.5
Matsumoto 2005 [31]	Oxymorphone ER 40mg bd ("To improve tolerability, patients randomized to the oxymorphone ER 40mg treatment group received oxymorphone ER 20mg every 12 hours during weeks 1 and 2 and oxymorphone ER 40mg every 12 hours during weeks 3 and 4") (40*2 + 20*2)/2= 60mg	60	180	3
Matsumoto 2005 [31]	Oxymorphone ER 20mg bd	40	120	3
Matsumoto 2005 [31]	Oxycontin (oxycodone) CR 20mg bd ("Patients randomized to oxycodone CR 20mg received oxycodone CR 10mg every 12 hours during weeks 1 and 2 and oxycodone CR 20mg every 12 hours during weeks 3 and 4.") (20*2 + 10*2)/2 = 30mg	30	45	1.5
Gana 2006a [32]	Tramadol ER 100mg daily	100	10	0.1
Gana 2006b [32]	Tramadol ER 200mg daily	200	20	0.1

Study	Drug	Daily dose (mg)	MME equivalent	CDC MME conversion factor
Gana 2006c [32]	Tramadol ER 300mg daily	300	30	0.1
Gana 2006d [32]	Tramadol ER 400mg daily	400	40	0.1
Kivitz 2006 [33]	Oxymorphone 10mg bd for 2 weeks	20	60	3
Kivitz 2006 [33]	Oxymorphone 20mg bd for first week then 40 mg bd for second week	60	180	3
Kivitz 2006 [33]	Oxymorphone 20mg bd for first week followed by 50 mg bd for second week	70	210	3
Langford 2006 [34]	Transdermal fentanyl 25-100µg/hour twice weekly	Median number of patches was 1.7 at 25µg/hour	102	7.2 (for further guidance see CDC conversion chart)
NCT00313846 2006 [35]	Buprenorphine 5,10 or 20µg	10	18	12.6 (for further guidance see CDC conversion chart)
NCT00531427 2007 [36]	Transdermal buprenorphine 10-20µg/hour weekly	15	27	12.6 (for further guidance see CDC conversion chart)
Burch 2007 [37]	Tramadol ER (Contramid)	275.4	27.54	0.1
Fishman 2007a [38]	Tramadol 100mg daily	100	10	0.1
Fishman 2007b [38]	Tramadol 100mg daily	200	20	0.1
Fishman 2007c [38]	Tramadol 100mg daily	300	30	0.1
Hartrick 2009 [39]	Tapentadol IR	50	20	0.4
Hartrick 2009 [39]	Tapentadol IR	75	30	0.4
Hartrick 2009 [39]	Oxycodone IR	10	15	1.5
NCT00832416a 2009 [40]	Tramadol ER 100mg daily	100	10	0.1
NCT00832416b 2009 [40]	Tramadol ER 100mg daily	200	20	0.1
NCT00832416c 2009 [40]	Tramadol ER 100mg daily	300	30	0.1
NCT00979953 2009 [41]	Oxycodone 10mg bd for 1-4 days then 20mg bd for days 5-14	34.28	51.42	1.5

Study	Drug	Daily dose (mg)	MME equivalent	CDC MME conversion factor
Afilalo 2010a [42]	Tapentadol ER 100-250mg twice daily	299.3mg	119.72	0.4
Afilalo 2010b [42]	Oxycodone CR 20-50mg twice daily	48.2mg	72.3	1.5
Breivik 2010 [43]	Transdermal buprenorphine 5-20µg/hour weekly	Mean dose was 11 (5.7)µg/hour	19.8	12.6 (for further guidance see CDC conversion chart)
Katz 2010 [44]	Morphine sulfate 20-160mg daily	43.5	43.5	1
Munera 2010 [45]	Buprenorphine patch		27.18	12.6 (for further guidance see CDC conversion chart)
DeLemos 2011a [46]	Tramadol ER 100mg daily	100	10	0.1
DeLemos 2011b [46]	Tramadol ER 200mg daily	200	20	0.1
DeLemos 2011c [46]	Tramadol ER 300mg daily	300	30	0.1
Friedman 2011 [47]	Oxycodone 27.5mg bd (mean)	55	82.5	1.5
Vojtaššák 2011 [48]	Hydromorphone 4-32mg daily	12.2	48.8	4
Rauck 2013a [49]	Hydromorphone 8mg daily	8	32	4
Rauck 2013b [49]	Hydromorphone 16mg daily	16	64	4
Spierings 2013 [50]	Oxycodone CR 10-40mg twice daily	23	34.5	1.5
Mayorga 2016 [51]	Oxycodone CR 20-50mg bd	70	105	1.5
Tominaga 2016 [52]	Tapentadol ER	237.1	94.84	0.4
Serrie 2017a [53]	Tapentadol PR	315.2	126.08	0.4
Serrie 2017b [53]	Oxycodone CR	54.1	81.15	1.5

CR=controlled release, bd=twice daily; ER=extended release; µg=micrograms; hr=hour; mg=milligrams; IR=immediate release; PR=prolonged release. Note the Centre for Disease Control (CDC) morphine milligram equivalent dose conversion chart[54] was used to calculate the log MME for each of the opioids included in this table.

Table 7. Bias assessment of included studies

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other e.g. Industry funding	Overall ROB Assessment
Quiding 1992 [18]	Unclear	Unclear	Unclear	Unclear	Low	High	Unclear	High
Roth 1998 [19]	Unclear	Unclear	Low	Low	High	Unclear	High	High
Caldwell 1999 [20]	Low	High	Low	Low	High	Unclear	High	High
Peloso 2000 [21]	Unclear	Unclear	Low	Low	High	Unclear	Low	High
Roth 2000 [22]	Unclear	Unclear	Low	Low	High	Unclear	High	High
Fleischmann 2001 [23]	Low	High	Low	Low	High	Unclear	High	High
Caldwell 2002 [24]	Unclear	Unclear	Low	Low	High	Unclear	Low	High
Silverfield 2002 [25]	Low	Low	Low	Low	Low	Unclear	Low	Low
Babul 2004 [26]	Low	Low	Low	Low	High	Low	Low	High
Emkey 2004 [27]	Unclear	Unclear	Low	Low	High	Unclear	High	High
Malonne 2004 [28]	Unclear	Unclear	Low	Low	Low	Unclear	Low	Unclear
Chindalore 2005 [29]	Unclear	Unclear	Low	Low	High	Unclear	High	High
Markenson 2005 [30]	Low	Low	Low	Low	High	Unclear	High	High
Matsumoto 2005 [31]	Low	Low	Low	Low	High	Unclear	High	High
Gana 2006 [32]	Low	Low	Low	Low	High	Low	High	High
Kivitz 2006 [33]	Low	Low	Low	Low	High	Unclear	High	High
Langford 2006 [34]	Low	Low	Low	Low	High	Unclear	High	High
NCT00313846 2006 [35]	Unclear	Unclear	Low	Low	Low	Low	High	High
NCT00531427 2007 [36]	Unclear	Unclear	Low	Low	High	Low	High	High
Burch 2007 [37]	Low	Low	Low	Low	High	High	High	High
Fishman 2007 [38]	Low	Low	Low	Low	High	Unclear	High	High
Hartick 2009 [39]	Unclear	Unclear	Unclear	Unclear	High	Low	High	High
NCT00832416 2009 [40]	Unclear	Unclear	Unclear	Unclear	High	High	High	High
NCT00979953 2009 [41]	Unclear	Unclear	Low	Low	Low	Low	High	High
Afilalo 2010 [42]	Low	Low	Low	Low	High	High	High	High
Breivik 2010 [43]	Low	Low	Low	Low	High	Unclear	High	High

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other e.g. Industry funding	Overall ROB Assessment
Katz 2010 [44]	Low	Low	Low	Low	High	Low	High	High
Munera 2010 [45]	Unclear	Unclear	Low	Low	High	Low	High	High
DeLemos 2011 [46]	Unclear	Unclear	Low	Low	High	Low	High	High
Friedman 2011 [47]	Unclear	Unclear	Low	Low	High	Unclear	High	High
Vojtassak 2011 [48]	Low	Low	Low	Low	High	High	High	High
Rauck 2013 [49]	Unclear	Unclear	Low	Low	High	Unclear	High	High
Spierings 2013 [50]	Unclear	Unclear	Low	Low	High	High	High	High
Mayorga 2016 [51]	Low	Low	Low	Low	High	Low	High	High
Tominaga 2016 [52]	Unclear	Unclear	Low	Low	High	High	High	High
Serrie 2017 [53]	Low	Low	Low	Low	High	Low	High	High

ROB=risk of bias

Table 8. Effect estimates for single ingredient opioid analgesics (or combination opioid with opioid antagonist)

Outcome and time point	Effect (95% CI)	Number of trials (number of participants)	Study limitation	Imprecision	Inconsistency	Publication bias	GRADE
Pain							
Immediate term pain	MD (95% CI) -4.90 (-6.46, -3.34)	13 (5320)	Yes	No	I^2=29%	No (Egger p=0.22)	Moderate
Short term pain	MD (95% CI) -6.38 (-8.45, -4.30)	19 (6949)	Yes	No	I^2=47%	No (Egger p= 0.40)	Moderate
Medium term pain	MD (95% CI) -4.59 (-7.17, -2.02)	19 (8965)	Yes	No	I^2=69%	No (Egger p=0.27)	Low
Disability (WOMAC physical function scale)*							
Immediate term	MD (95% CI) -4.11 (-6.92, -1.30)	3 (2105)	Yes	No	I^2=21%	NA	Moderate
Short term	MD (95% CI) -5.84 (-7.90, -3.79)	8 (3394)	Yes	No	I^2=19%	NA	Moderate
Medium term	MD (95% CI) -4.15 (-6.94, -1.35)	16 (6882)	Yes	No	I^2=76%	No (Egger p= 0.38)	Low
WOMAC total score							
Immediate term	MD (95% CI) -5.04 (-8.02, -2.07)	1 (1011)	Yes	No	I^2=0%	NA	Moderate
Short term	MD (95% CI) -6.26 (-9.29, -3.23)	5 (2235)	Yes	No	I^2=27%	NA	Moderate
Medium term	MD (95% CI) -4.07 (-7.14, -1.01)	14 (5788)	Yes	No	I^2=76%	No (Egger p=0.55)	Low
QOL Short term							
SF-36 PCS	MD (95% CI) 3.05 (1.13, 4.97)	2 (824)	Yes	No	I^2=22%	NA	Moderate
SF-36 MCS	MD (95% CI) -2.18 (-4.41, 0.05)	1 (467)	Yes	No	I^2=0	NA	Moderate

Outcome and time point	Effect (95% CI)	Number of trials (number of participants)	Study limitation	Imprecision	Inconsistency	Publication bias	GRADE
PGI	MD (95% CI) 8.80 (0.22, 17.38)	1 (107)	Yes	Yes	I^2=0	NA	Low
QOL Medium term							
European Quality of Life Scale	MD (95% CI) 2.96 (-0.76, 6.69)	3 (2125)	Yes	Yes	I^2=36%	NA	Low
SF-36 PCS	MD (95% CI) 0.70 (0.04, 1.37)	5 (3525)	No	No	I^2=40%	NA	High
SF-36 MCS	MD (95% CI) -0.65 (-1.62, 0.33)	5 (3525)	Yes	No	I^2=55%	NA	Low
PGI	MD (95% CI) 11.5 (2.37, 20.63)	1 (107)	Yes	Yes	I^2=0	NA	Low
Adverse events							
Immediate term	RR (95% CI) 2·13 (1·60 to 2·83)	1 (n=666)	Yes	No	I^2=35%	NA	Moderate
Short term	RR (95% CI) 1.60 (1.32, 1.94)	6 (1634)	Yes	No	I^2=59%	NA	Low
Medium term	RR (95% CI) 1.43 (1.29, 1.59)	16 (8482)	Yes	No	I^2=80%	Yes (Egger p=0.07)	Very Low
Meta-regression of log MME dose (regression coefficient), medium term regression co-efficient (95% CI)							
Pain	0.92 (-6.58, 8.41)	19 (8965)	Yes	Yes	I^2=68%	No	Very Low
Adverse events (log ratio)	0.08 (-0.17, 0.33)	16 (8482)	Yes	Yes	I^2=81%	Yes (p=0.07)	Very Low

* *Higher scores indicate worse limitation in physical function (sometimes the original study cited positive differences to indicate a favourable effect; therefore the direction of effect was corrected in the meta-analysis). PGI=Patient Generated Index; MME = morphine milligram equivalent; WOMAC = Western Ontario and McMaster Universities Arthritis Index; SF-36=short form (36) health survey; PCS=physical component score; MCS=mental component score*

Table 9. Data extracted from included publications: pain outcomes

Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Quiding 1992 [18]	1) Codeine 30mg/ibuprofen 200mg 6 doses in 24 hours 2) 210mg 3) 31.5MME	VAS 0-100 Average pain 0-8 hours after 6th dose	10 (22.2)	10 (22.2)	26	29.0 (22.2)	29.0 (22.2)	26
Roth 1998 [19]	1) Tramadol 2) 250mg 3) 25 MME tramadol 100mg followed by 50 mg every 6 hours for total 250 mg	Likert (0-3) mean pain at rest at end of treatment	0.9 (SE 0.3, SD=1.4)	28.3 (47.7)	20	1.3 (SE 0.3, SD=1.5)	44.0 (50.3)	21
Roth 1998 [19]	1) Tramadol 2) 250mg 3) 25MME tramadol 100mg followed by 50mg every 6 hours for total 250mg	Likert (0-4) mean pain on movement at end of treatment	1.1 (SE 0.3, SD=1.3)	27.5 (SE 7.5, SD= 33.5)	20	1.5 (SE 0.3, SD=1.4)	38.3 (SE 7.8, SD=35.5)	21
Caldwell 1999 [20]	1) Oxycodone CR 10mg 2) 40mg 3) 60 MME	Likert (0-3) mean change from end of titration to day 30	0.4 (SE 0.1, SD=0.8)	14.7 (25.3)	34	1.0 (SE 0.1, SD=0.8)	33.3 (26.0)	36
Caldwell 1999 [20]	1) Oxycodone IR 5mg + paracetamol 325mg 2) 40mg 3) 60 MME	Likert (0-3) mean change from end of titration to day 30	0.5 (SE 0.1, SD=0.7)	16.3 (22.3)	37	1.0 (SE 0.1, SD=0.8)	33.3 (26.0)	36

Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Peloso 2000 [21]	1) Codeine CR 100-400mg 2) 318 (104)mg 3) 47.7 MME	VAS (0-100) weekly pain intensity mean scores	Baseline: 65.4 (20.4) Week 1: 51.4 (20.4*) (estimated from Fig 2) Week 4: 29.4 (20.9) Mean change: 36.0 (27.6)	Baseline: 65.4 (20.4) Week 1: 51.39 (20.4**) Week 4: 29.4 (20.9)	31	Baseline: 57.4 (26.7) Week 1: 54.7 (26.7*) (estimated from Fig 2) Week 4: 47.8 (25.6) Mean change: 8.9 (22.2)	Baseline: 57.4 (26.7) Week 1: 54.7 (26·7**) Week 4: 47.8 (25.6)	35
Roth 2000 [22]	1) Oxycodone CR 10mg q12h 2) 20mg 3) 30 MME	Likert scale (0-3) mean scores estimated from Fig 2	Baseline: 2.5 (SE 0.1) Day 7: 1.9 (SE 0.1, SD=0.9) Day 14: 1.8 (SE 0.14, SD=0.9)	Week 1: 63.3 (28.7) Week 2: 63.3 (31.0)	44	Baseline: 2.4 (SE 0.1) Day 7: 2.0 (SE 0.1, SD=0.8) Day 14: 2.1 (SE 0.1, SD=0.7)	Week 1: 66.7 (26.7) Week 2: 70.0 (24.7)	45
Roth 2000 [22]	1) Oxycodone CR 20mg q12h 2) 40mg 3) 60 MME	Likert scale (0-3) mean scores estimated from Fig 2	Baseline: 2.4 (SE 0.1) Day 7: 1.6 (SE 0.13, SD=0.86) Day 14: 1.6 (SE 0.1, SD=0.9)	Week 1: 53.3 (28.7) Week 2: 53.3 (31.0)	44	Baseline: 2.4 (SE 0.1) Day 7: 2.0 (SE 0.1, SD=0.8) Day 14: 2.1 (SE 0.1, SD=0.7)	Week 1: 66.7 (26.7) Week 2: 70.0 (24.7)	45
Fleischmann 2001 [23]	1) Tramadol IR 300mg oral 2) 300mg 3) 30 MME	Likert (0-4) mean scores	Baseline: 2.7 (0.6) Day 91: 2.1 (1.1)	52.5 (26.5)	63	Baseline: 2.9 (0.7) Day 91: 2.5 (1.1)	62 (28.3)	66

Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Caldwell 2002 [24]	1) QAM - Morphine sulfate IR+ER (Avinza) 30mg mane 2) 30mg (0) 3) 30 MME	VAS (0-100) mean change from baseline	Week 1: -23.1% (SE 3.5) → -17.7 (SE 2.7, SD=22.9) Week 4: -26.7% (SE 3.5) → -20.4 (SE 2.7, SD=22.9)	Week 1: -17.7 (SE 2.68, SD=22.9) Week 4: -20.4 (SE 2.7, SD=22.9)	73	Week 1: -11.0% (SE 3.5) → -8.6 (SE 2.7, SD=23.4) Week 4: -14.6% (SE 3.5) → -11.4 (SE 2.7, SD=23.4)	Week 1: -8.6 (SE 2.7, SD=23.4) Week 4: -11.4 (SE 2.7, SD=23.4)	73
Caldwell 2002 [24]	1) QPM - Morphine sulfate IR+ER (Avinza) 30mg nocte 2) 30mg (0) 3) 30 MME	VAS (0-100) mean change from baseline	Week 1: -19.2% (SE 3.5) → -15.2 (SE 2.78, SD=23.7) Week 4: -22.8% (SE 3.5) → -18.1 (SE 2.8, SD=23.7)	Week 1: -15.2 (SE 2.78, SD=23.7) Week 4: -18.1 (SE 2.8, SD=23.7)	73	Week 1: -11.0% (SE 3.5) → -8.6 (SE 2.74, SD=23.4) Week 4: -14.6% (SE 3.5) → -11.4 (SE 2.7, SD=23.4)	Week 1: -8.6 (SE 2.7, SD=23.4) Week 4: -11.4 (SE 2.7, SD=23.4)	73
Caldwell 2002 [24]	1) MSC - Morphine sulfate CR (MS Contin) 15mg BD 2) 30mg (0) 3) 30 MME	VAS (0-100) mean change from baseline	Week 1: -19.5% (SE 3.5) → -15.4 (SE 2.8, SD=24.0) Week 4: -23.1% (SE 3.5) → -18.2 (SE 2.8, SD=24.0)	Week 1: -15.4 (SE 2.76, SD=24.0) Week 4: -18.2 (SE 2.8, SD=24.0)	76	Week 1: -11.0% (SE 3.5) → -8.6 (SE 2.74, SD=23.4) Week 4: -14.6% (SE 3.5) → -11.4 (SE 2.7, SD=23.4)	Week 1: -8.6 (SE 2.7, SD=23.4) Week 4: -11.4 (SE 2.7, SD=23.4)	73

Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Silverfield 2002 [25] ***used converted SD from baseline**	1) Tramadol/paracetamol 2) 225 3) 22.5mg NOT STATED - allowed range is from 150-300mg tramadol + 1300-2600mg paracetamol (can assume midpoint of 225mg tramadol)	Average daily pain intensity score (0-3)	Baseline: 2.4 (0.5) Day 5: 1.4 (0.5*) Day 10: 1.3 (0.5*)	Day 5: 46.7 (16.7*) Day 10: 43.3 (16.7*)	193	Baseline: 2.4 (0.5) Day 1 to day 5 average score: 1.7 (0.5*) Day 1 to day 10 average score: 1.6 (0.5*)	Day 5: 56.7 (16.7*) Day 10: 53.3 (16.7*)	109
Silverfield 2002 [25]	1) Tramadol/paracetamol 2) 225mg 3) 22.5 MME NOT STATED - allowed range is from 150-300mg tramadol + 1300-2600mg paracetamol (can assume midpoint of 225mg tramadol)	WOMAC pain subscale (0-10) at day 10	Baseline: 6.0 (1.5) Day 10: 3.4 (1.8)	34.1 (18.2)	192	Baseline: 6.0 (1.4) Day 10: 4.0 (1.9)	40.0 (19.1)	110
Babul 2004 [26] ***baseline SD used**	1) Tramadol ER oral 2) 276 (NS)mg 3) 27.6 MME	VAS (0-100) Average Pain Intensity LSM change from baseline	Week 1: -19.6 (10.0*) Week 4: -31.9 (10.0*) Week 12: -37.4 (10.0*)	Week 1: -19.6 (10.0*) Week 4: -31.9 (10.0*) Week 12: -37.4 (10.0*)	124	Week 1: -11.1 (16.5*) Week 4: -18.2 (16.5*) Week 12: -22.1 (16.5*)	Week 1: -11.1 (16.5*) Week 4: -18.2 (16.5*) Week 12: -22.1 (16.5*)	122
Emkey 2004 [27]	1) Tramadol/paracetamol IR oral 2) 154mg+1332mg 3) 15.4 MME	VAS (0-100) mean score	Baseline: 69.0 (12.5) Final: 41.5 (26.00)	41.5 (26.0)	153	Baseline: 69.5 (13.2) Final: 48.3 (26.6)	48.3 (26.7)	153

Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Malonne 2004 [28]	1) Tramadol ER 200mg 2) 200mg 3) 20	VAS (0-100) mean score	Baseline: 59.9 (13.9) Day 7: 41.2 (19.9) Day 14: 35.6 (19.0)	Week 1: 41.2 (19.9) Week 2: 35.6 (19.0)	85	Baseline: 59.4 (13.7) Day 7: 52.2 (20.5) Day 14: 43.9 (22.4)	Week 1: 52.2 (20.5) Week 2: 43.9 (22.4)	112
Chindalore 2005 [29]	1) Oxycodone QID 2) 28.8 (0)mg 3) 43.1 MME	NRS (0-10) mean score	Baseline: 7.4 (1.3) Week 1: 6.1 (2.2) Week 2: 5.8 (2.3) Week 3: 5.6 (2.3)	Week 1: 61 (22) Week 3: 56 (23)	102	Baseline: 7.7 (1.3) Week 1: 6.5 (2.1) Week 2: 6.2 (2.5) Week 3: 6.1 (2.8)	Week 1: 65 (21) Week 3: 61 (28)	51
Chindalore 2005 [29]	1) Oxycodone + naltrexone QID 2) 28.8 (0)mg 3) 43.1 MME	NRS (0-10) mean score	Baseline: 7.7 (1.4) Week 1: 6.3 (2.1) Week 2: 6.0 (2.2) Week 3: 5.7 (2.4)	Week 1: 63 (21) Week 3: 57 (24)	104	Baseline: 7.7 (1.3) Week 1: 6.5 (2.1) Week 2: 6.2 (2.5) Week 3: 6.1 (2.8)	Week 1: 65 (21) Week 3: 61 (28)	51
Chindalore 2005 [29]	1) Oxycodone + naltrexone BD 2) 28.8 (0)mg 3) 43.1 MME	NRS (0-10) mean score	Baseline: 7.6 (1.4) Week 1: 5.5 (2.1) Week 2: 5.0 (2.2) Week 3: 4.5 (2.4)	Week 1: 55 (21) Week 3: 45 (24)	103	Baseline: 7.7 (1.3) Week 1: 6.5 (2.1) Week 2: 6.2 (2.5) Week 3: 6.1 (2.8)	Week 1: 65 (21) Week 3: 61 (28)	51

Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Markenson 2005 [30]	1) Oxycodone CR 10-60mg q12h 2) 57+44 / 2 =50.5mg 3) 75.8 MME	BPI (0-10) average pain intensity LSM score at final visit	Baseline: 6.9 (SE 0.2) Day ≤15*: 5.1 (SE 0.3, SD=2.2) Day 90: 4.9 (SE 0.3, SD=2.2) *after stable dosing or day 15, whichever occurred first	Day ≤15*: 51 (SE 3, SD=22) Day 90: 49 (SE 3, SD=22)	56	Baseline: 6.3 (SE 0.2) Day ≤15*: 6.0 (SE 0.3, SD=2.1) Day 90: 6.0 (SE 0.4, SD=2.9) *after stable dosing or day 15, whichever occurred first	Day ≤15*: 60 (SE 3, SD=21) Day 90: 60 (SE 4, SD=29)	51
Matsumoto 2005 [31]	1) Oxymorphone ER 40mg BD 2) 60mg 3) 180 MME	VAS (0-100) LSM change from baseline to week 3 estimated from Fig 1	-26 (NS)	-26 (29.7*)	114	-17 (NS)	-17 (26.9*)	119
Matsumoto 2005 [31]	1) Oxymorphone ER 40mg BD 2) 60mg 3) 180 MME	WOMAC pain subscale (0-500) change from baseline to week 4 estimated from Fig 3	-116.5 (SE 8.2, SD=87.6)	-23.3 (SE 1.6, SD=17.5)	114	-58.6 (SE 8.2, SD=89.5)	-11.7 (SE 1.6, SD=17.9)	119

Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Matsumoto 2005 [31]	1) Oxymorphone ER 20mg BD 2) 40mg 3) 120 MME	VAS (0-100) LSM change from baseline to week 3 estimated from Fig 1	-24.7 (NS)	-24.7 (28.4*) *value taken from patient diary	114	-17 (NS)	-17 (26.9*) *value taken from patient diary	119
Matsumoto 2005 [31]	1) Oxymorphone ER 20mg BD 2) 40mg 3) 120 MME	WOMAC pain subscale (0-500) change from baseline to week 4 estimated from Fig 3	-101.2 (SE 8.2, SD=87.6)	-20.2 (SE 1.6, SD=17.5)	114	-58.6 (SE 8.2, SD=89.5)	-11.7 (SE 1.6, SD=17.9)	119
Matsumoto 2005 [31] ***SD taken from trial by Spierings as it evaluated the same drug, same time frame and had similar sample size**	1) Oxycodone CR 20mg BD 2) (20*2 + 10*2)/2 = 30mg 3) 45 MME "Patients randomized to oxycodone CR 20mg received oxycodone CR 10mg every 12 hours during weeks 1 and 2 and oxycodone CR 20mg every 12 hours during weeks 3 and 4."	VAS (0-100) LSM change from baseline to week 3 estimated from Fig 1	-22 (NS)	-22 (21*)	120	-17 (26.9)	-17 (26.9*)	119

Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Matsumoto 2005 [31]	1) Oxycodone CR 20mg BD 2) (20*2 + 10*2)/2 = 30mg 3) 45 MME "Patients randomized to oxycodone CR 20mg received oxycodone CR 10mg every 12 hours during weeks 1 and 2 and oxycodone CR 20mg every 12 hours during weeks 3 and 4."	WOMAC pain subscale (0-500) change from baseline to week 4 estimated from Fig 3	-87.6 (SE 8.2, SD=89.8)	-17.5 (SE 1.6, SD=18.0)	120	-58.6 (SE 8.2, SD=89.5)	-11.7 (SE 1.6, SD=17.9)	119
Gana 2006 [32]	1) Tramadol ER 100mg oral 2) 100mg 3) 10 MME	VAS (0-100) LSM change in pain intensity in index joint from baseline to week 12	-27.8 (SE 2.1, SD=29.9)	-27.8 (SE 2.1, SD=29.9)	202	-20.2 (SE 2.0, SD=28.6)	-20.2 (SE 2.0, SD=28.6)	205
Gana 2006 [32]	1) Tramadol ER 100mg oral 2) 100mg 3) 10 MME	WOMAC pain subscale (0-500) LSM change from baseline	Week 1: -56.9 (SE 7.3, SD=103.8) Week 3: -85.9 (SE 8.0, SD=113.7) Week 12: -107.2 (SE 8.6, SD=122.2)	Week 1: -11.4 (SD= 20.8) Week 3: -17.2 (SD =22.7) Week 12: -21.4 (SD= 21.4)	202	Week 1: -42.0 (SE 7.2, SD=103.1) Week 3: -68.6 (SE 7.9, SD=113.1) Week 12: -74.2 (SE 8.5, SD=117.4)	Week 1: -8.4 (SE 1.4, SD=20.6) Week 3: -13.7 (SE 1.6, SD=22.6) Week 12: -14.8 (SE 1.6, SD=24.34)	205
Gana 2006 [32]	1) Tramadol ER 200mg oral 2) 200mg 3) 20 MME	VAS (0-100) LSM change in pain intensity in index joint from baseline to week 12	-29.9 (SE 2.1, SD=29.8)	-29.9 (SE 2.1, SD=29.8)	201	-20.2 (SE 2.0, SD=28.6)	-20.2 (SE 2.0, SD=28.6)	205

Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Gana 2006 [32]	1) Tramadol ER 200mg oral 2) 200mg 3) 20 MME	WOMAC pain subscale (0-500) LSM change from baseline	Week 1: -63.7 (SE 7.4, SD=104.9) Week 3: -100.2 (SE 8.1, SD=114.8) Week 12: -111.5 (SE 8.7, SD=123.3)	Week 1: -12.7 (SE 1.5, SD=21.0) Week 3: -20.0 (SE 1.6, SD=23.0) Week 12: -22.3 (SE 1.7, SD=24.7)	201	Week 1: -42.0 (SE 7.2, SD=103.1) Week 3: -68.6 (SE 7.9, SD=113.1) Week 12: -74.2 (SE 8.5, SD=117.4)	Week 1: -8.4 (SE 1.4, SD=20.6) Week 3: -13.7 (SE 1.6, SD=22.6) Week 12: -14.8 (SE 1.6, SD=24.3)	205
Gana 2006 [32]	1) Tramadol ER 300mg oral 2) 300mg 3) 30 MME	VAS (0-100) LSM change in pain intensity in index joint from baseline to week 12	-30.2 (SE 2.1, SD=29.8)	-30.2 (SE 2.1, SD=29.8)	201	-20.2 (SE 2.0, SD=28.6)	-20.2 (SE 2.0, SD=28.6)	205
Gana 2006 [32]	1) Tramadol ER 300mg oral 2) 300mg 3) 30 MME	WOMAC pain subscale (0-500) LSM change from baseline	Week 1: -69.9 (SE 7.4, SD=104.9) Week 3: -100.6 (SE 8.1, SD=114.8) Week 12: -103.9 (SE 8.7, SD=123.3)	Week 1: -14.0 (SE 1.5, SD=20.1) Week 3: -20.1 (SE 1.6, SD=23.0) Week 12: -20.8 (SE 1.7, SD=24.7)	201	Week 1: -42.0 (SE 7.2, SD=103.1) Week 3: -68.6 (SE 7.9, SD=113.1) Week 12: -74.2 (SE 8.5, SD=117.4)	Week 1: -8.4 (SE 1.4, SD=20.6) Week 3: -13.7 (SE 1.6, SD=22.6) Week 12: -14.8 (SE 1.6, SD=24.3)	205
Gana 2006 [32]	1) Tramadol ER 400mg oral 2) 400mg 3) 40 MME	VAS (0-100) LSM change in pain intensity in index joint from baseline to week 12	-28.0 (SE 2.1, SD=29.9)	-28.0 (SE 2.1, SD=29.9)	202	-20.2 (SE 2.0, SD=28.6)	-20.2 (SE 2.0, SD=28.6)	205

Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Gana 2006 [32]	1) Tramadol ER 400mg oral 2) 400mg 3) 40 MME	WOMAC pain subscale (0-500) LSM change from baseline	Week 1: -64.1 (SE 7.4) Week 3: -103.1 (SE 8.1) Week 12: -107.8 (SE 8.7)	Week 1: -12.8 (SE 1.5, SD=21.0) Week 3: -20.6 (SE 1.6, SD=23.0) Week 12: -21.6 (SE 1.7, SD=24.7)	202	Week 1: -42.0 (SE 7.2, SD=103.1) Week 3: -68.6 (SE 7.9, SD=113.1) Week 12: -74.2 (SE 8.5, SD=117.4)	Week 1: -8.4 (SE 1.4, SD=20.6) Week 3: -13.7 (SE 1.6, SD=22.6) Week 12: -14.8 (SE 1.6, SD=24.3)	205
Kivitz 2006 [33]	1) Oxymorphone ER 20mg 2) 20mg 3) 60 MME Oxymorphone 10mg bd for 2 weeks	VAS (0-100) LSM change from baseline to week 2 estimated from Fig 2	-21 (SE 2.6, SD=24.9) All SE calculated from figure 2	-21 (SE 2.6, SD=24.9)	92	-17 (SE 2.9, SD=27.1)	-17 (SE 2.9, SD=27.1)	87
Kivitz 2006 [33]	1) Oxymorphone ER 80mg 2) 60mg 3) 180 MME Oxymorphone 20mg bd for first week then 40mg bd for second week	VAS (0-100) LSM change from baseline to week 2 estimated from Fig 2	-28 (SE 2.9, SD=27.7)	-28 (SE 2.9, SD=27.7)	91	-17 (SE 2.9, SD=27.1)	-17 (SE 2.9, SD=27.1)	87
Kivitz 2006 [33]	1) Oxymorphone ER 100mg 2) 70mg 3) 210 MME Oxymorphone 20mg bd for first week followed by 50mg bd for second week	VAS (0-100) LSM change from baseline to week 2 estimated from Fig 2	-29 (SE 2.9, SD=27.1)	-29 (SE 2.9, SD=27.1)	87	-17 (SE 2.9, SD=27.1)	-17 (SE 2.9, SD=27.1)	87

Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Langford 2006 [34]	1) Transdermal fentanyl patch 25µg/hour patch 2) 42.5µg/hour 3) 102 MME Median number of patches was 1.7 at 25µg/hour	VAS (0-100) mean change from baseline estimated from Figure 2	Baseline score: 73.1 Week 1: -13.4 (SE 2.4, SD=34.1) Week 4: -27.7 (SE 4.2, SD=48.3) Week 6: -33.5 (SE 4.9, SD=51.6) Final visit*: -23.6 (SE 1.8, SD=25.6) *After study medication was washed out	Week 1: -13.4 (SE 2.4, SD=34.1) Week 4: -27.7 (SE 4.2, SD=48.3) Week 6: -33.5 (SE 4.9, SD=51.6)	Baseline: 202 Week 1: 202 Week 4: 132 Week 6: 111 Final visit: 202 (LOCF)	Baseline: 73.3 Week 1: -7.3 (SE 2.2, SD=30.9) Week 4: -24.6 (SE 4.8, SD=51.3) Week 6: -32.4 (SE 5.8, SD=56.5) Final visit*: -17.9 (SE 1.9, SD=27.0) *After study medication was washed out	Week 1: -7.3 (SE 2.2, SD=30.9) Week 4: -24.6 (SE 4.8, SD=51.3) Week 6: -32.4 (SE 5.8, SD=56.5)	Baseline: 197 Week 1: 197 Week 4: 114 Week 6: 95 Final visit: 197 (LOCF)
NCT00313846 2006 [35]	1) Buprenorphine transdermal patch 5-20µg/hour 2) NOT STATED, estimated at 10µg/hour 3) 18 MME	NRS (0-10) daily maximum 'pain right now' score in the last 7 days of treatment	3.2 (SE 0.1 SD=1.8)	32 (SE 1.4 SD=17.9)	164	3.8 (SE 0.2 SD=1.9)	38 (SE 1.5 SD=19.1)	162
NCT00531427 2007 [36]	1) Buprenorphine transdermal patch 10-20µg/hour 2) NOT STATED- estimated at 15µg/hour 3) 27 MME	24-hr pain (NRS, 0-10) mean score	3.8 (2.6)	38.2 (26.4)	283	4.2 (2.6)	42.2 (26.4)	287

Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Burch 2007 [37]	1) Tramadol IR+ER oral 2) 275.4 (SD)mg 3) 27.5 MME	NRS (0-10) mean change from baseline to week 12	Baseline: 7.2 (1.6) Mean change from baseline: -3.0 (2.1)	-30.3 (21.2)	393	Baseline: 7.2 (1.6) Mean change from baseline:-2.3 (2.0)	-22.9 (19.7)	196
Fishman 2007 [38]	1) Tramadol Contramid OAD 100mg 2) 100mg 3) 10 MME	WOMAC pain score (%) Mean change from baseline	-41.6 (50.2)	-41.6 (50.2)	103	-32.3 (48.2)	-32.3 (48.2)	224
Fishman 2007 [38]	1) Tramadol Contramid OAD 200mg 2) 200mg 3) 20 MME	WOMAC pain subscale (%) Mean change from baseline	42.8 (46.4)	-42.8 (46.4)	107	-32.3 (48.2)	-32.3 (48.2)	224
Fishman 2007 [38]	1) Tramadol Contramid OAD 300mg 2) 300mg 3) 30 MME	WOMAC pain subscale (%) Mean change from baseline	46.0 (39.9)	-46.0 (39.9	105	-32.3 (48.2)	-32.3 (48.2)	224
NCT00832416 2009 [40]	1) Tramadol 100mg 2) 100mg 3) 10 MME	WOMAC pain subscale (0-100) Mean change from baseline to week 12	-36.3 (45.3)	-36.3 (45.3)	109	-38.0 (41.7)	-38.0 (41.7)	226
NCT00832416 2009 [40]	1) Tramadol 200mg 2) 200mg 3) 20 MME	WOMAC pain subscale (0-100) Mean change from baseline to week 12	-36.6 (40.9)	-36.6 (40.9)	110	-38.0 (41.7)	-38.0 (41.7)	226

Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
NCT00832416 2009 [40]	1) Tramadol 300mg 2) 300mg 3) 30 MME	WOMAC pain subscale (0-100) Mean change from baseline to week 12	-41.0 (44.5)	-41.0 (44.5)	113	-38.0 (41.7)	-38.0 (41.7)	226
NCT00979953 2009 [41]	1) Oxycodone CR 2) Oxycodone 10mg bd for 1-4 days then 20mg bd for days 5-14 =34.28mg 3) 51.42 MME	NRS (0-10) mean change from baseline to week 2	-2.24 (2.16)	-22.4 (21.6)	100	-2.20 (2.09)	-22.0 (20.9)	103
Afilalo 2010 [42]	1) Tapentadol ER oral 2) 299.3 (107.16)mg 3) 119.72 MME	NRS (0-10) score at end of maintenance period estimated from Fig. 2	Mean (SE) Week 1: 6.4 (0.08) Week 4: 4.65 (0.15) Week 12: 4.4 (0.16)	Week 1: 64 (14.8) Week 4: 46.5 (27.8) Week 12: 44 (29.7)	344	Mean (SE) Week 1: 6.5 (0.08) Week 4: 5.25 (0.1) Week 12: 5.0 (0.16)	Week 1: 65 (14.7) Week 4: 52.5 (18.4) Week 12: 50 (29.4)	337
Afilalo 2010 [42]	1) Oxycodone CR oral 2) 48.2 (23.94)mg 3) 72.3 MME	NRS (0-10) score at end of maintenance period estimated from Fig. 2	Mean (SE) Week 1: 5.9 (0.09) Week 4: 4.8 (0.12) Week 15: 4.7 (0.16)	Week 1: 59 (16.6) Week 4: 48 (22.2) Week 15: 47 (29.6)	342	Mean (SE) Week 1: 6.5 (0.08) Week 4: 5.25 (0.1) Week 15: 5.05 (0.16)	Week 1: 65 (14.7) Week 4: 52.5 (18.4) Week 15: 50.5 (29.4)	337
Breivik 2010 [43]	1) Buprenorphine patch 2) 11 (5.7)µg/hour 3) 19.8 MME	NRS (0-10) pain on movement end of treatment score	Baseline: 4.8 (1.5) EOT: 3.9 (1.8)	39 (18)	86	Baseline: 4.9 (1.5) EOT: 4.4 (2.0)	44 (20)	91

Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Breivik 2010 [43]	1) Buprenorphine patch 2) 11 (5.7)µg/hour 3) 19.8 MME	WOMAC pain subscale (0-20) end of treatment score	Baseline: 10.8 (2.6) EOT: 7.5 (3.6)	37.5 (18)	95	Baseline: 10.6 (2.8) EOT: 8.3 (3.5)	41.5 (17.5)	99
Katz 2010 [44]	1) Morphine sulfate + naltrexone hydrochloride ER 2) 43.5 (31.7)mg 3) 43.5 MME	NRS (0-10) in-clinic pain score (table 5)	Baseline: 2.8 (1.4) Week 12: 3.5 (2.2) Change: 0.7 (2.3)	Final score: 35 (22) Change score: 7 (23)	171	Baseline: 2.8 (1.5) Week 12: 4.3 (2.5) Change: 1.5 (2.3)	Final score: 43 (25) Change score: 15 (23)	173
Munera 2010 [45]	1) Buprenorphine patch 2) 15.1µg/hour 3) 27.18 MME	NRS (0-10) change from baseline to week 4	Week 4: -1.84 (SE 0.22, SD=2.69)	-18.4 (26.9)	149	Week 4: -1.40 (SE 0.21, SD=2.67)	-14.0 (26.7)	162
DeLemos 2011 [46] ***Baseline SD used**	1) Tramadol ER 100mg oral 2) 100mg 3) 10 MME	VAS (0-100) LS mean change from baseline to week 12 (daily arthritis pain intensity)	-16.7 (SE 1.8, SD=18.0)	-16.7 (SE 1.8, SD=18.0)	201	-16.5 (SE 1.9, SD=19.0)	-16.5 (SE 1.9, SD=19.0)	200

Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
DeLemos 2011 [46] ***Baseline SD used**	1) Tramadol ER 100mg oral 2) 100mg 3) 10 MME	WOMAC pain subscale scores (0-500) estimated from Fig 2A	Baseline: 298.4 (101.3) Week 1: 234.2 (101.3*) Week 4: 180.3 (101.3*) Week 12: 167.1 (101.3*)	Week 1: 46.8 (20.3*) Week 4: 36.1 (20.3*) Week 12: 33.4 (20.3*)	201	Baseline: 300.8 (103.5) Week 1: 232.9 (103.5*) Week 4: 192.5 (103.5*) Week 12: 163.2 (103.5*)	Week 1: 46.6 (20.7*) Week 4: 38.5 (20.7*) Week 12: 32.6 (20.7*)	200
DeLemos 2011 [46] ***Baseline SD used**	1) Tramadol ER 200mg oral 2) 200mg 3) 20 MME	VAS (0-100) LS mean change from baseline to week 12 (daily arthritis pain intensity)	-21.6 (SE 1.8, SD=18.0)	-21.6 (SE 1.8, SD=18.0)	199	-16.5 (SE 1.9, SD=19.0)	-16.5 (SE 1.9, SD=19.0)	200
DeLemos 2011 [46] ***Baseline SD used**	1) Tramadol ER 200mg oral 2) 200mg 3) 20 MME	WOMAC pain subscale scores (0-500) estimated from Figure 2A	Baseline: 302.9 (96.1) Week 1: 216.7 (96.1*) Week 4: 180.8 (96.1*) Week 12: 161.8 (96.1*)	Week 1: 43.3 (19.2*) Week 4: 36.2 (19.2*) Week 12: 32.4 (19.2*)	199	Baseline: 300.8 (103.5) Week 1: 232.9 (103.5*) Week 4: 192.5 (103.5*) Week 12: 163.2 (103.5*)	Week 1: 46.6 (20.7*) Week 4: 38.5 (20.7*) Week 12: 32.6 (20.7*)	200

Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
DeLemos 2011 [46] ***Baseline SD used**	1) Tramadol ER 300mg oral 2) 300mg 3) 30 MME	VAS (0-100) LS mean change from baseline to week 12 (daily arthritis pain intensity)	-25.7 (SE 1.8, SD=18.0)	-25.7 (SE 1.8, SD=18.0)	199	-16.5 (SE 1.9, SD=19.0)	-16.5 (SE 1.9, SD=19.0)	200
DeLemos 2011 [46] ***Baseline SD used**	1) Tramadol ER 300mg oral 2) 300mg 3) 30 MME	WOMAC pain subscale scores (0-500) estimated from Fig 2A	Baseline: 306.2 (107.3) Week 1: 216.7 (107.3*) Week 4: 156.1 (107.3*) Week 12: 137.7 (107.3*)	Week 1: 43.3 (21.5*) Week 4: 31.2 (21.5*) Week 12: 27.5 (21.5*)	199	Baseline: 300.8 (103.5) Week 1: 232.9 (103.5*) Week 4: 192.5 (103.5*) Week 12: 163.2 (103.5*)	Week 1: 46.6 (20.7*) Week 4: 38.5 (20.7*) Week 12: 32.6 (20.7*)	200
Vojtassak 2011 [48]	1) OROS hydromorphone ER 2) 12.2mg 3) 48.8 MME MEDIAN = 12.2mg (range 3-28) (estimated SD=6.25)	BPI (0-10) pain on average - DATA FROM CLINICAL TRIAL NCT00980798	Baseline: 6.6 (1.04) Week 1: 5.0 (1.63) Week 2: 4.6 (1.66) Week 4: 3.9 (2.02) Week 12: 3.4 (1.96) Week 16: 4.1 (2.2)	Week 1: 50 (16.3) Week 4: 39 (20.2) Week 12: 34 (19.6) Week 16: 41 (22.0)	132	Baseline: 6.5 (0.94) Week 1: 5.2 (1.43) Week 2: 4.8 (1.66) Week 4: 3.9 (1.9) Week 12: 3.6 (1.99) Week 16: 4.0 (2.3)	Week 1: 52 (14.3) Week 4: 39 (19.0) Week 12: 36 (19.9) Week 16: 40 (23.0)	143

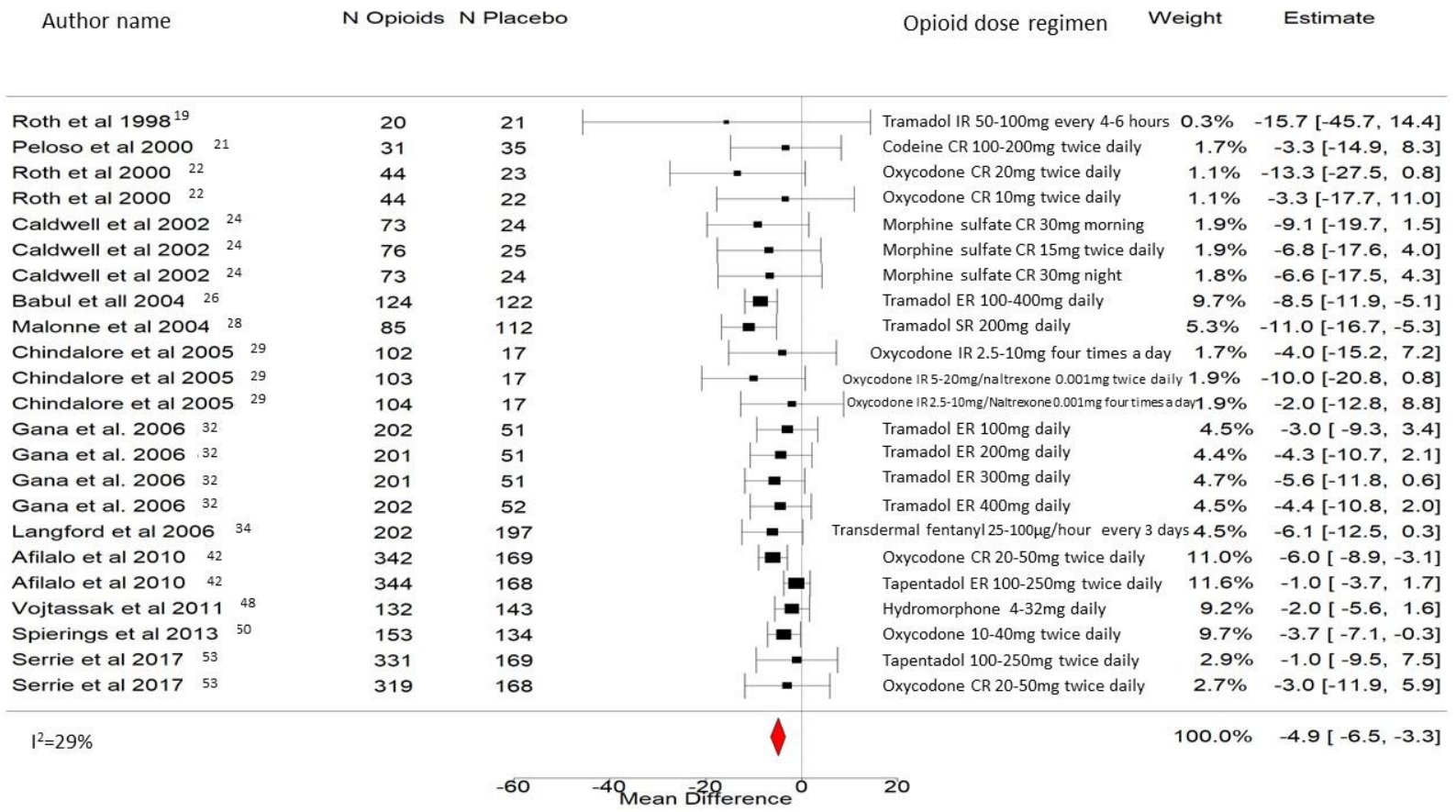
Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Rauck 2013 [49]	1) OROS hydromorphone ER 8mg 2) 8mg 3) 32 MME	NRS (0-10) LS mean change from baseline to week 12	-2.0 (SE 0.2, SD=2.9)	-20 (SE 1.6, SD=28.6)	319	-1.9 (SE 0.2, SD=2.9)	-19 (SE 1.6, SD=29.1)	331
Rauck 2013 [49]	1) OROS hydromorphone ER 16mg 2) 16mg 3) 64 MME	NRS (0-10) LS mean change from baseline to week 12	-2.5 (SE 0.2, SD=2.9)	-25 (SE 1.6, SD=29.1)	330	-1.9 (SE 0.2, SD=2.9)	-19 (SE 1.6, SD=29.1)	331
Spierings 2013 [50]	1) Oxycodone CR 2) 23mg 3) 34.5 MME	WOMAC pain subscale (0-10) LSM change from baseline. Data taken from clinical trial register EUCTR2009-013329-41-SE (table 10)	Baseline: 7.9 (1.3) Week 2: -5.8 (2.4) Week 4: -5.4 (2.4) Week 8: -5.5 (2.4) Week 12: -5.3 (2.5) Week 16: -5.3 (2.5)	Week 2: -57.8 (23.7) Week 4: -53.8 (24.3) Week 12: -52.9 (24.7) Week 16: -52.9 (24.6)	156	Baseline: 7.8 (1.2) Week 2: -5.8 (2.2) Week 4: -5.4 (2.3) Week 8: -5.2 (2.4) Week 12: -5.1 (2.4) Week 16: -4.9 (2.5)	Week 2: -57.7 (21.9) Week 4: -53.8 (23.1) Week 12: -50.6 (24.4) Week 16: -49.0 (25.2)	137

Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Spierings 2013 [50]	1) Oxycodone CR 2) 23mg 3) 34.5 MME	NRS (0-10) change in average pain score in index joint. Data taken from clinical trial register EUCTR2009-013329-41-SE (table 23)	Baseline score: 7.1 (1.7) Week 1: -1.2 (1.6) Week 2: -1.5 (2.0) Week 4: -1.7 (2.1) Week 12: -1.8 (2.3) Week 16: -1.8 (2.2)	Week 1: -11.6 (16.4) Week 2: -14.6 (19.6) Week 4: -17.0 (21.0) Week 12: -18.3 (22.7) Week 16: -18.4 (22.3)	153	Baseline score: 7.2 (1.8) Week 1: -0.80 (1.2) Week 2: -1.2 (1.6) Week 4: -1.6 (1.9) Week 12: -2.0 (2.3) Week 16: -2.0 (2.3)	Week 1: -7.9 (12.4) Week 4: -16.3 (18.5) Week 12: -19.6 (22.7) Week 16: -19.6 (23.1)	134
Mayorga 2016 [51]	1) Oxycodone CR 20-50mg BD 2) 70mg 3) 105 MME	NRS (0-10) average OA pain over past 12h, LS mean change from baseline (including 4 weeks of titration)	Week 12: -1.5 (SE 0.4, SD=2.5) Week 16: -1.5 (SE 0.4, SD=2.6)	Week 12: -15.2 (24.7)	50	Week 12: -3.0 (SE 0.4, SD=2.5) Week 16: -2.9 (SE 0.4, SD=2.6)	Week 12: -29.5 (24.9)	48
Tominaga 2016 [52]	1) Tapentadol ER 2) 237.1 (123.63)mg 3) 94.84 MME	NRS (0-10) pain scores for OA population only	Baseline: 6.7 (1.34) Final: 3.8 (2.36) Mean change: -3.0 (1.85)	Week 12: 38 (23.6) Change: -30 (18.5)	27	Baseline: 6.9 (1.17) Final: 3.9 (2.83) Mean change: -3.2 (2.30)	Week 12: 39 (28·3) Change: -32 (23.0)	13

Study	1) Opioid name, formulation, route 2) Mean daily dose (MDD) (SD) reported 3) Morphine Milligram Equivalent dose (MME)	Outcome measure (yellow = change score)	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Serrie 2017 [53]	1) Tapentadol PR 2) 315.2 (108)mg 3) 126.1 MME	NRS (0-10) mean scores estimated from Fig 3	Baseline: 5.4 (SE 0.3, SD=4.82) Week 1: 5.1 (SE 0.3, SD=4.8) Week 4: 4.8 (SE 0.3, SD=4.8) Week 12: 4.5 (SE 0.3, SD=4.8)	Week 1: 51 (SE 2.7, SD=48.2) Week 4: 48 (SE 2.7, SD=48.2) Week 12: 45 (SE 2.7, SD=48.2)	From graph: 319 Week 1: 233 Week 4: 211 Week 12: 100	Baseline: 5.6 (SE 0.3, SD=4.6) Week 1: 5.4 (SE 0.3, SD=4.6) Week 4: 5.2 (SE 0.3, SD=4.6) Week 12: 4.8 (SE 0.3, SD=4.6)	Week 1: 54 (SE 2.5, SD=45.9) Week 4: 52 (SE 2.5, SD=45.9) Week 12: 48 (SE 25, SD=45.9)	From graph: 337 Week 1: 276 Week 4: 246 Week 12: 136
Serrie 2017 [53]	1) Oxycodone CR 2) 54.1 (18.2)mg 3) 81.2 MME	NRS (0-10) mean scores estimated from Fig 3	Baseline: 5.4 (SE 0.3=4.6) Week 1: 5.3 (SE 0.3, SD=4.6) Week 4: 5.2 (SE 0.3, SD=4.6) Week 12: 5.0 (SE 0.3, SD=4.6)	Week 1: 53 (SE 2.5, SD=45.5) Week 4: 52 (SE 2.5, SD=45.5) Week 12: 50 (SE 2.5, SD=45.5)	From graph: 331 Week 1: 176 Week 4: 151 Week 12: 73	Baseline: 5.6 (SE 0.3, SD=4.6) Week 1: 5.4 (SE 0.3, SD=4.6) Week 4: 5.2 (SE 0.3, SD=4.6) Week 12: 4.8 (SE 0.3, SD=4.6)	Week 1: 54 (SE 2.5, SD=45.9) Week 4: 52 (SE 2.5, SD=45.9) Week 12: 48 (SE 2.5, SD=45.9)	From graph: 337 Week 1: 276 Week 4: 246 Week 12: 136

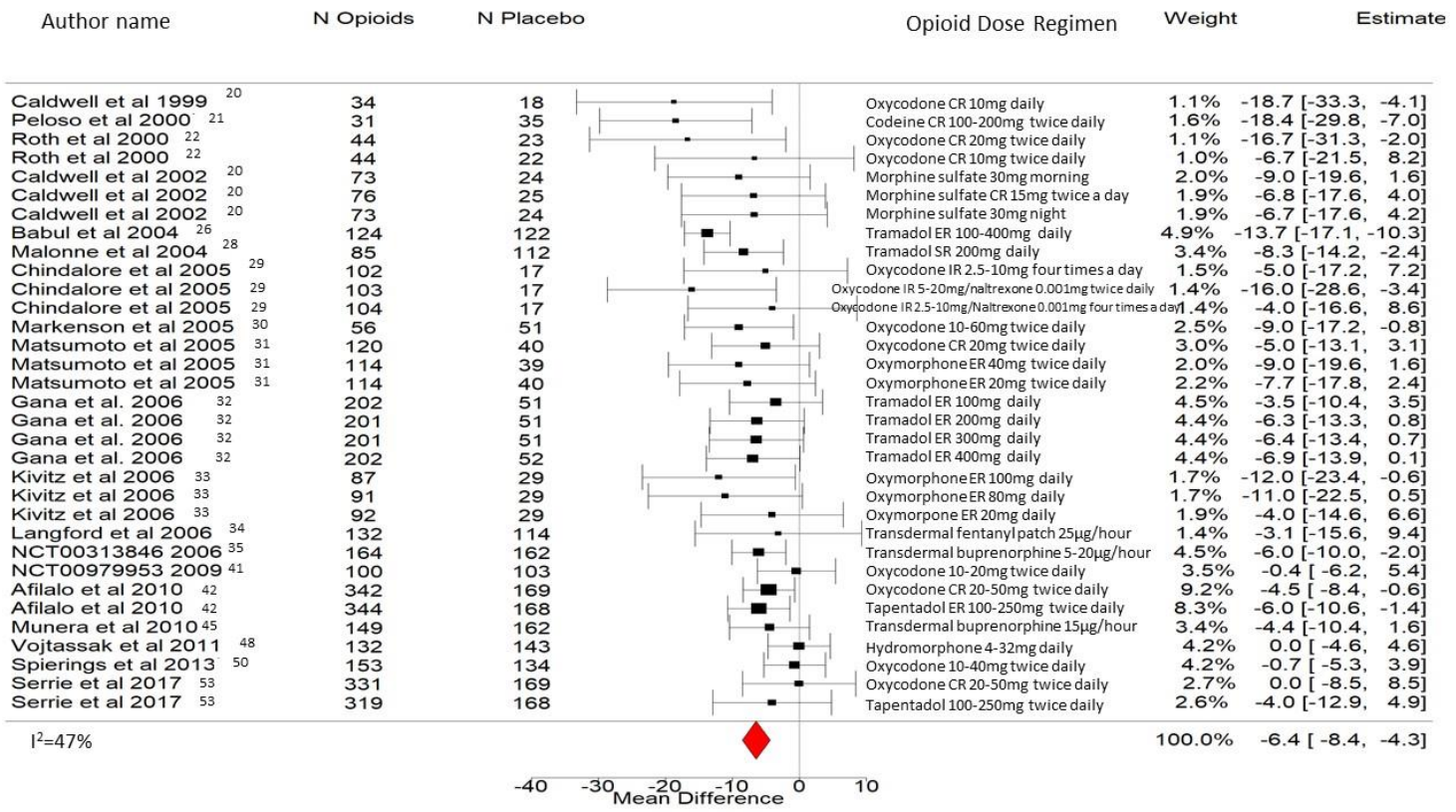
WOMAC= Western Ontario and McMaster Universities Arthritis Index; CR=controlled release, mg=milligram; OROS=osmotic release oral system; ER=extended release; BD=twice daily; SE=standard error; SD=standard deviation; q12h=every 12 hours; LSM=least squares mean. Values are presented to 1 decimal place.

Figure 2. Effects of opioids on pain in the immediate term: estimated mean differences (MDs) with 95% confidence intervals (CIs)



IR=immediate release; CR=controlled release; ER=extended release.

Figure 3. Effects of opioids on pain in the short term: estimated mean differences (MDs) with 95% confidence intervals (CIs)



IR=immediate release; CR=controlled release; ER=extended release.

Table 10. Data extracted from included publications: disability outcomes (WOMAC physical function)

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Peloso 2000 [21]	1) Codeine CR 100-400mg 2) 318 (104)mg 3) 47.7 MME	WOMAC physical function score (0-1700) mean change from baseline to week 4	Baseline: 900.5 (357.3) Week 4: -456.2 (316.2) Mean change: -444.2 (400.8)	Week 4: -26.8 (18.6) Change: -26.1 (23.6)	31	Baseline: 844.9 (405.3) Week 4: -687.5 (415.5) Mean change: -143.5 (284.7)	Week 4: -40.4 (24.4) Change: -8.4 (16.7)	35
Fleischmann 2001 [23]	1) Tramadol IR 300mg oral 2) 300mg 3) 30 MME	WOMAC physical function (0-10) mean score at end of study	4.19 (2.1)	41.9 (20.6)	63	4.92 (2.3)	49.2 (22.9)	66
Caldwell 2002 [24]	1) QAM - Morphine sulfate ER (Avinza) 30mg morning 2) 30mg (0) 3) 30 MME	WOMAC physical function change from baseline (0-1700)	Week 1: -164 (SE 43.3, SD=370.0) Week 4: -207 (SE 40.7, SD=347.7)	Week 1: -9.6 (SE 2.6, SD= 21.8) Week 4: -12.2 (SE 2.4, SD=20.5)	73	Week 1: -44.1 (SE 35.7, SD=305.0) Week 4: -96.7 (SE 43.0, SD=367.4)	Week 1: -2.6 (SE 2.1, SD=17.9) Week 4: -5.7 (SE 2.5, SD=21.6)	73
Caldwell 2002 [24]	1) QPM - Morphine sulfate ER (Avinza) 30mg night 2) 30mg (0) 3) 30 MME	WOMAC physical function change from baseline (0-1700)	Week 1: -148 (SE 35.3, SD=301.6) Week 4: -204 (SE 42.6, SD=364.0)	Week 1: -8.7 (SE 2.1, SD=17.7) Week 4: -12.0 (SE 2.5, SD=21.4)	73	Week 1: -44.1 (SE 35.7, SD=305.0) Week 4: -96.7 (SE 43.0, SD=367.4)	Week 1: -2.6 (SE 2.1, SD=17.9) Week 4: -5.7 (SE 2.5, SD=21.6)	73
Caldwell 2002 [24]	1) Morphine sulfate CR (MS Contin) 15mg BD 2) 30mg (0) 3) 30 MME	WOMAC physical function change from baseline (0-1700)	Week 1: -146 (SE 33.0=287.7) Week 4: -181 (SE 40.1=349.6)	Week 1: -8.6 (SE 1.94, SD=16.9) Week 4: -10.6 (SE 2.4, SD=20.6)	76	Week 1: -44.1 (SE 35.7, SD=305.0) Week 4: -96.7 (SE 43.0, SD=367.4)	Week 1: -2.6 (SE 2.1, SD=17.9) Week 4: -5.7 (SE 2.5, SD=21.6)	73

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Silverfield 2002 [25]	1) Tramadol/paracetamol 2) 225mg 3) 22.5 MME NOT STATED - allowed range is from 150-300mg tramadol + 1300-2600mg paracetamol (can assume midpoint of 225mg tramadol)	WOMAC physical function score (0-10) mean score at day 10	Baseline: 6.0 (1.5) Day 10: 3.8 (1.8)	37.7 (17.6)	193	Baseline: 5.9 (1.5) Day 10: 4.2 (1.8)	41.6 (18.2)	109
Babul 2004 [26]	1) Tramadol ER oral 2) 276 (NS)mg 3) 27.6 MME	WOMAC physical function score (0-1700), LS mean change from baseline to week 12	-407 (NS)	-23.9 (24.1*) *SD taken from study by DeLemos[46]	124	208.5 (NS)	-12.3 (24.2*)	122
Emkey 2004 [27]	1) Tramadol/paracetamol IR oral 2) 154mg+1332mg 3) 15.4 MME	WOMAC physical function (0-10) mean score	Baseline: 5.6 (1.5) Final: 3.9 (1.8)	39 (18.4)	153	Baseline: 5.9 (1.5) Final: 4.5 (1.9)	45 (18.6)	153
Markenson 2005 [30]	1) Oxycodone CR 10-60mg q12h 2) 57+44 / 2 =50.5mg 3) 75.75 MME	WOMAC physical functioning LSM scores (0-100)	Day 30: 48.6 (SE 2.6, SD=19.5) Day 90: 46.1 (SE 2.6, SD=19.5)	Day 30: 48.6 (SE 2.6, SD=19.5) Day 90: 46.1 (SE 2.6, SD=19.5)	56	Day 30: 58.0 (SE 2.9, SD=20.7) Day 90: 59.1 (SE 2.9, SD=20.7)	Day 30: 58.0 (SE 2.9, SD=20.7) Day 90: 59.1 (SE 2.9, SD=20.7)	51

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Matsumoto 2005 [31]	1) Oxymorphone ER 40mg BD 2) 60mg 3) 180 MME *"To improve tolerability, patients randomized to the oxymorphone ER 40mg treatment group received oxymorphone ER 20mg every 12 hours during weeks 1 and 2 and oxymorphone ER 40mg every 12 hours during weeks 3 and 4" (40*2 + 20*2)/2= 60mg	WOMAC physical function score (0-1700) LSM change from baseline to week 4 estimated from Fig 3	-319.8 (SE 40.9, SD=436.7)	-18.8 (SE 2.4, SD=25.7)	114	-184.9 (SE 40.5, SD=441.7)	-10.9 (SE 2.4, SD=26.0)	119
Matsumoto 2005 [31]	1) Oxymorphone ER 20mg BD 2) 40mg 3) 120 MME "patients randomized to oxycodone CR 20mg received oxycodone CR 10mg every 12 hours during weeks 1 and 2 and oxycodone CR 20mg every 12 hours during weeks 3 and 4."	WOMAC physical function score (0-1700) LSM change from baseline to week 4 estimated from Fig 3	-294.5 (SE 40.9, SD=436.7)	-17.3 (SE 2.4, SD=25.7)	114	-184.9 (SE 40.5, SD=441.7)	-10.9 (SE 2.4, SD=26.0)	119

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Matsumoto 2005 [31]	1) Oxycodone CR 20mg BD 2) (20*2 + 10*2)/2 = 30mg 3) 45 MME "patients randomized to oxycodone CR 20mg received oxycodone CR 10mg every 12 hours during weeks 1 and 2 and oxycodone CR 20mg every 12 hours during weeks 3 and 4."	WOMAC physical function score (0-1700) LSM change from baseline to week 4 estimated from Fig 3	-229.9 (SE 40.5, SD=443.6)	-13.5 (SE 2.4, SD=26.1)	120	-184.9 (SE 40.5, SD=441.7)	-10.9 (SE 2.4, SD=26.0)	119
Gana 2006 [32]	1) Tramadol ER 100mg oral 2) 100mg 3) 10 MME	WOMAC physical function score (0-1700) LSM change from baseline	Week 1: -192.4 (SE 23.3, SD=331.2) Week 3: -272.4 (SE 27.0, SD=383.7) Week 12: -331.7 (SE 28.5, SD=405.1)	Week 1: -11.3 (SE 1.4, SD=19.5) Week 3: -16.0 (SE 1.6, SD=16.0) Week 12: -19.5 (SE 1.7, SD=16.9)	202	Week 1: -119.6 (SE 23.0, SD=329.3) Week 3: -211.7 (SE 26.6, SD=380.9) Week 12: -234.4 (SE 28.1, SD=402.3)	Week 1: -7.0 (SE 1.4, SD=19.4) Week 3: -12.5 (SE 1.6, SD=15.9) Week 12: -13.8 (SE 1.7, SD=16.8)	205

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Gana 2006 [32]	1) Tramadol ER 200mg oral 2) 200mg 3) 20 MME	WOMAC physical function score (0-1700) LSM change from baseline	Week 1: -206.8 (SE 23.7, SD=336.0) Week 3: -316.1 (SE 27.4, SD=388.5) Week 12: -350.2 (SE 29.0, SD=411.2)	Week 1: -12.2 (SE 1.4, SD=19.8) Week 3: -18.6 (SE 1.6, SD=16.2) Week 12: -20.6 (SE 1.7, SD=17.1)	201	Week 1: -119.6 (SE 23.0, SD=329.3) Week 3: -211.7 (SE 26.6, SD=380.9) Week 12: -234.4 (SE 28.1, SD=402.3)	Week 1: 7.0 (SE 1.4=19.4) Week 3: 12.5 (SE 1.6=15.9) Week 12: 13.8 (SE 1.7=16.8)	205
Gana 2006 [32]	1) Tramadol ER 300mg oral 2) 300mg 3) 30 MME	WOMAC physical function score (0-1700) LSM change from baseline	Week 1: -225.8 (SE 23.6, SD=334.6) Week 3: -327.9 (SE 27.3, SD=387.0) Week 12: -336.1 (SE 28.8, SD=408.3)	Week 1: -13.3 (SE 1.4, SD=19.7) Week 3: -19.3 (SE 1.6, SD=16.1) Week 12: -19.8 (SE 1.7, SD=17.0)	201	Week 1: -119.6 (SE 23.0, SD=329.3) Week 3: -211.7 (SE 26.6, SD=380.9) Week 12: -234.4 (SE 28.1, SD=402.3)	Week 1: 7.0 (SE 1.4, SD=19.4) Week 3: 12.5 (SE 1.6, SD=15.9) Week 12: 13.8 (SE 1.7, SD=16.8)	205
Gana 2006 [32]	1) Tramadol ER 400mg oral 2) 400mg 3) 40 MME	WOMAC physical function score (0-1700) LSM change from baseline	Week 1: -205.3 (SE 23.5, SD=334.0) Week 3: -326.0 (SE 27.3, SD=388.01) Week 12: -329.8 (SE 28.8, SD=409.32)	Week 1: -12.1 (SE 1.4, SD=19.6) Week 3: -19.2 (SE 1.6, SD=16.2) Week 12: -19.4 (SE 1.7, SD=17.1)	202	Week 1: -119.6 (SE 23.0, SD=329.3) Week 3: -211.7 (SE 26.6, SD=380.9) Week 12: -234.4 (SE 28.1, SD=402.3)	Week 1: 7.0 (SE 1.4, SD=19.4) Week 3: 12.5 (SE 1.6, SD=15.9) Week 12: 13.8 (SE 1.7, SD=16.8)	205

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Kivitz 2006 [33]	1) Oxymorphone ER 20mg 2) 20mg 3) 60 MME Oxymorphone 10mg bd for 2 weeks	WOMAC physical function score (0-1700) LSM change from baseline to week 2 estimated from Fig 4	-235.4 (SE 32.7, SD=313.7)	-13.8 (SE 1.9, SD=18.4)	92	-116.8 (SE 35.4, SD=330.19)	-6.9 (SE 2.1, SD=19.4)	87
Kivitz 2006 [33]	1) Oxymorphone ER 80mg 2) 60mg 3) 180 MME Oxymorphone 20mg bd for first week then 40mg bd for second week	WOMAC physical function score (0-1700) LSM change from baseline to week 2 estimated from Fig 4	-253.2 (SE 39.8, SD=379.7)	-14.9 (SE 2.3, SD=22.3)	91	-116.8 (SE 35.4, SD=330.19)	-6.9 (SE 2.1, SD=19.4)	87
Langford 2006 [34]	1) Transdermal fentanyl patch 25µg/hour patch 2) 42.5µg/hour 3) 102 MME Median number of patches was 1.7 at 25µg/hour	WOMAC physical functioning (0-10) mean change from baseline to final visit (after washout)	-1·1 (SE 0.1, SD=1.4)	-11 (SE 1, SD=14)	202	-0.7 (SE 0.1, SD=1.4)	-7.0 (SE 1.0, SD=14.0)	197
Fishman 2007 [38]	1) Tramadol Contramid 100mg 2) 100mg 3) 10 MME	WOMAC physical function score (%) median change from baseline to week 12	-48 (46.0)	-48 (46.0)	103	-27 (44.3)	-27 (44.3)	224
Fishman 2007 [38]	1) Tramadol Contramid 200 mg 2) 200mg 3) 20 MME	WOMAC physical function score (%) median change from baseline to week 12	-45 (39.3)	-45 (39.3)	107	-27 (44.3)	-27 (44.3)	224
Fishman 2007 [38]	1) Tramadol Contramid 300mg 2) 300mg 3) 30 MME	WOMAC physical function score (%) median change from baseline to week 12	-46 (41.7)	-46 (41.7)	105	-27 (44.3)	-27 (44.3)	224

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
NCT00832416 2009 [40]	1) Tramadol 100mg 2) 100mg 3) 10 MME	WOMAC physical function sub-scale (0-100), mean change from baseline to week 12	-31.9 (46.0)	-31.9 (46.0)	109	-33.7 (44.3)	-33.7 (44.3)	226
NCT00832416 2009 [40]	1) Tramadol 200mg 2) 200mg 3) 20 MME	WOMAC physical function sub-scale (0-100), mean change from baseline to week 12	-37.0 (39.3)	-37.0 (39.3)	110	-33.7 (44.3)	-33.7 (44.3)	226
NCT00832416 2009 [40]	1) Tramadol 300mg 2) 300mg 3) 30 MME	WOMAC physical function sub-scale (0-100), mean change from baseline to week 12	-37.3 (41.7)	-37.3 (41.7)	113	-33.7 (44.3)	-33.7 (44.3)	226
Afilalo 2010 [42]	1) Tapentadol ER oral 2) 299.3 (107.16)mg 3) 119.72 MME	WOMAC physical function score (0-4), LS mean change from baseline to week 12	-1.2 (SE 0.06, SD = 0.7)	-29 (16.8)	148	-0.8 (SE 0.06, SD = 0.7)	-22 (17.3)	158
Afilalo 2010 [42]	1) Oxycodone CR oral 2) 48.2 (23.94)mg 3) 72.3 MME	WOMAC physical function score (0-4), LS mean change from baseline to week 12	-1.1 (SE 0.07, SD = 0.7)	-26.3 (16.8)	92	-0.8 (SE 0.06, SD = 0.7)	-22 (17.3)	158
Breivik 2010 [43]	1) Buprenorphine patch 2) 11 (5.7) µg/hour 3) 19.8 MME	WOMAC physical function score (0-68), end of treatment scores	Baseline: 37.4 (9.0) EOT: 27.5 (12.4)	40.4 (18.2)	94	Baseline: 35.1 (9.8) EOT: 28.6 (11.7)	42.1 (17.2)	96
Katz 2010 [44]	1) Morphine sulfate + naltrexone hydrochloride ER 2) 43.5 (31.7)mg 3) 43.5 MME	WOMAC physical function score (0-100) mean scores	Baseline: 30.7 (16.3) Week 12: 32.9 (21.1) Change: 2.3 (18.4)	Final score: 32.9 (21.1) Change score: 2.3 (18.4)	171	Baseline: 29.3 (16.4) Week 12: 35.5 (19.8) Change: 6.2 (17.8)	Final score: 35.5 (19.8) Change score: 6.2 (17.8)	173

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
DeLemos 2011 [46]	1) Tramadol ER 100mg oral 2) 100mg 3) 10 MME	WOMAC physical function (0-1700) LSM change from baseline to week 12	-272.3 (SE 29.0, SD=411.2)	-16.0 (SE 1.7, SD=24.2)	201	-290.1 (SE 29.1, SD=411.5)	-17.1 (SE 1.7, SD=24.2)	200
DeLemos 2011 [46]	1) Tramadol ER 100mg oral 2) 100mg 3) 10 MME	WOMAC physical function (0-1700) estimated from Fig 2(b)	Baseline: 1034.0 (341.6) Week 1: 810.5 (341.6*) Week 4: 651.0 (341.6*) Week 12: 597.1 (341.6*)	Week 1: 47.7 (20.1*) Week 4: 38.3 (20.1*) Week 12: 35.1 (20.1*)	201	Baseline: 1019.0 (354.7) Week 1: 814.6 (354.7*) Week 4: 690.3 (354.7*) Week 12: 591.7 (354.7*)	Week 1: 47.9 (20.9*) Week 4: 40.6 (20.9*) Week 12: 34.8 (20.9*)	200
DeLemos 2011 [46]	1) Tramadol ER 200mg oral 2) 200mg 3) 20 MME	WOMAC physical function (0-1700) LSM change from baseline to week 12	-271 (SE 29.1, SD=410.5)	-15.9 (SE 1.71, SD=24.1)	199	-290.1 (SE 29.1, SD=411.5)	-17.1 (SE 1.7, SD=24.2)	200
DeLemos 2011 [46]	1) Tramadol ER 200mg oral 2) 200mg 3) 20 MME	WOMAC physical function (0-1700) estimated from Fig 2(b)	Baseline: 1045.1 (319.9) Week 1: 791.5 (319.9*) Week 4: 644.2 (319.9*) Week 12: 605.2 (319.9*)	Week 1: 46.6 (18.8*) Week 4: 37.9 (18.8*) Week 12: 35.6 (18.8*)	199	Baseline: 1019.0 (354.7) Week 1: 814.6 (354.7*) Week 4: 690.3 (354.7*) Week 12: 591.7 (354.7*)	Week 1: 47.9 (20.9*) Week 4: 40.6 (20.9*) Week 12: 34.8 (20.9*)	200
DeLemos 2011 [46]	1) Tramadol ER 300mg oral 2) 300mg 3) 30 MME	WOMAC physical function (0-1700) LSM change from baseline to week 12	-357.2 (SE 29.0, SD=409.1)	-21.0 (SE 1.71, SD=24.1)	199	-290.1 (SE 29.1, SD=411.5)	-17.1 (SE 1.7, SD=24.2)	200

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
DeLemos 2011 [46]	1) Tramadol ER 300mg oral 2) 300mg 3) 30 MME	WOMAC physical function (0-1700) estimated from Fig 2(b)	Baseline: 1023.6 (364.7) Week 1: 756.1 (364.7*) Week 4: 564.1 (364.7*) Week 12: 511.5 (364.7*)	Week 1: 44.5 (21.5*) Week 4: 33.2 (21.5*) Week 12: 30.1 (21.5*)	199	Baseline: 1019.0 (354.7) Week 1: 814.6 (354.7*) Week 4: 690.3 (354.7*) Week 12: 591.7 (354.7*)	Week 1: 47.9 (20.9*) Week 4: 40.6 (20.9*) Week 12: 34.8 (20.9*)	200
Vojtassak 2011 [48]	1) OROS hydromorphone ER 2) 12.2mg 3) 48.8 MME MEDIAN = 12.2mg (range 3-28) (estimated SD=6.25)	WOMAC physical function score (0-68) mean change from baseline to week 16	Baseline: 41.2 (9.3) Mean change: -11.9 (13.2)	-17.5 (19.4)	132	Baseline: 39.8 (9.5) Mean change: -11.9 (14.4)	-17.5 (21.1)	144
Rauck 2013 [49]	1) OROS hydromorphone ER 8mg 2) 8mg 3) 32 MME	WOMAC physical function score (0-10) LS mean change from baseline to week 12	-1.6 (SE 0.1, SD=2.0)	-16 (SE 1.1, SD=19.6)	319	-1.3 (SE 0.1, SD=2.0)	-13 (SE 1.1, SD=20.0)	331
Rauck 2013 [49]	1) OROS hydromorphone ER 16mg 2) 16mg 3) 64 MME	WOMAC physical function score (0-10) LS mean change from baseline to week 12	-1.7 (SE 0.1, SD=2.0)	-17 (SE 1.1, SD=20.0)	330	-1.3 (SE 0.1, SD=2.0)	-13 (SE 1.1, SD=20.0)	331

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Spierings 2013 [50]	1) Oxycodone CR 2) 23mg 3) 34.5 MME	WOMAC physical function subscale (0-10) mean scores. Data taken from clinical trial register EUCTR2009-013329-41-SE (table 10)	Baseline: 7.3 (1.5) Week 2: 5.7 (2.3) Week 4: 5.4 (2.4) Week 8: 5.4 (2.4) Week 12: 5.3 (2.4) Week 16: 5.3 (2.4)	Week 2: 57.0 (22.7) Week 4: 54.3 (23.5) Week 12: 53.1 (23.8) Week 16: 52.9 (23.6)	156	Baseline: 7.2 (1.5) Week 2: 5.7 (2.2) Week 4: 5.4 (2.3) Week 8: 5.3 (2.4) Week 12: 5.1 (2.5) Week 16: 5.0 (2.5)	Week 2: 57.4 (21.8) Week 4: 54.3 (23.3) Week 12: 51.3 (24.6) Week 16: 49.7 (25.3)	136
Mayorga 2016 [51]	1) Oxycodone CR 20-50mg BD 2) 70mg 3) 105 MME	WOMAC physical function score (0-10) LS mean change from baseline	Week 12: -1.4 (SE 0.4, SD=2.7) Week 16: -1.3 (SE 0.4)	Week 12: -13.8 (26.9)	50	Week 12: -2.9 (SE 0.4, SD=2.7) Week 16: -3.0 (SE 0.4)	Week 12: -29.2 (27.0)	48
Serrie 2017 [53]	1) Tapentadol PR 2) 315.2 (108)mg 3) 126.08 MME	WOMAC physical function score (0-4) LS mean change from baseline to week 12	-1.0 (SE 0.06, SD=0.8)	-25.0 (SE 1.5, SD=20.3)	183	-0.9 (SE 0.05, SD=0.7)	-22.5 (SE 1.3, SD=18.5)	218
Serrie 2017 [53]	1) Oxycodone CR 2) 54.1 (18.2)mg 3) 81.15 MME	WOMAC physical function score (0-4) LS mean change from baseline to week 12	-1.0 (SE 0.07, SD=0.8)	-25.0 (SE 1.8, SD=18.8)	115	-0.9 (SE 0.05, SD=0.7)	-22.5 (SE 1.3, SD=18.5)	218

WOMAC= Western Ontario and McMaster Universities Arthritis Index; CR=controlled release; OROS=osmotic release oral system; ER=extended release; BD=twice daily; SE=standard error; SD=standard deviation; LSM=least squares mean. Note * the values were obtained from baseline or estimated from graphs or borrowed from the nearest eligible study as indicated. Values are presented to 1 decimal place.

Table 11. Data extracted from included publications: WOMAC total scores

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Fleischmann 2001 [23]	1) Tramadol IR 300mg oral 2) 300mg 3) 30MME	WOMAC overall score (0-10) mean score at end of treatment	4.16 (2.1)	41.6 (20.5)	63	5.0 (2.3)	50.4 (22.5)	66
Silverfield 2002 [25]	1) Tramadol/paracetamol 2) 225mg 3) 22.5 MME NOT STATED - allowed range is from 150-300mg tramadol + 1300-2600mg paracetamol (can assume midpoint of 225mg tramadol)	WOMAC overall score (0-10) mean score at day 10	Baseline: 6.1 (1.4) Day 10: 3.7 (1.7)	37.2 (17.0)	193	Baseline: 6.1 (1.4) Day 10: 4.2 (1.8)	41.9 (17.9)	110
Babul 2004 [26]	1) Tramadol ER oral 2) 276 (NS)mg 3) 27.6 MME	WOMAC overall score (0-2400), LS mean change from baseline to week 12	575.8 (NS)	24 (24.2*)	124	304.6 (NS)	12.7 (24.3*)	122
Emkey 2004 [27]	1) Tramadol/paracetamol IR oral 2) 154mg+1332mg 3) 15.4 MME	WOMAC overall score (0-10)	Baseline: 5.6 (1.4) Final: 4.0 (1.8)	40 (18.1)	153	Baseline: 5.9 (1.5) Final: 4.4 (1.7)	44 (17.3)	153

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Markenson 2005 [30]	1) Oxycodone CR 10-60mg q12h 2) 57+44 / 2 =50.5mg 3) 75.8 MME	WOMAC overall LSM scores (0-100)	Baseline: 64.7 (SE 2.1) Day 30: 49.5 (SE 2.7, SD=20.2) Day 90: 46.3 (SE 2.7, SD=20.2)	Day 30: 49.5 (SE 2.7, SD=20.2) Day 90: 46.3 (SE 2.7, SD=20.2)	56	Baseline: 63.8 (SE 2.1) Day 30: 61.3 (SE 3.0, SD=21.4) Day 90: 62.9 (SE 3.0, SD=21.4)	Day 30: 61.3 (SE 3.0, SD=21.4) Day 90: 62.9 (SE 3.0, SD=21.4)	51
Matsumoto 2005 [31]	1) Oxymorphone ER 40mg BD 2) 60mg 3) 180 MME *"To improve tolerability, patients randomized to the oxymorphone ER 40mg treatment group received oxymorphone ER 20mg every 12 hours during weeks 1 and 2 and oxymorphone ER 40mg every 12 hours during weeks 3 and 4" (40*2 + 20*2)/2= 60mg	WOMAC composite index (0-2400) LS mean change from baseline to week 4 estimated from Fig 3	-466.5 (SE 58.2, SD=621.0)	-19.4 (SE 2.4, SD=25.9)	114	-273.1 (SE 58.2, SD=634.5)	-11.4 (SE 2.4, SD=26.4)	119

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Matsumoto 2005 [31]	1) Oxymorphone ER 20mg BD 2) 40mg 3) 120 MME "patients randomized to oxycodone CR 20mg received oxycodone CR 10mg every 12 hours during weeks 1 and 2 and oxycodone CR 20 mg every 12 hours during weeks 3 and 4."	WOMAC composite index (0-2400) LS mean change from baseline to week 4 estimated from Fig 3	-435.9 (SE 58.2, SD=621.0)	-18.2 (SE 2.4, SD=25.9)	114	-273.1 (SE 58.2, SD=634.5)	-11.4 (SE 2.4, SD=26.4)	119
Matsumoto 2005 [31]	1) Oxycodone CR 20mg BD 2) (20*2 + 10*2)/2 = 30mg 3) 45 MME "patients randomized to oxycodone CR 20mg received oxycodone CR 10 mg every 12 hours during weeks 1 and 2 and oxycodone CR 20mg every 12 hours during weeks 3 and 4."	WOMAC composite index (0-2400) LS mean change from baseline to week 4 estimated from Fig 3	-347.8 (SE 58.2, SD=637.1)	-14.5 (SE 2.4, SD=26.5)	120	-273.1 (SE 58.2, SD=634.5)	-11.4 (SE 2.4, SD=26.4)	119

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Gana 2006 [32]	1) Tramadol ER 100mg oral 2) 100mg 3) 10 MME	WOMAC composite score (0-2400) LSM change from baseline	Week 1: 273.1 (SE 32.5, SD=461.9) Week 3: 393.7 (SE 37.5, SD=533.0) Week 12: 481.5 (SE 39.8, SD=565.7)	Week 1: 11.4 (SE 1.4, SD=19.2) Week 3: 16.4 (SE 1.6, SD=22.2) Week 12: 20.1 (SE 1.7, SD=23.6)	202	Week 1: 179.7 (SE 32.1=459.6) Week 3: 309.5 (SE 37.0=529.8) Week 12: 340.5 (SE 39.3=562.7)	Week 1: 7.5 (SE 1.3=19.2) Week 3: 12.9 (SE 1.5=22.1) Week 12: 14.2 (SE 1.6=23.4)	205
Gana 2006 [32]	1) Tramadol ER 200mg oral 2) 200mg 3) 20 MME	WOMAC composite score (0-2400) LSM change from baseline	Week 1: 305.3 (SE 33.1, SD=469.3) Week 3: 460.8 (SE 38.1, SD=540.1) Week 12: 510.0 (SE 40.5, SD=574.2)	Week 1: 12.7 (SE 1.4, SD=19.6) Week 3: 19.2 (SE 1.6, SD=22.5) Week 12: 21.3 (SE 1.7, SD=23.9)	201	Week 1: 179.7 (SE 32.1) Week 3: 309.5 (SE 37.0) Week 12: 340.5 (SE 39.3)	Week 1: 7.5 (SE 1.3, SD=19.2) Week 3: 12.9 (SE 1.5, SD=22.1) Week 12: 14.2 (SE 1.6, SD=23.4)	205

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Gana 2006 [32]	1) Tramadol ER 300mg oral 2) 300mg 3) 30 MME	WOMAC composite score (0-2400) LSM change from baseline	Week 1: 326.2 (SE 32.9, SD=466.4) Week 3: 473.7 (SE 38.0, SD=538.7) Week 12: 486.4 (SE 40.3, SD=571.4)	Week 1: 13.6 (SE 1.4, SD=19.4) Week 3: 19.7 (SE 1.6, SD=22.4) Week 12: 20.3 (SE 1.7, SD=23.8)	201	Week 1: 179.7 (SE 32.1) Week 3: 309.5 (SE 37.0) Week 12: 340.5 (SE 39.3)	Week 1: 7.5 (SE 1.3, SD=19.2) Week 3: 12.9 (SE 1.5, SD=22.1) Week 12: 14.2 (SE 1.6, SD=23.4)	205
Gana 2006 [32]	1) Tramadol ER 400mg oral 2) 400mg 3) 40 MME	WOMAC composite score (0-2400) LSM change from baseline	Week 1: 299.2 (SE 32.9, SD=467.6) Week 3: 469.6 (SE 37.9, SD=538.7) Week 12: 479.2 (SE 40.3, SD=572.8)	Week 1: 12.5 (SE 1.4, SD=19.5) Week 3: 19.6 (SE 1.6, SD=22.4) Week 12: 20.0 (SE 1.7, SD=23.9)	202	Week 1: 179.7 (SE 32.1) Week 3: 309.5 (SE 37.0) Week 12: 340.5 (SE 39.3)	Week 1: 7.5 (SE 1.3, SD=19.2) Week 3: 12.9 (SE 1.5, SD=22.1) Week 12: 14.2 (SE 1.6, SD=23.4)	205

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Kivitz 2006 [33]	1) Oxymorphone ER 20mg 2) 20mg 3) 60 MME Oxymorphone 10 mg bd for 2 weeks	WOMAC composite index (0-2400) LSM change from baseline to week 2 estimated from Fig 4(D)	-352.7 (SE 48.4, SD=464.2)	-14.7 (SE 2.0, SD=19.3)	92	-172.5 (SE 54.9, SD=512.1)	-7.2 (SE 2.3, SD=21.3)	87
Kivitz 2006 [33]	1) Oxymorphone ER 80mg 2) 60mg 3) 180 MME Oxymorphone 20mg bd for first week then 40mg bd for second week	WOMAC composite index (0-2400) LSM change from baseline to week 2 estimated from Fig 4(D)	-380.2 (SE 47.3, SD=451.2)	-15.8 (SE 2.0, SD=18.8)	91	-172.5 (SE 54.9, SD=512.1)	-7.2 (SE 2.3, SD=21.3)	87
Kivitz 2006 [33]	1) Oxymorphone ER 100mg 2) 70mg 3) 210 MME Oxymorphone 20mg bd for first week followed by 50mg bd for second week	WOMAC composite index (0-2400) LSM change from baseline to week 2 estimated from Fig 4(D)	-462.1 (SE 55.5, SD=517.7)	-19.3 (SE 2.3, SD=21.6)	87	-172.5 (SE 54.9, SD=512.1)	-7.2 (SE 2.3, SD=21.3)	87

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Langford 2006 [34]	1) Transdermal fentanyl patch 25µg/hour patch 2) 42.5µg/hour 3) 102 MME Median number of patches was 1.7 at 25µg/hour	WOMAC overall score (0-10) mean change from baseline to final visit (after washout)	-3.9 (SE 0.4, SD=5.7)	-39 (SE 4, SD=57)	202	-2.4 (SE 0.4, SD=5.6)	-24 (SE 4.0, SD=56)	197
Afilalo 2010 [42]	1) Tapentadol ER oral 2) 299.3 (107.2)mg 3) 119.7 MME	WOMAC overall score (0-4), LS mean change from baseline to week 12	-1.1 (SE 0.05, SD=0.7)	-28.0 (SE 1.4, SD=16.5)	149	-0.9 (SE 0.05, SD=0.7)	-22.8 (SE 1.4, SD=17.0)	158
Afilalo 2010 [42]	1) Oxycodone CR oral 2) 48.2 (23.94)mg 3) 72.3 MME	WOMAC overall score (0-4), LS mean change from baseline to week 12	-1.1 (SE 0.07, SD=0.7)	-27.0 (SE 1.7, SD=16.3)	92	-0.9 (SE 0.05, SD=0.7)	-22.8 (SE 1.4, SD=17.0)	158
Breivik 2010 [43]	1) Buprenorphine patch 2) 11 (5.7)µg/hour 3) 19.8 MME	WOMAC Total score (0-96) mean score at end of treatment	Baseline: 52.4 (12.2) EOT: 38.5 (16.7)	40.1 (17.4)	95	Baseline: 48.9 (14.1) EOT: 40.4 (16.0)	42.1 (16.7)	99
Katz 2010 [44]	1) Morphine sulfate + naltrexone hydrochloride ER 2) 43.5 (31.7)mg 3) 43.5 MME	WOMAC composite score (0-100)	Baseline: 31.2 (15.3) Week 12: 32.8 (20.0) Change: 1.6 (18.0)	Final score: 32.8 (20.0) Change score: 1.6 (18.0)	171	Baseline: 30.4 (15.4) Week 12: 36.2 (18.3) Change: 5.8 (16.8)	Final score: 36.2 (18.3) Change score: 5.8 (16.8)	173

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
DeLemos 2011 [46]	1) Tramadol ER 100mg oral 2) 100mg 3) 10 MME	WOMAC overall score (0-2400) LS mean change from baseline to week 12	387.4 (SE 41.1, SD=582.7)	16.1 (SE 1.7, SD=24.3)	201	425.2 (SE 41.2, SD=582.7)	17.7 (SE 1.7, SD=24.3)	200
DeLemos 2011 [46]	1) Tramadol ER 200mg oral 2) 200mg 3) 20 MME	WOMAC overall score (0-2400) LS mean change from baseline to week 12	389.8 (SE 41.2, SD=581.2)	16.2 (SE 1.7, SD=24.2)	199	425.2 (SE 41.2, SD=582.7)	17.7 (SE 1.7, SD=24.3)	200
DeLemos 2011 [46]	1) Tramadol ER 300mg oral 2) 300mg 3) 30 MME	WOMAC overall score (0-2400) LS mean change from baseline to week 12	530.5 (SE 41.1, SD=579.8)	22.1 (SE 1.7, SD=24.2)	199	425.2 (SE 41.2, SD=582.7)	17.7 (SE 1.7, SD=24.3)	200
Vojtassak 2011 [48]	1) OROS hydromorphone ER 2) 12.2mg 3) 48.8 MME MEDIAN = 12.2mg (range 3-28) (estimated SD=6.3)	WOMAC overall score (0.2) mean change from baseline to week 16	Baseline: 17.7 (3.4) Mean change: -5.4 (6.0)	-22.3 (25.0)	130	Baseline: 16.9 (3.9) Mean change: -5.2 (6.2)	-21.5 (25.6)	143
Rauck 2013 [49]	1) OROS hydromorphone ER 8mg 2) 8mg 3) 32 MME	WOMAC overall score (0-10) LS mean change from baseline to week 12	-1.6 (SE 0.1, SD=2.0)	-16 (SE 1.1, SD=19.6)	319	-1.3 (SE 0.1, SD=2.0)	-13 (SE 1.1, SD=20.0)	331

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Rauck 2013 [49]	1) OROS hydromorphone ER 16mg 2) 16mg 3) 64 MME	WOMAC overall score (0-10) LS mean change from baseline to week 12	-1.7 (SE 0.1, SD=2.0)	-17 (SE 1.1, SD=20.0)	330	-1.3 (SE 0.1, SD=2.0)	-13 (SE 1.1, SD=20.0)	331
Spierings 2013 [50]	1) Oxycodone CR 2) 23mg 3) 34.5 MME	WOMAC average score (0-10) mean change from baseline. Data taken from clinical trial register EUCTR2009-013329-41-SE (table 29)	Baseline: 7.5 (1.3) Week 2: -1.7 (1.9) Week 4: -2.1 (2.1) Week 8: -2.1 (2.2) Week 12: -2.2 (2.2) Week 16: -2.2 (2.2)	Week 2: -17.4 (19.4) Week 4: -20.8 (21.3) Week 12: -22.0 (22.1) Week 16: -22.0 (21.9)	156	Baseline: 7.4 (1.3) Week 2: -1.6 (1.7) Week 4: -1.9 (1.9) Week 8: -2.1 (2.0) Week 12: -2.3 (2.2) Week 16: -2.4 (2.4)	Week 2: -16.0 (17.0) Week 4: -19.4 (19.3) Week 12: -22.5 (21.9) Week 16: -24.0 (23.6)	137
Mayorga 2016 [51]	1) Oxycodone CR 20-50mg BD 2) 70mg 3) 105 MME	WOMAC overall score (0-10) LS mean change from baseline	Week 12: -1.40 (SE 0.37, SD=2.62) Week 16: -1.28 (SE 0.37)	Week 12: -14.0 (26.2)	50	Week 12: -2.99 (SE 0.38, SD=2.63) Week 16: -3.01 (SE 0.38)	Week 12: -29.9 (26.3)	48
Serrie 2017 [53]	1) Tapentadol PR 2) 315.2 (108)mg 3) 126.1 MME	WOMAC overall score (0-4) LS mean change from baseline to week 12	-0.9 (SE 0.06, SD=0.6)	-22.5 (SE 1.5, SD=20.3)	183	-0.9 (SE 0.05, SD=0.5)	-22.5 (SE 1.3, SD=18.5)	218

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Serrie 2017 [53]	1) Oxycodone CR 2) 54.1 (18.2)mg 3) 81.2 MME	WOMAC overall score (0-4) LS mean change from baseline to week 12	-1.0 (SE 0.07, SD=0.5)	-25 (SE 1.8, SD=18.8)	115	-0.9 (SE 0.05, SD=0.5)	-22.5 (SE 1.3, SD=18.5)	218

ER=Extended release; mg=milligrams; SD=standard deviation; CR=controlled release; OROS=osmotic extended release oral delivery system; mg=milligrams; µg=micrograms; WOMAC= The Western Ontario and McMaster Universities Arthritis Index Note * the values were obtained from baseline or estimated from graphs or borrowed from the nearest eligible study.

Table 12. Data extracted from included publications: health-related quality of life

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Emkey 2004 [27]	1) Tramadol/paracetamol IR oral 2) 154mg+1332mg 3) 15.4 MME	SF-36 physical component (0-100) mean score	Baseline: 28.4 (7.5) Final: 34.0 (10.2)	34.0 (10.2)	153	Baseline: 27.8 (6.7) Final: 32.6 (8.8)	32.6 (8.8)	153
Emkey 2004 [27]	1) Tramadol/paracetamol IR oral 2) 154mg+1332mg 3) 15.4 MME	SF-36 mental component (0-100) mean score	Baseline: 52.6 (10.4) Final: 53.5 (10.1)	53.5 (10.09)	153	Baseline: 51.6 (10.9) Final: 52.6 (11.0)	52.6 (11.0)	153
Markenson 2005 [30]	1) Oxycodone CR 10-60mg q12h 2) 57+44 / 2 =50.5mg 3) 75.75 MME	Patient generated index (0-100)	Day 30: 46.4 (SE 2.9=21.7) Day 45: 51.2 (SE 3.1=23.2)	Day 30: 46.4 (SE 2.9, SD=21.7) Day 45: 51.2 (SE 3.1, SD=23.2)	56	Day 30: 37.6 (SE 3.3, SD=23.6) Day 45: 39.7 (SE 3.5, SD=25.0)	Day 30: 37.6 (SE 3.3, SD=23.6) Day 45: 39.7 (SE 3.5, SD=25.0)	51

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Matsumoto 2005 [31]	1) Oxymorphone ER 40mg BD 2) 60mg 3) 180 MME *"To improve tolerability, patients randomized to the oxymorphone ER 40mg treatment group received oxymorphone ER 20mg every 12 hours during weeks 1 and 2 and oxymorphone ER 40mg every 12 hours during weeks 3 and 4" (40*2 + 20*2)/2= 60mg	SF-36 (0-100) LSM change from baseline to week 4	Physical: 4.5 (SE 0.9, SD=9.6) Mental: -0.4 (SE 1.1, SD=11.7)	Physical: 4.5 (SE 0.9, SD=9.6) Mental: -0.4 (SE 1.1, SD=11.7)	114	Physical: 1.8 (SE 0.7, SD=7.6) Mental: 2.2 (SE 0.9, SD=9.8)	Physical: 1.8 (SE 0.7, SD=7.6) Mental: 2.2 (SE 0.9, SD=9.8)	119
Matsumoto 2005 [31]	1) Oxymorphone ER 20mg BD 2) 40mg 3) 120 MME "patients randomized to oxycodone CR 20mg received oxycodone CR 10mg every 12 hours during weeks 1 and 2 and oxycodone CR 20mg every 12 hours during weeks 3 and 4."	SF-36 (0-100) LSM change from baseline to week 4	Physical: 3.4 (SE 0.9, SD=9.6) Mental: 1.5 (SE 1.1, SD=11.7)	Physical: 3.4 (SE 0.9, SD=9.6) Mental: 1.5 (SE 1.1, SD=11.7)	114	Physical: 1.8 (SE 0.7, SD=7.6) Mental: 2.2 (SE 0.9, SD=9.8)	Physical: 1.8 (SE 0.7, SD=7.6) Mental: 2.2 (SE 0.9, SD=9.8)	119

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Matsumoto 2005 [31]	1) Oxycodone CR 20mg BD 2) (20*2 + 10*2)/2 = 30mg 3) 45 MME "patients randomized to oxycodone CR 20mg received oxycodone CR 10mg every 12 hours during weeks 1 and 2 and oxycodone CR 20mg every 12 hours during weeks 3 and 4."	SF-36 (0-100) LSM change from baseline to week 4	Physical: 4·0 (SE 0.8, SD=8.8) Mental: -0.8 (SE 0.9, SD=9.9)	Physical: 4.0 (SE 0.8, SD=8.8) Mental: -0.8 (SE 0.9, SD=9.9)	120	Physical: 1.8 (SE 0.7, SD=7.6) Mental: 2.2 (SE 0.9, SD=9.8)	Physical: 1.8 (SE 0.7, SD=7.6) Mental: 2.2 (SE 0.9, SD=9.8)	119
Gana 2006 [32]	1) Tramadol ER 100mg oral 2) 100mg 3) 10 MME	SF-36 (0-100) LSM change from baseline to week 12	Physical: 3.6 (SE 0.6, SD=8.5) Mental: 1.1 (SE 0.6, SD=8.5)	Physical: 3.6 (SE 0.6, SD=8.5) Mental: 1.1 (SE 0.6, SD=8.5)	202	Physical: 2.4 (SE 0.6, SD=8.6) Mental: -0.3 (SE 0.6, SD=8.6)	Physical: 2.4 (SE 0.6, SD=8.6) Mental: -0.3 (SE 0.6, SD=8.6)	205
Gana 2006 [32]	1) Tramadol ER 200mg oral 2) 200mg 3) 20 MME	SF-36 (0-100) LSM change from baseline to week 12	Physical: 3.9 (SE 0.6, SD=8.5) Mental: 0.6 (SE 0.6, SD=8.5)	Physical: 3.9 (SE 0.6, SD=8.5) Mental: 0.6 (SE 0.6, SD=8.5)	201	Physical: 2.4 (SE 0.6, SD=8.6) Mental: -0.3 (SE 0.6, SD=8.6)	Physical: 2.4 (SE 0.6, SD=8.6) Mental: -0.3 (SE 0.6, SD=8.6)	205

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Gana 2006 [32]	1) Tramadol ER 300mg oral 2) 300mg 3) 30 MME	SF-36 (0-100) LSM change from baseline to week 12	Physical: 3.6 (SE 0.6, SD=8.5) Mental: -0.7 (SE 0.6, SD=8.5)	Physical: 3.6 (SE 0.6, SD=8.5) Mental: -0.7 (SE 0.6, SD=8.5)	201	Physical: 2.4 (SE 0.6, SD=8.6) Mental: -0.3 (SE 0.6, SD=8.6)	Physical: 2.4 (SE 0.6, SD=8.6) Mental: -0.3 (SE 0.6, SD=8.6)	205
Gana 2006 [32]	1) Tramadol ER 400mg oral 2) 400mg 3) 40 MME	SF-36 (0-100) LSM change from baseline to week 12	Physical: 3.2 (SE 0.6, SD=8.5) Mental: -0.5 (SE 0.6, SD=8.5)	Physical: 3.2 (SE 0.6, SD=8.5) Mental: -0.5 (SE 0.6, SD=8.5)	202	Physical: 2.4 (SE 0.6, SD=8.6) Mental: -0.3 (SE 0.6, SD=8.6)	Physical: 2.4 (SE 0.6, SD=8.6) Mental: -0.3 (SE 0.6, SD=8.6)	205
Kivitz 2006 [33]	1) Oxymorphone ER 20mg 2) 20mg 3) 60 MME Oxymorphone 10mg bd for 2 weeks	SF-36 physical component (0-100) LSM change from baseline to week 2	3.9 (NS)	3.9 (9·6*)	92	-0.1 (NS)	-0.1 (7.6*)	87
Kivitz 2006 [33]	1) Oxymorphone ER 80mg 2) 60mg 3) 180 MME Oxymorphone 20mg bd for first week then 40mg bd for second week	SF-36 physical component (0-100) LSM change from baseline to week 2	4.6 (NS)	4.6 (9.6*)	91	-0.1 (NS)	-0.1 (7.6*)	87

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Kivitz 2006 [33]	1) Oxymorphone ER 100mg 2) 70mg 3) 210 MME Oxymorphone 20mg bd for first week followed by 50mg bd for second week	SF-36 physical component (0-100) LSM change from baseline to week 2	3.6 (NS)	3.6 (9.6*)	87	-0.1 (NS)	-0.1 (7.6*)	87
Langford 2006 [34]	1) Transdermal fentanyl patch 25µg/hour patch 2) 42.5µg/hour 3) 102 MME Median number of patches was 1.7 at 25µg/hr	SF-36 (0-100) mean change from baseline to week 12	Physical: 3.4 (SE 0.5, SD=7.1) Mental: -0.9 (SE 0.9, SD=12.8)	Physical: 3.4 (SE 0.5, SD=7.1) Mental: -0.9 (SE 0.9, SD=12.8)	202	Physical: 2.4 (SE 0.5, SD=7.0) Mental: 1.1 (SE 0.7, SD=9.8)	Physical: 2.4 (SE 0.5, SD=7.0) Mental: 1.1 (SE 0.7, SD=9.8)	197
Afilalo 2010 [42]	1) Tapentadol ER oral 2) 299.3 (107.16)mg 3) 119.7 MME	EuroQol-5DQ health status index (0-1) mean change/LSM change from baseline to week 12	Mean change: 0.2 (SE=0.02 SD=0.4) LSM change: 0.2 (NS)	20.0 (SE 2.0, SD=37.0)	344	Mean change: 0.1 (SE 0.02, SD=0.4) LSM change: 0.1 (NS)	10.0 (SE 1.0, SD=37.0)	337
Afilalo 2010 [42]	1) Oxycodone CR oral 2) 48.2 (23.94)mg 3) 72.3 MME	EuroQol-5DQ health status index (0-1) mean change from baseline to week 12	Mean change: 0.1 (SE 0.02, SD=0.4) LSM change: 0.1 (NS)	10.0 (SE 2.0, SD=37.0)	342	Mean change: 0.1 (SE 0.02, SD=0.37) LSM change: 0.1 (NS)	10.0 (SE 1.0, SD=37.0)	337

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Afilalo 2010 [42]	1) Tapentadol ER oral 2) 299.3 (107.16)mg 3) 119.72 MME	SF-36 (0-100) LSM change from baseline to week 12	Physical: 6.2 (NS) Mental: 0.9 (NS)	Physical: 6.2 (8.5*) Mental: 0.9 (8.5*)	344	Physical: 3.5 (NS) Mental: 2.0 (NS)	Physical: 3.5 (8.5*) Mental: 2.0 (8.5*)	337
Afilalo 2010 [42]	1) Oxycodone CR oral 2) 48.2 (23.94)mg 3) 72.3 MME	SF-36 (0-100) LSM change from baseline to week 12	Physical: 3.7 (NS) Mental: -0.1 (NS)	Physical: 3.7 (8.5*) Mental: -0.1 (8.5*)	342	Physical: 3.5 (NS) Mental: 2.0 (NS)	Physical: 3.5 (8.5*) Mental: 2.0 (8.5*)	337
DeLemos 2011 [46]	1) Tramadol ER 100mg oral 2) 100mg 3) 10 MME	SF-36 (0-100) LS mean change from baseline to week 12	Physical: 2.8 (SE 0.6, SD=8.5) Mental: -0.3 (SE 0.6, SD=8.5)	Physical: 2.8 (SE 0.6, SD=8.5) Mental: -0.3 (SE 0.6, SD=8.5)	201	Physical: 3.0 (SE 0.6, SD=8.5) Mental: -0.3 (SE 0.6, SD=8.5)	Physical: 3.0 (SE 0.6, SD=8.5) Mental: -0.3 (SE 0.6, SD=8.5)	200
DeLemos 2011 [46]	1) Tramadol ER 200mg oral 2) 200mg 3) 20 MME	SF-36 (0-100) LS mean change from baseline to week 12	Physical: 3.1 (SE 0.6, SD=8.5) Mental: -0.3 (SE 0.6, SD=8.5)	Physical: 3.1 (SE 0.6=8.5) Mental: -0.3 (SE 0.6=8.5)	199	Physical: 3.0 (SE 0.6, SD=8.5) Mental: -0.3 (SE 0.6, SD=8.5)	Physical: 3.0 (SE 0.6, SD=8.5) Mental: -0.3 (SE 0.6, SD=8.5)	200

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
DeLemos 2011 [46]	1) Tramadol ER 300mg oral 2) 300mg 3) 30 MME	SF-36 (0-100) LS mean change from baseline to week 12	Physical: 3.5 (SE 0.6, SD=8.5) Mental: -0.9 (SE 0.6, SD=8.5)	Physical: 3.5 (SE 0.6, SD=8.5) Mental: -0.9 (SE 0.6, SD=8.5)	199	Physical: 3.0 (SE 0.6, SD=8.5) Mental: -0.3 (SE 0.6, SD=8.5)	Physical: 3.0 (SE 0.6, SD=8.5) Mental: -0.3 (SE 0.6, SD=8.5)	200
Spierings 2013 [50]	1) Oxycodone CR 2) 23mg 3) 34.5 MME	SF-36 (0-100) LSM change from baseline to week 12. Data taken from clinical trial register EUCTR2009-013329-41-SE (table 36)	Physical: 0.5 (SE 0.1=1.4) Mental: 0.2 (SE 0.1=1.6)	Physical: 0.5 (SE 0.1, SD=1.4) Mental: 0.2 (SE 0.1, SD=1.6)	156	Physical: 0.5 (SE 0.1, SD=1.4) Mental: 0.3 (SE 0.1, SD=1.6)	Physical: 0.5 (SE 0.1, SD=1.4) Mental: 0.3 (SE 0.1, SD=1.6)	137
Spierings 2013 [50]	1) Oxycodone CR 2) 23mg 3) 34.5 MME	EuroQol-5D health state utility (0-1) LSM change from baseline to week 12. Data taken from clinical trial register EUCTR2009-013329-41-SE (table 37)	Baseline: 0.4 (0.3) Change: 0.2 (SE 0.03, SD=0.2)	15.0 (SE=3.0, SD=23.0)	59	Baseline: 0.4 (0.3) Change: 0.2 (SE 0.04, SD=0.3)	19.0 (SE 4.0, SD=30.0)	56

Study	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Outcome measure	Intervention Mean (SD)	STANDARDISED Intervention Mean (SD)	Intervention Sample size	Control Mean (SD)	STANDARDISED Control Mean (SD)	Control Sample size
Spierings 2013 [50]	1) Oxycodone CR 2) 23mg 3) 34.5 MME	SF-36 mental component (0-100) estimated from Fig 4	Baseline: 41.4 Week 4: 44.0 (NS)	44.0 (8.7*)	94	Baseline: 41.4 Week 4: 42.0 (NS)	42.0 (7.7*)	88
Serrie 2017 [53]	1) Tapentadol PR 2) 315.2 (108)mg 3) 126.08 MME	EuroQol-5D health status index (0-100)	Baseline: 50.1 (20.0) EOT: 62.8 (20.0*)	62.8 (20.0*)	319	Baseline: 53.2 (42.7) EOT: 61.2 (42.7*)	61.2 (42.7*)	337
Serrie 2017 [53]	1) Oxycodone CR 2) 54.1 (18.2)mg 3) 81.15 MME	EuroQol-5D health status index (0-100)	Baseline: 51.3 (19.6) EOT: 58.7 (19.6*)	58.7 (19.6*)	331	Baseline: 53.2 (42.7) EOT: 61.2 (42.7*)	61.2 (42.7*)	337
Serrie 2017 [53]	1) Tapentadol PR 2) 315.2 (108)mg 3) 126.1 MME	EuroQol-5D WEIGHTED health status index (0.1)	Baseline: 0.4 (0.3) EOT: 0.6 (0.3*)	56 (30.0*)	319	Baseline: 0.4 (0.3) EOT: 0.53 (0.3)	53 (30*)	337
Serrie 2017 [53]	1) Oxycodone CR 2) 54.1 (18.2)mg 3) 81.15 MME	EuroQol-5D WEIGHTED health status index (0-1)	Baseline: 0.4 (0.3) EOT: 0.56 (0.3*)	56 (30*)	331	Baseline: 0.4 (0.3) EOT: 0.53 (0.3)	53 (30*)	337

WOMAC= Western Ontario and McMaster Universities Arthritis Index; CR=controlled release, mg=milligram; OROS=osmotic release oral system; ER=extended release; BD=twice daily; q12h = every 12 hours; PGI=patient generated index; SF-36=36-item short form survey; LSM=least squares mean; SE=standard error; SD=standard deviation. NS=Not Specified. Note * the values were obtained from baseline or estimated from graphs in the study or borrowed from the nearest eligible study (evaluating the same drug); EuroQol=European quality of life scale. Values are presented to 1 decimal place or 1 significant figure.

Table 13. Numbers of trial participants who experienced adverse events

Study	Length of treatment	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Intervention total AEs	Intervention sample size	Control total AEs	Control Sample size
Quiding 1992 [18]	24 hours	1) Ibuprofen 200mg/codeine 30mg up to six doses 2) 180mg 3) 27 MME	NR	11	NR	6
Roth 1998 [19]	13 days	1) Tramadol 2) 250mg 3) 25 MME tramadol 100mg followed by 50 mg 6 hourly for total 250mg	NR	20	NR	21
Caldwell 1999 [20]	30 days	1) Oxycodone CR 10mg 2) 40 mg 3) 60 MME	NR	34	NR	36
Caldwell 1999 [20]	30 days	1) Oxycodone IR 5mg + paracetamol 325mg 2) 40mg 3) 60 MME	NR	37	NR	36
Peloso 2000 [21]	4 weeks	1) Codeine CR 100-400mg 2) 318 (104)mg 3) 47.7 MME	25	31	22	35
Roth 2000 [22]	2 weeks	1) Oxycodone CR 10mg q12h 2) 20mg 3) 30 MME	NR	44	NR	45
Roth 2000 [22]	2 weeks	1) Oxycodone CR 20mg q12h 2) 40mg 3) 60 MME	NR	44	NR	45
Fleischmann 2001 [23]	13 weeks	1) Tramadol IR 300 mg oral 2) 300mg 3) 30 MME	NR	63	NR	66
Caldwell 2002 [24]	4 weeks	1) Morphine sulfate ER (Avinza) 30mg mane 2) 30mg (0) 3) 30 MME	NR	73	NR	73

Study	Length of treatment	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Intervention total AEs	Intervention sample size	Control total AEs	Control Sample size
Caldwell 2002 [24]	4 weeks	1) Morphine sulfate ER (Avinza) 30mg nocte 2) 30mg (0) 3) 30 MME	NR	73	NR	73
Caldwell 2002 [24]	4 weeks	1) Morphine sulfate CR (MS Contin) 15mg BD 2) 30mg (0) 3) 30 MME	NR	76	NR	73
Silverfield 2002 [25]	10 days	1) Tramadol/paracetamol 2) 225mg 3) 22.5 MME NOT STATED - allowed range is from 150-300mg tramadol + 1300-2600mg paracetamol (can assume midpoint of 225mg tramadol)	88	197	26	111
Babul 2004 [26]	12 weeks	1) Tramadol ER oral 2) 276 (NS)mg 3) 27.6 MME	98	124	78	122
Emkey 2004 [27]	13 weeks	1) Tramadol/paracetamol IR oral 2) 154mg+1332mg 3) 15.4 MME	NR	153	NR	153
Malonne 2004 [28]	2 weeks	1) Tramadol SR 200mg 2) 200mg 3) 20 MME	50	111	23	119
Chindalore 2005 [29]	3 weeks	1) Oxycodone QID 2) 28.8 (0)mg 3) 43.1 MME	NR	102	NR	51
Chindalore 2005 [29]	3 weeks	1) Oxycodone + naltrexone QID 2) 28.8 (0)mg 3) 43.1 MME	NR	104	NR	51
Chindalore 2005 [29]	3 weeks	1) Oxycodone + naltrexone BD 2) 28.8 (0)mg 3) 43.1 MME	NR	103	NR	51

Study	Length of treatment	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Intervention total AEs	Intervention sample size	Control total AEs	Control Sample size
Markenson 2005 [30]	90 days	1) Oxycodone CR 10-60mg q12h 2) 57+44 / 2 =50.5 mg 3) 75.8 MME	52	56	28	51
Matsumoto 2005 [31]	4 weeks	1) Oxymorphone ER 40mg BD 2) 60mg 3) 180 MME *"To improve tolerability, patients randomized to the oxymorphone ER 40 mg treatment group received oxymorphone ER 20mg every 12 hours during weeks 1 and 2 and oxymorphone ER 40 mg every 12 hours during weeks 3 and 4" (40*2 + 20*2)/2= 60mg	110	121	71	124
Matsumoto 2005 [31]		1) Oxymorphone ER 20mg BD 2) 40mg 3) 120 MME "patients randomized to oxycodone CR 20mg received oxycodone CR 10mg every 12 hours during weeks 1 and 2 and oxycodone CR 20mg every 12 hours during weeks 3 and 4."	113	119	71	124
Matsumoto 2005 [31]		1) Oxycodone CR 20mg BD 2) (20*2 + 10*2)/2 = 30mg 3) 45 MME "patients randomized to oxycodone CR 20mg received oxycodone CR 10mg every 12 hours during weeks 1 and 2 and oxycodone CR 20mg every 12 hours during weeks 3 and 4."	110	125	71	124
Gana 2006 [32]	12 weeks	1) Tramadol ER 100mg oral 2) 100mg 3) 10 MME	144	202	114	205

Study	Length of treatment	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Intervention total AEs	Intervention sample size	Control total AEs	Control Sample size
Gana 2006 [32]	12 weeks	1) Tramadol ER 200mg oral 2) 200mg 3) 20 MME	147	201	114	205
Gana 2006 [32]	12 weeks	1) Tramadol ER 300mg oral 2) 300mg 3) 30 MME	153	201	114	205
Gana 2006 [32]	12 weeks	1) Tramadol ER 400mg oral 2) 400mg 3) 40 MME	170	202	114	205
Kivitz 2006 [33]	2 weeks	1) Oxymorphone ER 20mg 2) 20mg 3) 60 MME Oxymorphone 10 mg bd for 2 weeks	NR	95	NR	91
Kivitz 2006 [33]	2 weeks	1) Oxymorphone ER 80mg 2) 60mg 3) 180 MME Oxymorphone 20mg bd for first week then 40mg bd for second week	NR	93	NR	91
Kivitz 2006 [33]	2 weeks	1) Oxymorphone ER 100mg 2) 70mg 3) 210 MME Oxymorphone 20mg bd for first week followed by 50mg bd for second week	NR	91	NR	91
Langford 2006 [34]	6 weeks	1) Transdermal fentanyl patch 25µg/hour patch 2) 42.5µg/hour 3) 102 MME Median number of patches was 1.7 at 25µg/hour	169	216	101	200
NCT00313846 [35]	28 days	1) Buprenorphine transdermal patch 5-20µg/hour 2) NOT STATED, estimated at 10µg/hour 3) 18 MME	29	164	15	162

Study	Length of treatment	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Intervention total AEs	Intervention sample size	Control total AEs	Control Sample size
NCT00531427 [36]	12 weeks	transdermal patch 10-20µg/hour 2) NOT STATED- estimated at 15µg/hour 3) 27 MME	121	282	56	285
Burch 2007 [37]	12 weeks	1) Tramadol ER oral 2) 275.4 (NS)mg 3) 27.5 MME	254	432	not reported	214
Fishman 2007 [38]	12 weeks (+6 day titration)	1) Tramadol Contramid 100mg 2) 100mg 3) 10 MME	62	106	116	227
Fishman 2007 [38]	12 weeks (+6 day titration)	1) Tramadol Contramid 200mg 2) 200mg 3) 20 MME	74	111	116	227
Fishman 2007 [38]	12 weeks (+6 day titration)	1) Tramadol Contramid 300mg 2) 300mg 3) 30 MME	81	108	116	227
Hartrick 2009 [39]	10 days	1) Tapentadol IR 50mg 2) 50mg 3) 20 MME	81	157	54	169
Hartrick 2009 [39]	10 days	1) Tapentadol IR 75mg 2) 75mg 3) 30 MME	120	168	54	169
Hartrick 2009 [39]	10 days	1) Oxycodone HCI IR 10mg 2) 10mg 3) 15 MME	144	172	54	169
NCT00832416 2009 [40]	12 weeks	1) Tramadol 100mg 2) 100mg 3) 10 MME	33	110	41	227
NCT00832416 2009 [40]	12 weeks	1) Tramadol 200mg 2) 200mg 3) 20 MME	50	113	41	227

Study	Length of treatment	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Intervention total AEs	Intervention sample size	Control total AEs	Control Sample size
NCT00832416 2009 [40]	12 weeks	1) Tramadol 300mg 2) 300mg 3) 30 MME	61	115	41	227
NCT00979953 2009 [41]	2 weeks	1) Oxycodone CR 2) oxycodone 10mg bd for 1-4 days then 20mg bd for days 5.1 =34.3 3) 51.4 MME	75	104	38	104
Afilalo 2010 [42]	12 weeks (+3 weeks titration)	1) Tapentadol ER oral 2) 299.3 (107.2)mg 3) 119.7 MME	261	344	206	337
	12 weeks (+3 weeks titration)	1) Oxycodone CR oral 2) 48.2 (23.9)mg 3) 72.3 MME	299	342	206	337
Breivik 2010 [43]	24 weeks	1) Buprenorphine patch 2) 11 (5.7)µg/hour 3) 19.8 MME	92	100	73	99
Katz 2010 [44]	12 weeks (≤45 days titration period)	1) Morphine sulfate + naltrexone hydrochloride ER 2) 43.5 (31.7)mg 3) 43.5 MME	91	171	84	173
Munera 2010 [45]	4 weeks	1) Buprenorphine patch 2) 15.1µg/hour 3) 27.18 MME	106	152	86	163
DeLemos 2011 [46]	12 weeks	1) Tramadol ER 100mg oral 2) 100mg 3) 10 MME	127	201	120	200
DeLemos 2011 [46]	12 weeks	1) Tramadol ER 200mg oral 2) 200mg 3) 20 MME	149	199	120	200

Study	Length of treatment	1) Opioid name, formulation (IR/ER), route 2) Mean daily dose (MDD) (SD) 3) Morphine Milligram Equivalent dose (MME)	Intervention total AEs	Intervention sample size	Control total AEs	Control Sample size
DeLemos 2011 [46]	12 weeks	1) Tramadol ER 300mg oral 2) 300mg 3) 30 MME	144	199	120	200
Vojtassak 2011* [48] ***Data from clinical trial registry NCT00980798**	12 weeks (4 weeks titration)	1) Hydromorphone ER 2) 12.2mg 3) 48.8 MME MEDIAN = 12.2mg (range 3-28) (estimated SD=6.3)	110	139	57	149
Rauck 2013 [49]	12 weeks (≤16 day titration phase)	1) OROS hydromorphone ER 8mg 2) 8mg 3) 32 MME	259	319	212	332
Rauck 2013 [49]	12 weeks (≤16 day titration phase)	1) OROS hydromorphone ER 16mg 2) 16mg 3) 64 MME	289	330	212	332
Spierings 2013 [50]	16 weeks	1) Oxycodone CR 2) 23mg 3) 34.5 MME	100	158	50	141
Mayorga 2016 [51]	16 weeks	1) Oxycodone CR 20-50mg BD 2) 70mg 3) 105 MME	40	50	37	48
Serrie 2017 [53]	12 weeks (3 weeks titration)	1) Tapentadol PR 2) 315.2 (108)mg 3) 126.1 MME	214	319	187	337
Serrie 2017 [53]	12 weeks (3 weeks titration)	1) Oxycodone CR 2) 54.1 (18.2)mg 3) 81.2 MME	281	331	187	337

CR=Controlled released; bd=twice daily; PR=prolonged release; IR=immediate release; ER=extended release; q12 hrly=every 12 hours.

Table 14. Nature and rates of adverse events

Study	Constipation	Nausea	Vomiting	Dry mouth	Diarrhoea	Fatigue	Pruritis	Somnolence	Dizziness	Headache
Roth 1998 [19]	TER: (9/20) PER: (0/21) RR: 19.9 [1.23-321]	TER: (7/20) PER: (3/21) RR: 2.45 [0.73-8.2]	TER: (2/20) PER: (2/21) RR: 1.05 [0.16-6.76]	TER: (2/20) PER: (2/21) RR: 1.05 [0.16-6.76]			TER: (1/20) PER: (0/21) RR: 3.14 [0.14-72.9]	TER: (5/20) PER: (3/21) RR: 1.75 [0.48-6.38]	TER: (3/20) PER: (0/21) RR: 7.33 [0.40-134]	TER: (1/20) PER: (3/21) RR: 0.35 [0.04-3.09]
Caldwell 1999 [20] Oxycodone CR	TER: (24/34) PER: (16/36) RR: 1.59 [1.04-2.43]	TER: (5/34) PER: (13/36) RR: 0.41 [0.16-1.02]	TER: (2/34) PER: (0/36) RR: 5.29 [0.26-106]	TER: (11/34) PER: (12/36) RR: 0.97 [0.50-1.90]			TER: (11/34) PER: (10/36) RR: 1.16 [0.57-2.38]	TER: (18/34) PER: (13/36) RR: 1.47 [0.86-2.51]	TER: (4/34) PER: (10/36) RR: 0.42 [0.15-1.22]	
Caldwell 1999 [20] Oxycodone IR + paracetamol	TER: (20/34) PER: (16/36) RR: 1.22 [0.76-1.95]	TER: (14/34) PER: (13/36) RR: 1.05 [0.58-1.91]	TER: (4/34) PER: (0/36) RR: 8.76 [0.49-157]	TER: (20/34) PER: (12/36) RR: 1.62 [0.94-2.81]			TER: (14/37) PER: (10/36) RR: 1.36 [0.70-2.66]	TER: (26/37) PER: (13/36) RR: 1.95 [1.20-3.15]	TER: (9/37) PER: (10/36) RR: 0.88 [0.40-1.90]	
Peloso 2000 [21]	TER: (15/31) PER: (4/35) RR: 4.23 [1.57-11.41]							TER: (12/31) PER: (3/35) RR: 4.52 [1.40-15]	TER: (10/31) PER: (3/35) RR: 3.76 [1.14-12.5]	
Roth 2000 [22] Oxycodone CR 10 mg	TER: (10/44) PER: (3/45) RR: 3.41 [1.00-11.6]	TER: (12/44) PER: (5/45) RR: 2.45 [0.94-6.39]	TER: (5/44) PER: (3/45) RR: 1.70 [0.43-6.71]				TER: (8/44) PER: (1/45) RR: 8.18 [1.07-62.7]	TER: (11/44) PER: (2/45) RR: 5.63 [1.32-23.9]	TER: (13/44) PER: (4/45) RR: 3.32 [1.17-9.41]	TER: (4/44) PER: (3/34) RR: 1.36 [0.32-5.74]
Roth 2000 [22] Oxycodone CR 20 mg	TER: (14/44) PER: (3/45) RR: 4.77 [1.47-15.5]	TER: (18/44) PER: (5/45) RR: 3.68 [1.50-9.05]	TER: (10/44) PER: (3/45) RR: 3.41 [1.00-11.6]				TER: (7/44) PER: (1/45) RR: 7.16 [0.92-55.8]	TER: (12/44) PER: (2/45) RR: 6.14 [1.46-25.9]	TER: (9/44) PER: (4/45) RR: 2.30 [0.76-6.93]	TER: (5/44) PER: (3/45) RR: 1.70 [0.43-6.71]
Fleischmann 2001 [23]	TER: (8/63) PER: (0/66) RR: 17.8 [1.05-302]	TER: (11/63) PER: (2/66) RR: 5.76 [1.33-24.9]							TER: (6/63) PER: (2/66) RR: 3.14 [0.66-15.0]	TER: (5/63) PER: (0/66) RR: 11.52 [0.65-204]

Study	Constipation	Nausea	Vomiting	Dry mouth	Diarrhoea	Fatigue	Pruritis	Somnolence	Dizziness	Headache
Caldwell 2002 [24] Morphine morning dose	TER: (36/73) PER: (3/73) RR: 12.0 [3.87-37.2]	TER: (15/73) PER: (7/73) RR: 2.14 [0.93-4.95]	TER: (4/73) PER: (1/73) RR: 4.00 [0.46-34.9]	TER: (4/73) PER: (1/73) RR: 4.00 [0.46-34.9]	TER: (0/73) PER: (4/73) RR: 0.11 [0.01-2.03]		TER: (4/73) PER: (0/73) RR: 9.00 [0.49-164.2]	TER: (12/73) PER: (0/73) RR: 25.0 [1.51-415]	TER: (7/73) PER: (1/73) RR: 7.00 [0.88-55.5]	TER: (4/73) PER: (4/73) RR: 1.00 [0.26-3.85]
Caldwell 2002 [24] Morphine night dose	TER: (29/73) PER: (3/73) RR: 9.67 [3.08-30.3]	TER: (23/73) PER: (7/73) RR: 3.29 [1.50-7.18]	TER: (12/73) PER: (1/73) RR: 12.0 [1.60-89.9]	TER: (3/73) PER: (1/73) RR: 3.00 [0.32-28.2]	TER: (4/73) PER: (6/73) RR: 0.67 [0.20-2.26]		TER: (7/73) PER: (0/73) RR: 15.0 [0.87-258]	TER: (9/73) PER: (0/73) RR: 19.0 [1.13-321]	TER: (7/73) PER: (1/73) RR: 7.0 [0.88-55.5]	TER: (3/73) PER: (4/73) RR: 0.75 [0.17-3.23]
Caldwell 2002 [24] Morphine 15 mg twice a day	TER: (22/76) PER: (3/73) RR: 7.04 [2.20-22.5]	TER: (20/76) PER: (7/73) RR: 2.74 [1.23-6.10]	TER: (6/76) PER: (1/73) RR: 5.76 [0.71-46.7]	TER: (2/76) PER: (1/73) RR: 1.92 [0.18-20.7]	TER: (1/76) PER: (4/73) RR: 0.24 [0.03-2.10]		TER: (2/76) PER: (0/73) RR: 4.81 [0.23-98.4]	TER: (9/76) PER: (0/76) RR: 18.3 [1.08-308]	TER: (9/76) PER: (1/73) RR: 8.64 [1.12-66.5]	TER: (5/76) PER: (4/73) RR: 1.20 [0.34-4.30]
Silverfield 2002 [25]	TER: (9/197) PER: (4/111) RR: 1.27 [0.40-4.02]	TER: (34/197) PER: (4/111) RR: 4.79 [1.75-13.1]	TER: (18/197) PER: (2/111) RR: 5.07 [1.20-21.5]		TER: (6/197) PER: (5/111) RR: 0.68 [0.21-2.17]		TER: (12/197) PER: (1/111) RR: 6.76 [0.89-51.3]	TER: (14/197) PER: (2/111) RR: 3.94 [0.91-17.0]	TER: (23/197) PER: (5/111) RR: 2.59 [1.01-6.63]	TER: (5/197) PER: (9/111) RR: 0.31 [0.11-0.91]
Babul 2004 [26]	TER: (26/124) PER: (6/122) RR: 4.26 [1.82-9.99]	TER: (24/124) PER: (8/122) RR: 2.95 [1.38-6.31]	TER: (7/124) PER: (0/122) RR: 14.8 [0.85-256]	TER: (3/124) PER: (1/122) RR: 2.95 [0.31-28.0]	TER: (10/124) PER: (4/122) RR: 2.46 [0.79-7.63]	TER: (7/124) PER: (2/122) RR: 3.44 [0.73-16.3]	TER: (7/124) PER: (2/122) RR: 3.44 [0.73-16.3]	TER: (8/124) PER: (2/122) RR: 3.94 [0.85-18.2]	TER: (33/124) PER: (12/122) RR: 2.71 [1.47-4.99]	TER: (15/124) PER: (16/122) RR: 1.16 [0.40-3.32]
Emkey 2004 [27]	TER: (18/153) PER: (5/153) RR: 3.60 [1.37-9.45]	TER: (23/153) PER: (7/153) RR: 3.29 [1.45-7.43]	TER: (4/153) PER: (0/153) RR: 9.00 [0.49-65.7]			TER: (10/153) PER: (2/153) RR: 5.00 [1.11-22.4]		TER: (18/153) PER: (1/153) RR: 18.00 [2.43-133.16]	TER: (10/153) PER: (4/153) RR: 2.50 [0.80-7.80]	
Malonne 2004 [28]	TER: (11/111) PER: (2/119) RR: 5.90 [1.34-26.0]	TER: (25/111) PER: (8/119) RR: 3.35 [1.58-7.11]	TER: (19/111) PER: (1/119) RR: 20.37 [2.77-49.6]		TER: (1/111) PER: (2/119) RR: 0.54 [0.05-5.83]	TER: (5/111) PER: (1/110) RR: 5.36 [0.64-45.2]		TER: (13/111) PER: (0/119) RR: 28.9 [1.74-481]	TER: (9/111) PER: (2/119) RR: 4.82 [1.07-21.8]	TER: (5/111) PER: (4/119) RR: 1.34 [0.37-4.86]

Study	Constipation	Nausea	Vomiting	Dry mouth	Diarrhoea	Fatigue	Pruritis	Somnolence	Dizziness	Headache
Chindalore 2005 [29] Oxycodone CR	TER: (19/102) PER: (4/51) RR: 2.38 [0.85-6.62]	TER: (37/102) PER: (6/51) RR: 3.08 [1.39-6.82]	TER: (15/102) PER: (3/51) RR: 2.50 [0.76-8.24]	TER: (9/102) PER: (0/51) RR: 9.59 [0.57-162]	TER: (9/102) PER: (4/51) RR: 1.13 [0.36-3.48]	TER: (8/102) PER: (4/51) RR: 1.00 [0.32-3.17]	TER: (12/102) PER: (2/51) RR 3.00 [0.70, 12.9]	TER (21/102) PER (2/51) RR 3.50 [1.09, 11.2]	TER (26/102) PER (0/51) RR 26.8 [1.66, 430]	TER (24/102) PER (12/51) RR 1.00 [0.55, 1.83]
Chindalore 2005 [31] Oxycodone + naltrexone four times a day	TER (23/104) PER (4/51) RR 2.82 [1.03, 7.72]	TER (25/104) PER (6/51) RR 2.04 [0.89, 4.67]	TER (5/104) PER (3/51) RR 0.82 [0.20, 3.29]	TER: (9/104) PER: (0/51) RR: 9.41 [0.56-159]	TER: (14/104) PER: (4/51) RR: 1.72 [0.59-4.95]	TER: (13/104) PER: (4/51) RR: 1.59 [0.55-4.64]	TER: (7/104) PER: (2/51) RR: 1.72 [0.37-7.97]	TER: (23/104) PER: (3/51) RR: 3.76 [1.18-11.9]	TER: (27/104) PER: (0/51) RR: 27.24 [1.69-437.8]	TER: (18/104) PER: (12/51) RR: 0.74 [0.38-1.41]
Chindalore 2005 [29] Oxycodone + naltrexone twice a day	TER: (18/103) PER: (4/51) RR: 2.23 [0.80-6.24]	TER: (40/103) PER: (6/51) RR: 3.30 [1.50-7.27]	TER: (12/103) PER: (3/51) RR: 1.98 [0.58-6.71]	TER: (15/103) PER: (0/51) RR: 15.5 [0.95-254]	TER: (10/103) PER: (4/51) RR: 1.24 [0.41-3.76]	TER: (7/103) PER: (4/51) RR: 0.87 [0.27-2.82]	TER: (19/103) PER: (2/51) RR: 4.70 [1.14-19.4]	TER: (19/103) PER: (3/51) RR: 3.14 [0.97-10.1]	TER: (33/103) PER: (0/51) RR: 33.5 [2.09-536]	TER: (18/103) PER: (12/51) RR: 0.74 [0.39-1.42]
Markenson 2005 [30]	TER: (27/56) PER: (5/51) RR: 4.92 [2.05-11.8]	TER: (23/56) PER: (7/51) RR: 2.99 [1.40-6.37]	TER: (7/56) PER: (1/51) RR: 6.38 [0.81-50.1]		TER: (7/56) PER: (4/51) RR: 1.59 [0.50-5.13]		TER: (12/56) PER: (0/51) RR: 22.8 [1.38-376]	TER: (18/56) PER: (5/51) RR: 3.28 [1.31-8.19]	TER: (18/56) PER: (3/51) RR: 5.46 [1.71-17.5]	TER: (11/56) PER: (10/51) RR: 1.00 [0.46-2.16]
Matsumoto 2005 [31] Oxymorphone 50mg	TER: (29/121) PER: (14/124) RR: 2.12 [1.18-3.82]	TER: (72/121) PER: (13/124) RR: 5.68 [3.32-9.69]	TER: (41/121) PER: (2/124) RR: 21.0 [5.20-84.9]	TER: (14/121) PER: (1/124) RR: 14.4 [1.92-107.4]			TER: (30/121) PER: (3/124) RR: 10.3 [3.21-32.7]	TER: (38/121) PER: (6/124) RR: 6.49 [2.85-14.8]	TER: (38/121) PER: (5/124) RR: 7.79 [3.17-19.1]	TER: (13/121) PER: (14/124) RR: 0.95 [0.47-1.94]
Matsumoto 2005 [31] Oxymorphone 40mg	TER: (48/119) PER: (14/124) RR: 3.57 [2.08-6.13]	TER: (73/119) PER: (13/124) RR: 5.85 [3.43-9.98]	TER: (27/119) PER: (2/124) RR: 14.1 [3.42-57.9]	TER: (14/119) PER: (1/124) RR: 14.59 [1.95-109.2]			TER: (23/119) PER: (3/124) RR: 7.99 [2.46-25.9]	TER: (36/119) PER: (6/124) RR: 6.25 [2.73-14.3]	TER: (34/119) PER: (5/124) RR: 7.09 [2.87-17.5]	TER: (7/119) PER: (14/124) RR: 0.52 [0.22-1.25]

Study	Constipation	Nausea	Vomiting	Dry mouth	Diarrhoea	Fatigue	Pruritis	Somnolence	Dizziness	Headache
Matsumoto 2005 [31] Oxycodone CR 40mg	TER: (45/125) PER: (14/124) RR: 3.19 [1.85-5.50]	TER: (54/125) PER: (13/124) RR: 4.12 [2.37-7.16]	TER: (13/125) PER: (2/124) RR: 6.45 [1.49-28.0]	TER: (19/125) PER: (1/124) RR: 18.85 [2.56-138.6]			TER: (10/125) PER: (3/124) RR: 3.31 [0.93-11.7]	TER: (34/125) PER: (6/124) RR: 5.62 [2.45-12.9]	TER: (32/125) PER: (5/124) RR: 6.35 [2.56-15.8]	TER: (23/125) PER: (14/124) RR 1.63 [0.88, 3.02]
Gana 2006 Tramadol 100mg [34]	TER (26/202) PER (12/205) RR 2.20 [1.14, 4.24]	TER: (30/202) PER: (15/205) RR: 2.03 [1.13-3.66]	TER: (11/202) PER: (6/205) RR: 1.86 [0.70-4.94]	TER: (11/202) PER: (2/205) RR: 5.58 [1.25-24.9]	TER: (7/202) PER: (5/205) RR: 1.42 [0.46-4.40]	TER: (9/202) PER: (2/205) RR: 4.57 [1.00-20.9]	TER: (12/202) PER: (3/205) RR: 4.06 [1.16-14.2]	TER: (17/202) PER: (5/205) RR: 3.45 [1.30-9.18]	TER: (34/202) PER: (13/205) RR: 2.65 [1.44-4.88]	TER: (29/202) PER: (17/205) RR: 1.73 [0.98-3.05]
Gana Tramadol 200mg 2006 [32]	TER: (33/201) PER: (12/205) RR: 2.80 [1.49-5.27]	TER: (47/201) PER: (15/205) RR: 3.20 [1.85-5.53]	TER: (15/201) PER: (6/205) RR: 2.55 [1.01-6.44]	TER: (13/201) PER: (2/205) RR: 6.63 [1.52-29.0]	TER: (12/201) PER: (5/205) RR: 2.45 [0.88-6.82]	TER: (11/201) PER: (2/205) RR: 5.61 [1.26-25.0]	TER: (16/201) PER: (3/205) RR: (5.44 [1.61-18.4]	TER: (21/201) PER: (5/205) RR: 4.28 [1.65-11.1]	TER: (37/201) PER: (13/205) RR: 2.90 [1.59-5.30]	TER: (30/201) PER: (17/205) RR: 1.80 [1.03-3.16]
Gana Tramadol 300mg 2006 [32]	TER: (45/201) PER: (12/205) RR: 3.82 [2.09-7.01]	TER: (49/201) PER: (15/205) RR: 3.33 [1.93-5.74]	TER: (14/201) PER: (6/205) RR: 2.38 [0.93-6.07]	TER: (22/201) PER: (2/205) RR: 11.2 [2.67-47.1]	TER: (14/201) PER: (5/205) RR: 2.86 [1.05-7.78]	TER: (13/201) PER: (2/205) RR: 6.63 [1.52-29.0]	TER: (13/201) PER: (3/205) RR: 4.42 [1.28-15.3]	TER: (21/201) PER: (5/205) RR: 3.67 [1.39-9.70]	TER: (41/201) PER: (13/205) RR: 3.22 [1.78-5.82]	TER: (21/201) PER: (17/205) RR: 1.26 [0.69-2.32]
Gana Tramadol 400mg 2006 [32]	TER: (60/202) PER: (12/205) RR: 5.07 [2.82-9.14]	TER: (52/202) PER: (15/205) RR: 3.52 [2.05-6.04]	TER: (19/202) PER: (6/205) RR: 3.21 [1.31-7.88]	TER: (18/202) PER: (2/205) RR: 9.13 [2.15-38.9]	TER: (10/202) PER: (5/205) RR: 2.03 [0.71-5.83]	TER: (13/202) PER: (2/205) RR: 6.60 [1.51-28.0]	TER: (24/202) PER: (3/205) RR: 8.12 [2.48-26.5]	TER: (41/202) PER: (5/205) RR: 8.32 [3.36-20.6]	TER: (57/2020) PER: (13/205) RR: 4.45 [2.52-7.87]	TER: (32/202) PER: (17/205) RR: 1.91 [1.10-3.33]
Kivitz Oxymorphone 20mg 2006 [33]	TER: (17/95) PER: (4/91) RR: 4.07 [1.42-11.6]	TER: (22/95) PER: (8/91) RR: 2.63 [1.24-5.61]	TER: (9/95) PER: (2/91) RR: 4.31 [0.96-19.4]	TER: (6/95) PER: (0/91) RR: 12.5 [0.71-218]	TER: (0/95) PER: (6/91) RR: 0.07 [0.00-1.29]	TER: (5/95) PER: (1/91) RR: 4.79 [0.57-40.2]	TER: (5/95) PER: (1/91) RR: 4.79 [0.57-40.2]	TER: (9/95) PER: (3/91) RR: 2.87 [0.80-10.3]	TER: (15/95) PER: (5/91) RR: 2.87 [1.09-7.58]	TER: (10/95) PER: (9/91) RR: 1.06 [0.45-2.50]

Study	Constipation	Nausea	Vomiting	Dry mouth	Diarrhoea	Fatigue	Pruritis	Somnolence	Dizziness	Headache
Kivitz Oxymorphone 80mg 2006 [33]	TER: (25/93) PER: (4/91) RR: 5.99 [2.17-16.5]	TER: (38/93) PER: (8/91) RR: 4.55 [2.25-9.22]	TER: (25/93) PER: (2/91) RR: 12.0 [2.92-49.1]	TER: (10/93) PER: (0/91) RR: 20.1 [1.20-339]	TER: (3/93) PER: (6/91) RR: 0.48 [0.12-1.86]	TER: (11/93) PER: (1/91) RR: 10.5 [1.39-80.0]	TER: (19/93) PER: (1/91) RR: 18.2 [2.49-133]	TER: (21/93) PER: (3/91) RR: 6.71 [2.07-21.7]	TER: (20/93) PER: (5/91) RR: 3.83 [1.50-9.78]	TER: (14/93) PER: (9/91) RR: 1.49 [0.68-3.27]
Kivitz Oxymorphone 100mg 2006 [33]	TER: (20/91) PER: (4/91) RR: 5.00 [1.78-14.1]	TER: (50/91) PER: (8/91) RR: 6.25 [3.14-12.4]	TER: (32/91) PER: (2/91) RR: 16.0 [3.95-64.8]	TER: (8/91) PER: (0/91) RR: 17.0 [1.00-290]	TER: (6/91) PER: (6/91) RR: 1.00 [0.33-2.99]	TER: (3/91) PER: (1/91) RR: 3.00 [0.32-28.3]	TER: (22/91) PER: (1/91) RR: 22.00 [3.03-160]	TER: (19/91) PER: (3/91) RR: 6.33 [1.94-20.7]	TER: (28/91) PER: (5/91) RR: 5.60 [2.26-13.9]	TER: (17/91) PER: (9/91) RR: 1.89 [0.89-4.01]
Langford 2006 [34]	TER: (22/216) PER: (3/200) RR: 6.79 [2.06-22.3]	TER: (94/216) PER: (37/200) RR: 2.35 [1.69-3.27]	TER: (61/216) PER: (5/200) RR: 11.3 [4.63-27.5]					TER: (48/216) PER: (7/200) RR: 6.35 [2.94-13.7]	TER: (26/216) PER: (10/200) RR: 2.41 [1.19-4.86]	TER: (23/216) PER: (23/200) RR: 0.93 [0.54-1.60]
NCT00313846 2006 [35]	TER: (10/164) PER: (6/162) RR: 1.65 [0.61-4.42]	TER: (12/164) PER: (3/162) RR: 3.95 [1.14-13.7]	TER: (1/164) PER: (0/162) RR: 2.96 [0.12-72.2]					TER: (2/164) PER: (0/162) RR: 4.94 [0.24-102.1]	TER: (5/164) PER: (4/162) RR: 1.23 [0.34-4.52]	
NCT00531427 2007 [36]	TER: (19/282) PER: (2/285) RR: 9.60 [2.26-40.8]	TER: (34/282) PER: (14/285) RR: 2.45 [1.35-4.47]	TER: (19/282) PER: (5/285) RR: 3.84 [1.45-10.1]			TER: (7/282) PER: (4/285) RR: 2.36 [0.62-9.03]		TER: (10/282) PER: (5/285) RR: 2.02 [0.70-5.84]	TER: (7/282) PER: (6/285) RR: 1.18 [0.40-3.46]	TER: (18/282) PER: (20/282) RR: 0.91 [0.49-1.68]
Burch 2007 [37]	TER: (61/432) PER: (9/214) RR: 3.36 [1.70-6.63]	TER: (66/432) PER: (12/214) RR: 2.72 [1.51-4.93]						TER: (29/432) PER: (8/214) RR: 1.80 [0.84-3.86]	TER: (42/432) PER: (8/214) RR: 2.60 [1.24-5.44]	
Fishman 2007 [38] Tramadol 100mg	TER: (12/106) PER: (3/227) RR: 8.57 [2.47-29.7]	TER: (12/106) PER: (13/227) RR: 1.98 [0.93-4.18]	TER: (4/106) PER: (1/227) RR: 8.57 [0.97-75.7]	TER: (3/106) PER: (2/227) RR: 3.21 [0.54-18.9]			TER: (8/106) PER: (0/227) RR: 36.2 [2.11-622]	TER: (9/106) PER: (2/227) RR: 9.64 [2.12-43.8]	TER: (12/106) PER: (11/227) RR: 2.34 [1.07-5.12]	TER: (6/106) PER: (18/227) RR: 0.71 [0.29-1.75]

Study	Constipation	Nausea	Vomiting	Dry mouth	Diarrhoea	Fatigue	Pruritis	Somnolence	Dizziness	Headache
Fishman 2007 [38] Tramadol 200mg	TER: (16/111) PER: (3/227) RR: 10.91 [3.25-36.7]	TER: (22/111) PER: (13/227) RR: 3.46 [1.81-6.61]	TER: (6/111) PER: (1/227) RR: 12·27 [1.50-100.7]	TER: (10/111) PER: (2/227) RR: 10.23 [2.28-45.9]			TER: (9/111) PER: (0/227) RR: 38.68 [2.27-658.6]	TER: (17/111) PER: (2/227) RR: 17.38 [4.09-73.9]	TER: (11/111) PER: (11/227) RR: 2.05 [0.91-4.57]	TER: (10/111) PER: (18/227) RR: 1.14 [0.54-2.38]
Fishman 2007 [38] Tramadol 300mg	TER: (11/108) PER: (3/227) RR: 7.71 [2.20-27.1]	TER: (28/108) PER: (13/227) RR: 4.53 [2.44-8.39]	TER: (16/108) PER: (1/227) RR: 33.6 [4.52-250]	TER: (1/108) PER: (2/227) RR: 1.05 [0.10-11.5]			TER: (10/108) PER: (0/227) RR: 43.9 [2.60-743]	TER: (13/108) PER: (2/108) RR: 13.7 [3.14-59.5]	TER: (23/108) PER: (11/227) RR: 4.39 [2.22-8.68]	TER: (6/108) RR: (18/227) RR: 0.70 [0.29-1.71]
Hartrick 2009 [39]	TER: (7/157) PER: (4/169) RR: 1.88 [0.56-6.31]	TER: (29/157) PER: (9/169) RR: 3.47 [1.70-7.09]	TER: (11/157) PER: (7/169) RR: 1.69 [0.67-4.25]		TER: (2/157) PER: (5/169) RR: 0.43 [0.08-2.19]	TER: (1/157) PER: (2/169) RR: 0.54 [0.05-5.88]	TER: (3/157) PER: (1/169) RR: 3.23 [0.34-30.7]	TER: (10/157) PER: (2/169) RR: 5.38 [1.20-24.2]	TER: (29/157) PER: (8/169) RR: 3.90 [1.84-8.28]	TER: (10/157) PER: (10/169) RR: 1.08 [0.46-2.52]
NCT00979953 2009 [41]	TER: (30/104) PER: (4/104) RR: 7.50 [2.74-20.5]	TER: (32/104) PER: (4/104) RR: 8.00 [2.93-21.8]	TER: (15/104) PER: (0/104) RR: 31.0 [1.88-511]	TER: (13/104) PER: (6/104) RR: 2.17 [0.86-5.48]	TER: (3/104) PER: (1/104) RR: 3.00 [0.32-28.4]	TER: (17/104) PER: (7/104) RR: 2.43 [1.05-5.61]	TER: (17/104) PER: (2/104) RR: 8.50 [2.01-35.9]	TER: (20/104) PER: (8/104) RR: 2.50 [1.15-5.42]	TER: (17/104) PER: (2/104) RR: 8.50 [2.01-35.9]	TER: (13/104) PER: (3/104) RR: 4.33 [1.27-14.8]
Afilalo 2010 [42] Tapentadol	TER: (65/344) PER: (22/337) RR: 2.89 [1.83-4.58]	TER: (74/344) PER: (23/337) RR: 3.15 [2.02-4.91]	TER: (18/344) PER: (11/337) RR: 1.60 [0.77-3.34]	TER: (22/344) PER: (8/337) RR: 2.69 [1.22-5.97]	TER: (16/344) PER: (20/337) RR: 0.78 [0.41-1.49]	TER: (37/344) PER: (15/337) RR: 2.42 [1.35-4.32]	TER: (24/344) PER: (4/337) RR: 5.88 [2.06-16.8]	TER: (37/344) PER: (14/337) RR: 2.59 [1.43-4.70]	TER: (61/344) PER: (16/337) RR: 3.73 [2.20-6.34]	TER: (51/344) PER: (56/337) RR: 0.89 [0.64-1.26]
Afilalo 2010 [42] Oxycodone	TER: (126/342) PER: (22/337) RR: 5.64 [3.68-8.65]	TER: (125/342) PER: (23/337) RR: 5.36 [3.52-8.14]	TER: (61/342) PER: (11/337) RR: 5.46 [2.93-10.2]	TER: (15/342) PER: (8/337) RR: 1.85 [0.79-4.30]	TER: (17/342) PER: (20/337) RR: 0.84 [0.45-1.57]	TER: (35/342) PER: (15/337) RR: 2.30 [1.28-4.13]	TER: (43/342) PER: (4/337) RR: 10.59 [3.84-29.18]	TER: (67/342) PER: (14/337) RR: 4.72 [2.70-8.22]	TER: (65/342) PER: (16/337) RR: 4.00 [2.37-6.77]	TER: (50/342) PER: (56/337) RR: 0.92 [0.48-1.78]

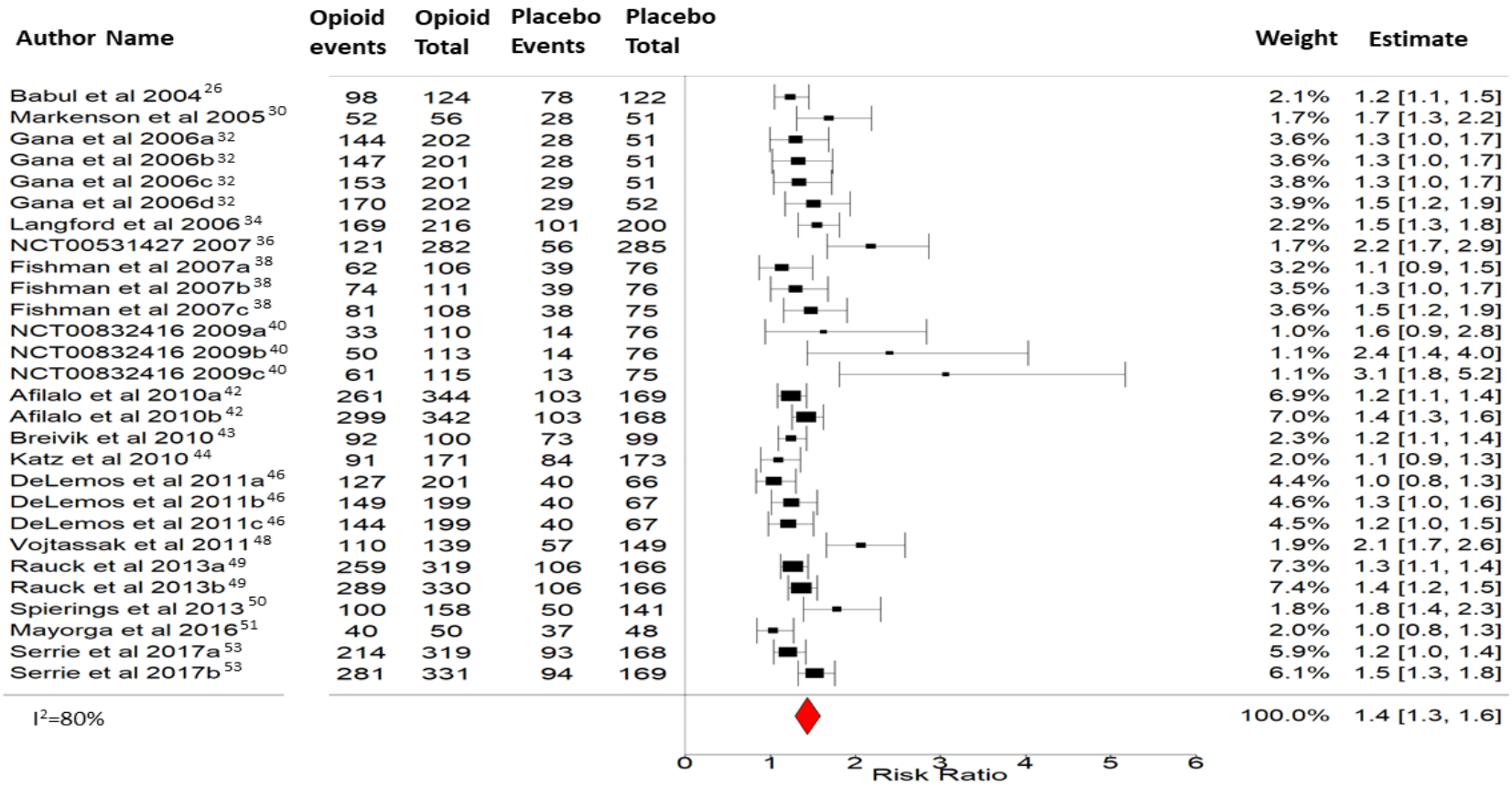
Study	Constipation	Nausea	Vomiting	Dry mouth	Diarrhoea	Fatigue	Pruritis	Somnolence	Dizziness	Headache
Breivik 2010 [43]	TER: (24/100) PER: (5/99) RR: 4.75 [1.89-12.0]	TER: (37/100) PER: (10/99) RR: 3.66 [1.93-6.95]	TER: (16/100) PER: (2/99) RR: 7.92 [1.87, 33.5]					TER: (4/100) PER: (0/99) RR: 8.91 [0.49-163.4]	TER: (25/100) PER: (9/99) RR: 2.75 [1.35-5.59]	TER: (7/100) PER: (6/100) RR: 1.16 [0.40-3.32]
Katz 2010 [44]	TER: (12/171) PER: (7/173) RR: 1.73 [0.70-4.30]	TER: (20/171) PER: (13/173) RR: 1.56 [0.80-3.03]	TER: (12/171) PER: (4/173) RR: 3.04 [1.00-9.22]	TER: (3/171) PER: (2/173) RR: 1.52 [0.26-8.97]	TER: (21/171) PER: (21/173) RR: 1.01 [0.57, 1.78]		TER (1/171) PER (1/173) RR 1.01 [0.06, 16.0]	TER (2/171) PER (5/173) RR 0.40 [0.08, 2.06]	TER (3/171) PER (3/173) RR 1.01 [0.21, 4.94]	TER (12/171) PER (6/173) RR 2.02 [0.78, 5.27]
Munera 2010 [47]	TER (15/152) PER (3/163) RR 5.36 [1.58, 18.2]	TER (41/152) PER (13/163) RR 3.38 [1.89, 6.06]	TER (16/152) PER (4/163) RR 4.29 [1.47, 12.5]	TER (12/152) PER (2/163) RR 6.43 [1.46, 28.3]			TER (8/152) PER (4/163) RR 2.14 [0.66, 6.98]	TER (23/152) PER (8/163) RR 3.08 [1.42, 6.68]	TER (30/152) PER (14/163) RR: 2.30 [1.27-4.16]	TER: (34/152) PER: (25/163) RR: 1.46 [0.91-2.33]
DeLemos 2011 [46] Tramadol 100mg	TER: (23/201) PER: (5/200) RR 4.58 [1.78-11.8]	TER: (31/201) PER: (17/200) RR: 1.81 [1.04-3.17]	TER: (9/201) PER: (5/200) RR: 1.79 [0.61-5.25]	TER: (9/201) PER: (4/200) RR: 2.24 [0.70-7.15]	TER: (8/201) PER: (12/200) RR: 0.66 [0.28-1.59]	TER: (5/201) PER: (5/200) RR: 1.00 [0.29-3.38]	TER: (12/201) PER: (1/200) RR: 11.9 [1.57-91.0]	TER: (16/201) PER: (2/200) RR: 7.96 [1.85-34.2]	TER: (30/201) PER: (15/200) RR: 1.99 [1.11-3.58]	TER: (21/201) PER: (26/200) RR: 0.80 [0.47-1.38]
DeLemos 2011 [46] Tramadol 200mg	TER: (35/199) PER: (5/200) RR: 7.04 [2.81-17.6]	TER: (41/199) PER: (17/200) RR: 2.42 [1.43-4.12]	TER: (14/199) PER: (5/200) RR: 2.81 [1.03-7.67]	TER: (16/199) PER: (4/200) RR: 4.02 [1.37-11.8]	TER: (15/199) PER: (12/200) RR: 1.26 [0.60-2.62]	TER: (12/199) PER: (5/200) RR: 2.41 [0.87-6.72]	TER: (18/199) PER: (1/200) RR: 18.1 [2.44-134]	TER: (24/199) PER: (2/200) RR: 12.1 [2.89-50.4]	TER: (45/199) PER: (15/200) RR: 3.02 [1.74-5.23]	TER: (31/199) PER: (26/200) RR: 1.20 [0.74-1.94]
DeLemos 2011 [46] Tramadol 300mg	TER: (40/199) PER: (5/200) RR: 8.04 [3.24-20.0]	TER: (52/199) PER: (17/200) RR: 3.07 [1.84-5.13]	TER: (20/199) PER: (5/200) RR: 4.02 [1.54-10.5]	TER: (17/199) PER: (4/200) RR: 4.27 [1.46-12.5]	TER: (20/199) PER: (12/200) RR: 1.68 [0.84-3.33]	TER: (13/199) PER: (5/200) RR: 2.61 [0.95-7.19]	TER: (18/199) PER: (1/200) RR: 17.1 [2.30-127]	TER: (11/199) PER: (2/200) RR: 5.53 [1.24-24.6]	TER: (48/199) PER: (15/200) RR: 3.22 [1.86-5.55]	TER: (25/199) PER: (26/200) RR: 0.97 [0.58-1.61]

Study	Constipation	Nausea	Vomiting	Dry mouth	Diarrhoea	Fatigue	Pruritis	Somnolence	Dizziness	Headache
Vojtassak 2011* [48] Data from clinical trial registry NCT00980798	TER: (63/139) PER: (10/149) RR: 6.75 [3.61-12.6]	TER: (41/139) PER: (10/149) RR: 4.39 [2.29-8.43]	TER: (15/139) PER: (2/149) RR: 8.04 [1.87-34.5]	TER: (11/139) PER: (7/149) RR: 1.68 [0.67-4.22]	TER: (1/139) PER: (0/149) RR: 3.21 [0.13-78.3]		TER: (10/139) PER: (1/149) RR: 10.7 [1.39-82.7]	TER: (45/139) PER: (22/149) RR: 2.19 [1.39-3.45]	TER: (15/139) PER: (5/149) RR: 3.22 [1.20-8.61]	TER: (8/139) PER: (4/149) RR: 2.14 [0.66-6.96]
Rauck 2013 [49] Hydromorphone 8mg	TER: (131/319) PER: (39/332) RR: 3.50 [2.53-4.83]	TER: (96/319) PER: (32/332) RR: 3.12 [2.16-4.52]	TER: (29/319) PER: (7/332) RR: 4.31 [1.92-9.70]				TER: (27/319) PER: (8/332) RR: 3.51 [1.62-7.62]	TER: (51/319) PER: (16/332) RR: 3.32 [1.93-5.69]	TER: (34/319) PER: (20/332) RR: 1.77 [1.04-3.01]	TER: (41/319) PER: (38/332) RR: 1.12 [0.74-1.70]
Rauck 2013 [49] Hydromorphone 16mg	TER: (155/330) PER: (39/332) RR: 4.00 [2.91-5.49]	TER: (120/330) PER: (32/332) RR: 3.77 [2.63-5.40]	TER: (38/330) PER: (7/332) RR: 5.46 [2.47-12.1]				TER: (39/330) PER: (8/332) RR: 4.90 [2.33-10.3]	TER: (51/330) PER: (16/332) RR: 3.21 [1.87-5.51]	TER: (48/330) PER: (20/332) RR: 2.41 [1.47-3.98]	TER: (43/330) PER: (28/332) RR: 1.14 [0.76-1.71]
Spierings 2013 [50]	TER: (24/158) PER: (2/141) RR: 10.7 [2.58-44.5]	TER: (25/158) PER: (0/141) RR: 45.6 [2.80-741]	TER: (15/158) PER: (1/141) RR: 13.4 [1.79-100.1]			TER: (7/158) PER: (1/141) RR: 6.25 [0.78-50.2]	TER: (10/158) PER: (1/141) RR: 8.92 [1.16-68.9]	TER: (7/158) PER: (0/141) RR: 13.40 [0.77-232.5]	TER: (10/158) PER: (2/141) RR: 4.46 [0.99-, 20.02]	TER (8/158) PER (7/141) RR: 1.02 [0.38-2.74]
Mayorga 2016 [51]	TER: (16/50) PER: (0/48) RR: 31.7 [1.96-514]	TER: (14/50) PER: (4/48) RR: 3.36 [1.19-9.49]	TER: (8/50) PER: (3/48) RR: 2.56 [0.72-9.08]		TER: (1/50) PER: (2/48) RR: 0.48 [0.04-5.12]	TER: (5/50) PER: (1/48) RR: 4.80 [0.58-39.6]	TER: (4/50) PER: (0/48) RR: 8.65 [0.48-156]	TER: (11/50) PER: (2/48) RR: 5.28 [1.23-22.6]	TER: (7/50) PER: (1/48) RR: 6.72 [0.86-52.6]	TER: (2/50) PER: (5/48) RR: 0.38 [0.08-1.89]
Serrie 2017 [53] Tapentadol	TER: (57/319) PER: (31/337) RR: 1.94 [1.29-2.93]	TER: (65/319) PER: (21/337) RR: 3.27 [2.05-5.22]	TER: (33/319) PER: (13/337) RR: 2.68 [1.44-5.00]	TER: (19/319) PER: (7/337) RR: 2.87 [1.22-6.73]	TER: (16/319) PER: (15/337) RR: 1.13 [0.57-2.24]	TER: (25/319) PER: (11/337) RR: 2.40 [1.20-4.80]	TER: (4/319) PER: (6/337) RR: 0.70 [0.20-2.47]	TER: (34/319) PER: (13/337) RR: 2.76 [1.49-5.14]	TER: (70/319) PER: (29/337) RR: 2.55 [1.70-3.82]	TER: (33/319) PER: (31/337) RR: 1.12 [0.71-1.79]

Study	Constipation	Nausea	Vomiting	Dry mouth	Diarrhoea	Fatigue	Pruritis	Somnolence	Dizziness	Headache
Serrie 2017 [53] Oxycodone	TER: (116/331) PER: (31/337) RR: 3.81 [2.64-5.49]	TER: (124/331) PER: (21/337) RR: 6.01 [3.88-9.31]	TER: (86/331) PER: (13/337) RR: 6.74 [3.84-11.8]	TER: (13/331) PER: (7/337) RR: 1.89 [0.76-4.68]	TER: (26/331) PER: (15/337) RR: 1.76 [0.95-3.27]	TER: (33/331) PER: (11/337) RR: 3.05 [1.57-5.94]	TER: (36/331) PER: (6/337) RR: 6.11 [2.61-14.3]	TER: (48/337) PER: (13/337) RR: 3.76 [2.08-6.81]	TER: (89/331) PER: (20/337) RR: 3.12 [2.11-4.62]	TER: (27/331) PER: (31/337) RR: 0.89 [0.54-1.45]

TER: Treatment Event rate; PER: Placebo Event Rate; RR: risk ratio. Note 95% confidence intervals have been presented for risk ratios

Figure 4. Medium term effects of opioid medications on adverse events in people with osteoarthritis pain



Note: refer to Supplementary table 6 for opioid dose regimens

Table 15. Sensitivity analyses

Outcome and time point	Effect (95% CI)	Number of trials (number of participants)	Study limitation	Imprecision	Inconsistency	Publication bias	GRADE
Medium term pain							
With industry funding	MD (95% CI) -4.01 (-6.10, -1.91)	18 (8719)	Yes	No	I^2=51%	No (Egger p=0.73)	Low
Modified release	MD (95% CI) -4.39 (-7.06, -1.72)	18 (8836)	Yes	No	I^2=70%	No (Egger p=0.13)	Low
Immediate release	MD (95% CI) -9.50 (-19.0, -0.04)	1 (129)	Yes	Yes	I^2=0	NA	Low
Tramadol only	MD (95% CI) -8.13 (-11.76, -4.51)	7 (3871)	Yes	No	I^2=60%	NA	Low
Published, peer reviewed trials	MD (95% CI) -4.86 (-7.72, -2.00)	17 (7837)	Yes	No	I^2=72%	No (Egger 0.24)	Low
Unpublished trials	MD (95% CI) -2.92 (-6.64, 0.80)	2 (1128)	Yes	No	I^2=0%	NA	Moderate
Enrichment design	MD (95% CI) -6.49 (-9.35, -3.64)	3 (1503)	Yes	No	I^2=0	NA	Moderate
Non-Enrichment design	MD (95% CI) -3.73 (-7.00, -0.45)	16 (7355)	Yes	No	I^2=72%	No (Egger 0.16)	Low
With rescue analgesia	MD (95% CI) -1.60 (-5.35, 2.16)	8 (2937)	Yes	No	I^2=70%	NA	Low
Without rescue analgesia	MD (95% CI) -6.82 (-9.83, -3.81)	11 (6028)	Yes	No	I^2=58%	No (Egger 0.43)	Low
Medium term disability							
With industry funding	MD (95% CI) -3.69 (-6.44, -0.93)	15 (6636)	Yes	No	I^2=74%	No (Egger 0.44)	Low
Modified release	MD (95% CI) -3.97 (-6.95, -1.00)	15 (6753)	Yes	No	I^2=78%	No (Egger 0.43)	Low

Outcome and time point	Effect (95% CI)	Number of trials (number of participants)	Study limitation	Imprecision	Inconsistency	Publication bias	GRADE
Immediate release	MD (95% CI) -7.3 (-14.83, 0.23)	1 (129)	Yes	Yes	I^2=0	NA	Low
Tramadol only	MD (95% CI) -7.44 (-12.72, -2.16)	6 (3282)	Yes	No	I^2 =72%	NA	Low
Published, peer reviewed trials	MD (95% CI) -4.27 (-7.27, -1.27)	15 (6234)	Yes	No	I^2=80%	No (Egger p=0.22)	Low
Unpublished trials	MD (95% CI) -1.88 (-9.16, 5.40)	1 (588)	Yes	Yes	I^2=0	NA	Low
Enrichment design	MD (95% CI) -3.90 (-7.73, -0.07)	1 (344)	Yes	No	I^2=0	NA	Low
Non-Enrichment design	MD (95% CI) -4.16 (-7.25, -1.07)	15 (6538)	Yes	No	I^2=78%	No (Egger p=0.39)	Low
With rescue analgesia	MD (95% CI) -1.49 (-4.00, 1.01)	7 (2579)	Yes	No	I^2=57%	NA	Low
Without rescue analgesia	MD (95% CI) -7.00 (-10.67, -3.33)	9 (4303)	Yes	No	I^2=68%	NA	Low

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