Supplementary Online Content

Busse JW, Wang L, Kamaleldin M, et al. Opioids for chronic noncancer pain: a systematic review and meta-analysis. *JAMA*. doi:10.1001/jama.2018.18472

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1: Literature Search Strategies[a]

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present (1 April 2018)

Search Strategy:

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1 (chronic adj4 pain*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (58120)
2 Chronic Pain/ (9487)
3 exp Osteoarthritis/ (54546)
4 osteoarthrit*.mp. (75997)
5 osteo-arthritis.mp. (367)
6 degenerative arthrit*.mp. (1219)
7 exp Arthritis, Rheumatoid/ (104666)
8 exp Neuralgia/ (17706)
9 Diabetic Neuropathies/ (13601)
10 (neuropath* adj5 (pain* or diabet*)).mp. (36937)
11 neuralg*.mp. (23772)
12 zoster.mp. (19225)
13 Irritable Bowel Syndrome/ (6066)
14 (IBS or irritable colon or irritable bowel).mp. (14347)
15 Migraine Disorders/ (23014)
16 migraine.mp. (34507)
17 Fibromyalgia/ (7573)
18 fibromyalg*.mp. (10324)
19 complex regional pain syndromes/ or exp causalgia/ or exp reflex sympathetic dystrophy/ (5219)
20 (complex regional pain syndromes or causalgia).mp. (2139)
21 Pain, Intractable/ (6021)
22 Phantom Limb/ (1737)
23 Hyperalgesia/ (10026)
24 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (16519)
25 or/1-24 (374187)
26 exp back pain/ or exp failed back surgery syndrome/ or exp low back pain/ (34838)
27 Radiculopathy/ or radiculopathy.mp. (8057)
28 musculoskeletal pain/ or headache/ (27891)
29 exp Arthralgia/ (10991)
30 exp Headache Disorders/ (31166)
31 headache*.mp. (83353)
32 Temporomandibular Joint Dysfunction Syndrome/ (4838)
33 ((TMJ or TMJD) and pain*).mp. (2434)
34 whiplash.mp. or exp whiplash injury/ (3756)
35 exp Cumulative Trauma Disorders/ (12612)
36 exp Peripheral Nervous System Diseases/dt [Drug Therapy] (12959)
37 Pain Measurement/de [Drug Effects] (6352)
38 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (39779)
39 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (144063)

[a] a preliminary search was performed in 2010 using the strategy published in the review protocol, see Supplement 1 p. 7-8

40 or/26-39 (299548)
41 (acute or emergency or preoperative or postoperative).ti,ab. (1700816)
42 40 not 41 (252546)
43 25 or 42 (532409)
44 exp Analgesics, Opioid/ (103616)
45 (opioid* or opiate*).mp. (114059)
46 (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.(143753)
47 or/44-46 (199233)
48 exp Narcotics/ (111500)
49 narcotic*.mp. (57165)
50 (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (9563)
51 or/44-50 (227775)
52 43 and 51 (22678)
53 epidemiologic studies/ (7641)
54 exp Case-Control Studies/ (904344)
55 exp Cohort Studies/ (1723417)
56 Case control.tw. (106622)
57 (cohort adj (study or studies)).tw. (151570)
58 Cohort analy$.tw. (6083)
59 (Follow up adj (study or studies)).tw. (44718)
60 ((observational or epidemiol*) adj (study or studies)).tw. (156420)
61 Longitudinal.tw. (201362)
62 Retrospective.mp. or prospective.tw. (1247587)
63 Cross sectional.tw. (272577)
64 Cross-sectional studies/ (260504)
65 or/53-64 (2717825)
66 exp animals/ not humans.sh. (4438182)
67 65 not 66 (2649950)
68 52 and 67 (3763)
69 randomized controlled trial.pt. (456617)
70 controlled clinical trial.pt. (92277)
71 randomized.ab. (406479)

72 placebo.ab. (187496)
73 drug therapy.fs. (2003496)
74 randomly.ab. (287373)
75 trial.ab. (422125)
76 groups.ab. (1777409)
77 or/69-76 (4167722)
78 clinical trial.mp. or clinical trial.pt. or random:.mp. or tu.xs. (5199787)
79 randomized controlled trial.pt. or randomized controlled trial.mp. (476635)
80 randomized controlled trial.pt. or randomized.mp. or placebo.mp. (790362)
81 or/78-80 (5214838)
82 77 or 81 (6680171)
83 exp animals/ not humans.sh. (4438182)
84 82 not 83 (5604099)
85 43 and 51 and 84 (14496)
86 limit 85 to yr="2010 -Current" (6438)
87 68 or 86 (8377)
88 (MEDLINE or systematic review or literature search).tw. or meta analysis.mp,pt. (256038)
89 43 and 51 and 88 (881)
90 87 or 89 (8697)
91 exp Sleep Apnea Syndromes/ (30607)
92 sleep apn?ea.mp. (38637)
93 sleep-disordered breathing.mp. (5685)
94 hypogonadism.mp. or Hypogonadism/ (13040)
95 ((testosterone or androgen) and (deprivation or deficiency)).mp. (12336)
96 OPIAD.mp. (10)
97 or/91-96 (64161)
98 52 and 97 (144)
99 90 or 98 (8736)

EMBASE
Database: Embase <1974 to 2018 March 30> via OVID
Search Strategy:
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1 (chronic adj4 pain*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (95808)
2 chronic pain/ (49908)
3 exp osteoarthritis/ (111874)
4 osteoarthrit*.mp. (121825)
5 osteo-arthritis.mp. (446)
6 degenerative arthrit*.mp. (1509)
7 exp rheumatoid arthritis/ (185025)
8 exp neuralgia/ (93521)
9 diabetic neuropathy/ (21550)
10 (neuropath* adj5 (pain* or diabet*)).mp. (64767)
11 neuralg*.mp. (28411)
12 zoster.mp. (34755)
13 irritable colon/ (22437)
14 (Irritable Bowel Syndrome or IBS).mp. (21332)
15 exp migraine/ (55747)
16 migraine.mp. (61627)
17 fibromyalgia/ (17530)

18 fibromyalg*.mp. (18837)
19 reflex sympathetic dystrophy.mp. (2313)
20 (complex regional pain syndromes or causalgia).mp. (1322)
21 intractable pain/ (4424)
22 phantom limb.mp. or agnosia/ or phantom pain/ or amputation stump/ (7918)
23 hyperalgesia/ (17434)
24 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (23916)
25 or/1-24 (648410)
26 exp backache/ (94040)
27 radiculopathy.mp. or exp radiculopathy/ (34877)
28 musculoskeletal pain/ (8712)
29 exp arthralgia/ (51350)
30 headache/ (188012)
31 headache*.mp. (244285)
32 temporomandibular joint disorder/ (12271)
33 ((TMJ or TMJD) and pain*).mp. (3303)
34 whiplash.mp. or whiplash injury/ (4954)
35 exp cumulative trauma disorder/ (18608)
36 or/26-35 (427712)
37 (acute or emergency or preoperative or postoperative).ti,ab. (2308527)
38 36 not 37 (361643)
39 25 or 38 (914630)
40 exp narcotic analgesic agent/ (301417)
41 (opioid* or opiate*).mp. (169179)
42 (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. (267802)
43 (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. (48881)
44 or/40-43 (382196)
45 39 and 44 (49840)
46 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (25820080)
47 human/ or normal human/ or human cell/ (19514704)
48 46 and 47 (19466620)
49 46 not 48 (6353460)
50 45 not 49 (45275)

51 animals/ not humans/ (1328770)
52 nonhuman/ (5394936)
53 exp Animal Experiment/ (2198806)
54 exp Experimental Animal/ (580077)
55 animal model/ (1084121)
56 exp Rodent/ (3466641)
57 (rat or rats or mouse or mice).ti. (1469571)
58 or/51-57 (7760169)
59 50 not 58 (40524)
60 clinical study/ (154139)
61 case control study/ (123874)
62 longitudinal study/ (110417)
63 intervention study/ (35810)
64 prospective study/ (436528)
65 retrospective study/ (630317)
66 cohort analysis/ (358255)
67 ((cohort or case control or follow up or observational or epidemiologic* or cross sectional) adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (957938)
68 clinical trial/ (967957)
69 exp controlled clinical trial/ (675251)
70 observational study/ (135359)
71 or/60-70 (3179080)
72 59 and 71 (11191)
73 (MEDLINE or systematic review or literature search).tw. or meta analysis.mp,pt. (357638)
74 59 and 73 (2020)
75 72 or 74 (12304)
76 double-blind:.mp. or placebo:.tw. or blind:.tw. or random*.ab. (1519420)
77 59 and 76 (6499)
78 limit 77 to yr="2010 -Current" (3619)
79 75 or 78 (13450)
80 exp sleep disordered breathing/ (36309)
81 sleep apn?ea.mp. (59543)
82 hypogonadism/ (14910)
83 hypogonadism.mp. (22352)
84 ((testosterone or androgen) adj2 (deficiency or deprivation)).mp. (17718)
85 OPIAD.mp. (14)
86 androgen deficiency/ (2706)
87 or/80-86 (106886)
88 59 and 87 (599)
89 79 or 88 (13856)

PsycInfo
Database: PsycINFO <1806 to March Week 4 2018> via OVID

Search Strategy:
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1 (chronic adj4 pain*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (19944)
2 chronic pain/ (12078)
3 exp arthritis/ (3853)

4 osteoarthrit*.mp. (1758)
5 osteo-arthritis.mp. (8)
6 degenerative arthrit*.mp. (15)
7 exp neuralgia/ (892)
8 exp neuropathy/ (5931)
9 (neuropath* adj5 (pain* or diabet*)).mp. (6256)
10 neuralg*.mp. (1530)
11 zoster.mp. (550)
12 irritable bowel syndrome/ (1055)
13 (IBS or irritable colon or irritable bowel).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (1832)
14 migraine headache/ (8772)
15 migraine.mp. (11715)
16 fibromyalgia/ (1768)
17 fibromyalg*.mp. (3042)
18 complex regional pain syndromes.mp. (55)
19 "complex regional pain syndrome (type i)"/ (137)
20 (complex regional pain syndromes or causalgia).mp. (109)
21 somatosensory disorders/ (1266)
22 hyperalgesi*.mp. (3914)
23 somatoform pain disorder/ (801)
24 somatoform disorders/ (7528)
25 conversion disorder/ (998)
26 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (3008)
27 or/1-26 (58879)
28 back pain.mp. or exp Back Pain/ (5353)
29 radiculopathy.mp. (202)
30 musculoskeletal pain.mp. (1410)
31 Arthralgia.mp. (105)
32 headache.mp. or exp HEADACHE/ (19164)
33 ((TMJ or TMJD) and pain*).mp. (142)
34 WHIPLASH/ or whiplash.mp. (571)
35 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (5452)
36 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (18302)
37 or/28-36 (39808)
38 (acute or emergency or preoperative or postoperative).ti,ab. (111436)
39 37 not 38 (35095)
40 27 or 39 (71492)
41 exp opiates/ (22978)
42 (opioid* or opiate*).mp. (27750)
43 (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. (27830)
44 exp narcotic drugs/ (27031)
45 narcotic*.mp. (5729)

46 (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. (928)
47 or/41-46 (47945)
48 37 and 47 (2028)
49 animals/ not humans/ (7067)
50 animal models/ (29760)
51 animal research/ (368)
52 exp rodents/ (201732)
53 (rat or rats or mouse or mice).ti. (110418)
54 or/49-53 (226624)
55 48 not 54 (1547)

Database: AMED (Allied and Complementary Medicine) <1985 to May 2018> via OVID
Search Strategy:
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1 analgesics opioid/ (335)
2 (opioid* or opiate*).mp. (1449)
3 (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. [mp=abstract, heading words, title] (1097)
4 narcotics/ (177)
5 narcotic*.mp. (345)
6 (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. [mp=abstract, heading words, title] (109)
7 or/1-6 (2268)

8 (chronic adj4 pain).mp. [mp=abstract, heading words, title] (4640)
9 exp arthritis/ (5636)
10 arthralgia/ (189)
11 fibromyalgia/ (1656)
12 neuralgia/ (157)
13 diabetic neuropathies/ (264)
14 (neuropath* adj5 (pain* or diabet*)).mp. (981)
15 neuralg*.mp. [mp=abstract, heading words, title] (335)
16 osteoarthrit*.mp. [mp=abstract, heading words, title] (3321)
17 irritable bowel syndrome/ (133)
18 (IBS or irritable colon or irritable bowel).mp. [mp=abstract, heading words, title] (297)
19 fibromyalg*.mp. [mp=abstract, heading words, title] (1846)
20 Migraine/ or migraine.mp. (651)
21 complex regional pain syndromes/ or reflex sympathetic dystrophy/ (188)
22 (complex regional pain syndromes or causalgia).mp. [mp=abstract, heading words, title] (77)
23 pain intractable/ (431)
24 hyperalgesia/ or phantom limb/ (181)
25 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. [mp=abstract, heading words, title] (675)
26 or/8-25 (15230)
27 exp backache/ (6186)
28 radiculopathy.mp. (290)
29 exp Headache/ or headache.mp. (1709)
30 Temporomandibular joint syndrome/ (67)
31 ((TMJ or TMJD) and pain*).mp. (28)
32 Whiplash injuries/ or whiplash.mp. (594)
33 repetition strain injury/ (312)
34 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (2429)
35 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (12871)
36 or/27-35 (17684)
37 (acute or emergency or preoperative or postoperative).ti,ab. (12782)
38 36 not 37 (16319)
39 26 or 38 (25280)
40 7 and 39 (532)
41 (rat or rats or mouse or mice).ti. (5925)
42 animals/ not humans/ (7083)
43 exp Rodents/ (8142)
44 41 or 42 or 43 (10161)
45 40 not 44 (512)

CINAHL via EBSCO

S97 S88 OR S96
S96 S52 AND S95
S95 S89 OR S90 OR S91 OR S92 OR S93 OR S94
S94 ((testosterone or androgen) and (deprivation or deficiency)).
S93 (MH "Hypogonadism") OR "hypogonadism"

S92 "sleep-disordered breathing"
S91 "sleep apnoea"
S90 "sleep apnea"
S89 (MH "Sleep Apnea Syndromes+")
S88 S63 OR S87
S87 S8 Limiters - Published Date: 20100101-20161231
Search modes - Boolean/Phrase
S86 S52 AND S85
S85 S83 NOT S84
S84 (MH "Animals+")
S83 S70 OR S75 OR S82
S82 S76 OR S77 OR S78 OR S79 OR S80 OR S81
S81 (MH "Prospective Studies+")
S80 (MH "Evaluation Research+")
S79 (MH "Comparative Studies")
S78 "latin square"
S77 (MH "Study Design") OR (MH "Crossover Design") OR (MH "Experimental Studies+")
S76 (MH "Random Sample+")
S75 S71 OR S72 OR S73 OR S74
S74 "random*"
S73 "placebo*"
S72 (MH "Placebos")
S71 (MH "Placebo Effect")
S70 S64 OR S65 OR S66 OR S67 OR S68 OR S69
S69 "triple-blind"
S68 "single-blind"
S67 "double-blind"
S66 clinical W3 trial
S65 "randomi?ed controlled trial*"
S64 (MH "Clinical Trials+")
S63 S54 OR S62
S62 S52 AND S61
S61 S55 OR S56 OR S57 OR S58 OR S59 OR S60
S60 (observational N2 (study or studies))
S59 (cohort N2 (study or studies))
S58 (MH "Cross Sectional Studies")
S57 (MH "Correlational Studies")
S56 (MH "Case Control Studies+")
S55 (MH "Prospective Studies+")
S54 S52 AND S53
S53 ((TI meta analys* or AB meta analys* or MW meta analy*) or (TI systematic review or AB systematic review or PT systematic review))
S52 S43 AND S51
S51 S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50
S50 adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or

duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram

S49 alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol

S48 "narcotic*"

S47 (MH "Narcotics+")

S46 "opiate*"

S45 "opioid*"

S44 (MH "Analgesics, Opioid+")

S43 S26 OR S42

S42 S40 NOT S41

S41 acute or emergency or preoperative or postoperative

S40 S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39

S39 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) N3 pain)

S38 backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi*

S37 (MH "Peripheral Nervous System+/DE")

S36 (MH "Cumulative Trauma Disorders+")

S35 (MH "Whiplash Injuries") OR "whiplash"

S34 ((TMJ or TMJD) and pain*)

S33 (MH "Temporomandibular Joint Syndrome")

S32 "headache*"

S31 (MH "Headache")

S30 (MH "Arthralgia+")

S29 "musculoskeletal pain"

S28 (MH "Radiculopathy") OR "radiculopathy"

S27 (MH "Back Pain+")

S26 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25

S25 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) N3 pain)

S24 (MH "Hyperalgesia")

S23 (MH "Phantom Limb") OR (MH "Phantom Pain")

S22 "intractable pain"

S21 "causalgia"
S20 (MH "Complex Regional Pain Syndromes+")
S19 "fibromyalg*"
S18 (MH "Fibromyalgia")
S17 "migraine"
S16 (MH "Migraine")
S15 "IBS"
S14 (irritable (bowel or colon))
S13 (MH "Irritable Bowel Syndrome")
S12 "zoster"
S11 "neuralg*"
S10 (neuropath* N5 (pain* or diabet*))
S9 (MH "Diabetic Neuropathies")
S8 (MH "Neuralgia+")
S7 (MH "Arthritis, Rheumatoid+")
S6 "degenerative arthrit*"
S5 "osteo-arthritis"
S4 "osteoarthrit*"
S3 (MH "Osteoarthritis+")
S2 chronic N4 pain
S1 (MH "Chronic Pain")

Central (Cochrane Library via Wiley)

Search Name:
Date Run: 01/04/18 23:42:22.741
Description:

ID	Search	Hits
#1	chronic near/3 pain	9973
#2	MeSH descriptor: [Chronic Pain] explode all trees	1178
#3	MeSH descriptor: [Osteoarthritis] explode all trees	4754
#4	osteoarthrit*	10561
#5	osteo-arthritis	69
#6	degenerative arthrit*	359
#7	MeSH descriptor: [Arthritis, Rheumatoid] explode all trees	4858
#8	MeSH descriptor: [Neuralgia] explode all trees	1049
#9	MeSH descriptor: [Diabetic Neuropathies] explode all trees	1397
#10	neuropath* near/5 (pain* or diabet*)	4465
#11	neuralg*	1913
#12	zoster	1641
#13	MeSH descriptor: [Irritable Bowel Syndrome] explode all trees	674
#14	irritable (colon or bowel)	2448
#15	IBS	1629
#16	MeSH descriptor: [Migraine Disorders] explode all trees	1959
#17	migraine	4659
#18	MeSH descriptor: [Fibromyalgia] explode all trees	851
#19	fibromyalg*	1987

#20 MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees 238
#21 complex regional pain syndromes or causalgia 203
#22 MeSH descriptor: [Pain, Intractable] explode all trees 273
#23 MeSH descriptor: [Phantom Limb] explode all trees 75
#24 MeSH descriptor: [Hyperalgesia] explode all trees 454
#25 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) near/3 pain) 2107
#26 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 40797
#27 MeSH descriptor: [Back Pain] explode all trees 3879
#28 MeSH descriptor: [Radiculopathy] explode all trees 303
#29 MeSH descriptor: [Musculoskeletal Pain] explode all trees 478
#30 MeSH descriptor: [Arthralgia] explode all trees 1313
#31 MeSH descriptor: [Headache Disorders] explode all trees 2415
#32 MeSH descriptor: [Headache] explode all trees 1798
#33 headache* 26942
#34 MeSH descriptor: [Temporomandibular Joint Dysfunction Syndrome] explode all trees 179
#35 ((TMJ or TMJD) and pain*) 266
#36 MeSH descriptor: [Whiplash Injuries] explode all trees 208
#37 whiplash 460
#38 MeSH descriptor: [Cumulative Trauma Disorders] explode all trees 668
#39 backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi* 13481
#40 ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) near/3 pain) 28955
#41 radiculopathy 893
#42 #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 60275
#43 acute or emergency or preoperative or postoperative 200646
#44 42 not 43 59058
#45 #26 or #44 97623
#46 opioid* or opiate* 17932
#47 narcotic* 6752
#48 MeSH descriptor: [Analgesics, Opioid] explode all trees 6462
#49 MeSH descriptor: [Narcotics] explode all trees 7246
#50 alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol 32420
#51 adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or

theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram 5622
#52 #46 or #47 or #48 or #49 or #50 or #51 42294
#53 #45 and #52 2656

PubMed (1 April 2018)

Search ((chronic pain) AND (opioid OR opiate OR narcotic)) AND (((publisher [sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint)))

eAppendix 2: Reference List of Eligible Trials

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related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. *Clin Drug Investig.* 2010;30(8):489-505.
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eTable 1: Conversion factors for opioids[a]

Oral formulations	
Opioid	*Conversion factor for oral morphine equivalent*
Codeine[b]	0.1 to 0.2
Dihydrocodeine	0.1
Hydrocodone[b]	1.0 to 1.5
Hydromorphone	5.0
Meperidine	0.1
Morphine	1.0
Oxycodone	1.5
Oxymorphone	3.0
Tapentadol[b]	0.3 to 0.4
Tramadol[b]	0.1 to 0.2

Transdermal formulations		
Opioid	*Hourly dose in micrograms*	*Mean morphine equivalent dose (range)*
Fentanyl	25 mcg/hr	97 mg/day (60 to 134)
Fentanyl	37 mcg/hr	157 mg/day (135 to 179)
Fentanyl	50 mcg/hr	202 mg/day (180 to 224)
Fentanyl	62 mcg/hr	247 mg/day (225 to 269)
Fentanyl	75 mcg/hr	292 mg/day (270 to 314)
Fentanyl	87 mcg/hr	337 mg/day (315 to 359)
Fentanyl	100 mcg/hr	382 mg/day (360 to 404)

[a] These factors are for calculation purposes only and should not be used in isolation to calculate clinical equivalencies for dosing patients.

[b] For opioids in which a range of conversion factors was reported, we used the average of the range (e.g. 0.15 for Codeine)

eTable 2: Criteria for assessing the credibility of significant subgroup effects

1. Is the subgroup variable a characteristic measured at baseline or after randomization?
2. Is the effect suggested by comparisons within rather than between studies?
3. Was the hypothesis specified a priori?
4. Was the direction of the subgroup effect specified a priori?
5. Was the subgroup effect one of a small number of hypothesized effects tested?
6. Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?
7. Is the significant subgroup effect independent?
8. Is the size of the subgroup effect large?
9. Is the interaction consistent across studies?
10. Is the interaction consistent across closely related outcomes within the study?
11. Is there indirect evidence that supports the hypothesized interaction (biological rationale)?

eTable 3: Characteristics of 96 eligible randomized clinical trials

First Author	Year	Total patients randomized	Clinical condition(s)	Duration of chronic pain (months)		Age (years)		Female sex	No. of study arms	Interventions	
				Mean/ median	SD or Range	Mean/ median	SD or Range	No. (%)		Opioid(s)	Control
Opioids vs placebo (76 RCTs)											
Vlok[1]	1987	31	Osteoarthritis	NR	NR	59.2	NR	26 (84)	2	Codeine + Acetaminophen+ Ibuprofen	Ibuprofen
Kjaersgaard-Andersen[2]	1990	158	Osteoarthritis	NR	NR	66.5	NR	72 (46)	2	Codeine + Acetaminophen	Acetaminophen
Moran[3]	1991	10[a]	Rheumatoid arthritis	NR	NR	NR	NR	1 (5)	2	Morphine	Placebo
Moulin[4]	1996	61[a]	Chronic post-traumatic pain nos	40.8	9 to 252	40.4	NR	36 (59)	2	Morphine	Active placebo
Harati[5]	1998	131	Painful diabetic neuropathy	NR	NR	59	NR	53 (40)	2	Tramadol	Placebo
Watson[6]	1998	50[a]	Postherpetic neuralgia	31	29	70	11	22 (44)	2	Oxycodone	Placebo
Caldwell[7]	1999	107	Osteoarthritis	NR	NR	56.7	NR	67 (62)	3	Oxycodone; Oxycodone+ Acetaminophen	Placebo

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				Mean/ median	SD or Range	Mean/ median	SD or Range	No. (%)		Opioid(s)	Control
Schnitzer[8]	1999	240	Osteoarthritis	NR	NR	NR	NR	147 (61)	2	Tramadol + Naproxen	Naproxen
Sindrup[9]	1999	45[a]	Painful polyneuropathy	36	6 to 132	57	NR	11 (24)	2	Tramadol	Placebo
Peloso[10]	2000	103	Osteoarthritis	NR	NR	61.6	11.2	41 (40)	2	Codeine	Placebo
Russell[11]	2000	69	Fibromyalgia	NR	NR	NR	NR	65 (94)	2	Tramadol	Placebo
Schnitzer[12]	2000	254	Low back pain nos	NR	NR	47.1	12.9	127 (50)	2	Tramadol + Naproxen	Placebo + Naproxen
Fleischmann[13]	2001	129	Osteoarthritis	7.9	6.6	62.5	9.2	80 (62)	2	Tramadol	Placebo
Huse[14]	2001	12[a]	Phantom limb pain	NR	NR	50.6	14	2 (17)	2	Morphine	Placebo
Caldwell[15]	2002	295	Osteoarthritis	NR	NR	62.4	10.4	184 (62)	4	Morphine (three doses)	Placebo
Bennett[16]	2003	315	Fibromyalgia	NR	NR	50	10.5	294 (93)	2	Tramadol + Acetaminophen	Placebo
Boureau[17]	2003	127	Postherpetic neuralgia	6.9	2.9	66.8	11.8	77 (61)	2	Tramadol	Placebo

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First Author	Year	Total patients randomized	Clinical condition(s)	Duration of chronic pain (months)		Age (years)		Female sex	No. of study arms	Interventions	
				Mean/ median	SD or Range	Mean/ median	SD or Range	No. (%)		Opioid(s)	Control
Gimbel[18]	2003	159	Painful diabetic neuropathy	NR	NR	58.9	11.3	76 (48)	2	Oxycodone	Placebo
Ruoff[19]	2003	322	Low back pain nos	NR	NR	53.9	12	201 (62)	2	Tramadol + Acetaminophen	Placebo
Babul[20]	2004	246	Osteoarthritis	154.8	126	61.4	10.1	151 (61)	2	Tramadol	Placebo
Brunnmuller[21]	2004	20	Rheumatoid arthritis	NR	NR	57	NR	13 (65)	2	Tilidine + Naloxone	Placebo
Emkey[22]	2004	307	Osteoarthritis	NR	NR	61	9	209 (68)	2	Tramadol + Acetaminophen	Placebo
Peloso[23]	2004	338	Low back pain nos	NR	NR	57.5	12.5	210 (62)	2	Tramadol + Acetaminophen	Placebo
Matsumoto[24]	2005	491	Osteoarthritis	NR	≥3	62.3	1	297 (60)	4	Oxymorphone (two doses); Oxycodone	Placebo
Gana[25]	2006	1020	Osteoarthritis	NR	NR	58.2	9.9	631 (62)	5	Tramadol (four doses)	Placebo

eTable 3: Characteristics of 96 eligible randomized clinical trials

First Author	Year	Total patients randomized	Clinical condition(s)	Duration of chronic pain (months)		Age (years)		Female sex	No. of study arms	Interventions	
				Mean/ median	SD or Range	Mean/ median	SD or Range	No. (%)		Opioid(s)	Control
Langford[26]	2006	399	Osteoarthritis	NR	≥3	63	0.7	265 (67)	2	Fentanyl	Placebo
Webster[27]	2006	719	Low back pain nos	NR	NR	48.1	NR	442 (61)	4	Oxycodone; Oxytrex (two doses)	Placebo
Burch[28]	2007	646	Osteoarthritis	NR	NR	62	9	408 (63)	2	Tramadol	Placebo
Freeman[29]	2007	313	Painful diabetic neuropathy	NR	NR	55.7	10.3	128(41)	2	Tramadol + Acetaminophen	Placebo
Fishman[30]	2007	552	Osteoarthritis	NR	NR	61.19	9.22	333 (62)	4	Tramadol (three doses)	Placebo
Hale[31]	2007	143	Low back pain nos	NR	NR	47.1	11.5	64 (45)	2	Oxymorphone	Placebo
Katz[32]	2007	205	Low back pain nos	NR	NR	49.7	13.2	109 (53)	2	Oxymorphone	Placebo
Hanna[33]	2008	338	Painful diabetic neuropathy	NR	NR	60.2	10.2	118 (35)	2	Oxycodone + Gabapentin	Placebo + Gabapentin
Ma[34]	2008	116	Chronic neck pain nos	NR	NR	55.7	14.5	44 (38)	2	Oxycodone	Placebo
Thorne[35]	2008	100[a]	Osteoarthritis	NR	81.6	61	10.3	55 (55)	2	Tramadol	Placebo

eTable 3: Characteristics of 96 eligible randomized clinical trials

First Author	Year	Total patients randomized	Clinical condition(s)	Duration of chronic pain (months)		Age (years)		Female sex	No. of study arms	Interventions	
				Mean/ median	SD or Range	Mean/ median	SD or Range	No. (%)		Opioid(s)	Control
Vondrackova[36]	2008	464	Low back pain nos	NR	NR	56.3	11	285 (61)	3	Oxycodone alone; Oxycodone + Naloxone	Placebo
Vorsanger[37]	2008	386	Low back pain nos	NR	NR	47.8	14.3	192 (50)	3	Tramadol (two doses)	Placebo
Norrbrink[38]	2009	36	Post-traumatic neuralgia	NR	NR	51.3	10.7	28 (78)	2	Tramadol	Placebo
Afilalo[39]	2010	1030	Osteoarthritis	NR	NR	58.3	9.8	618 (60)	3	Tapentadol; Oxycodone	Placebo
Breivik[40]	2010	199	Osteoarthritis	NR	NR	62.9	9.5	136 (68)	2	Buprenorphine	Placebo
Buynak[41]	2010	981	Low back pain nos	NR	NR	49.9	13.8	569 (58)	3	Tapentadol; Oxycodone	Placebo
Gordon[42] ISRCTN 06013881	2010	78[a]	Low back pain nos	NR	NR	50.7	11.9	47 (60)	2	Buprenorphine	Placebo

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First Author	Year	Total patients randomized	Clinical condition(s)	Duration of chronic pain (months)		Age (years)		Female sex	No. of study arms	Interventions	
				Mean/ median	SD or Range	Mean/ median	SD or Range	No. (%)		Opioid(s)	Control
Gordon[43]	2010	79[a]	Mixed neuropathic & non-neuropathic conditions	169.2	128.4	54.5	12.7	25 (47) [c]	2	Buprenorphine	Placebo
Hale[44]	2010	268	Low back pain nos	NR	NR	48.6	10.6	134 (50)	2	Hydromorphone	Placebo
Katz[45]	2010	344	Osteoarthritis	NR	NR	54.5	12.3	201 (58)	2	Morphine	Placebo
Munera[46]	2010	315	Osteoarthritis	NR	NR	61	1	212 (67)	2	Buprenorphine	Placebo
Zin[47]	2010	62	Postherpetic neuralgia & painful diabetic neuropathy	NR	NR	68.5	11.6	27 (44)	2	Oxycodone	Placebo
Friedmann[48]	2011	412	Osteoarthritis	NR	NR	58.3	8.2	288 (70)	2	Oxycodone	Placebo

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First Author	Year	Total patients randomized	Clinical condition(s)	Duration of chronic pain (months)		Age (years)		Female sex	No. of study arms	Interventions	
				Mean/ median	SD or Range	Mean/ median	SD or Range	No. (%)		Opioid(s)	Control
Schwartz[49]	2011	395	Painful diabetic neuropathy	76.8	66.3	62	10.5	169 (43)	2	Tapentadol	Placebo
Steiner[50]	2011	541	Low back pain nos	108.6	106	49.4	13	298 (55)	2	Buprenorphine	Placebo
Vojtassak[51]	2011	288	Osteoarthritis	NR	NR	65.5	NR	207 (72)	2	Hydromorphone	Placebo
Chu[52]	2012	139	Low back pain nos	NR	NR	45	13.9	61 (44)	2	Morphine	Placebo
Sindrup[53]	2012	64[a]	Painful polyneuropathy	NR	NR	58.2	NR	60 (94)	3	Tramadol; GRT9906 (excluded)[b]	Placebo
Uberall[54]	2012	240	Low back pain nos	NR	79.9	NR	12.1	220 (62)	2	Tramadol	Placebo
Cloutier[55]	2013	83[a]	Low back pain nos	NR	NR	50.6	10.9	27 (33)	2	Oxycodone + Naloxone	Placebo
Lee[56]	2013	248	Low back pain nos	NR	NR	60.2	10.3	183 (74)	2	Tramadol + Acetaminophen	Placebo

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First Author	Year	Total patients randomized	Clinical condition(s)	Duration of chronic pain (months)		Age (years)		Female sex	No. of study arms	Interventions	
				Mean/ median	SD or Range	Mean/ median	SD or Range	No. (%)		Opioid(s)	Control
Rauck[57]	2013	990	Osteoarthritis	NR	NR	59.7	10.8	627 (64)	3	Hydromorphone (two doses)	Placebo
Niesters[58]	2014	25	Painful diabetic neuropathy	NR	NR	63.5	NR	10 (40)	2	Tapentadol	Placebo
Rauck[59]	2014	302	Low back pain nos	NR	NR	50.6	11.7	167 (55)	2	Hydrocodone	Placebo
Vinik[60]	2014	320	Painful diabetic neuropathy	NR	NR	58.8	9.8	131 (41)	2	Tapentadol	Placebo
Arai[61 d]	2015	150	Mixed neuropathi[c] & non-neuropathic conditions	NR	NR	66.5	13.2	80 (49)	2	Fentanyl	Placebo
Arai[61 d]	2015	163	Mixed neuropathic conditions	NR	NR	66.6	14	101 (67)	2	Fentanyl	Placebo

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				Mean/ median	SD or Range	Mean/ median	SD or Range	No. (%)		Opioid(s)	Control
Hale[62]	2015	370	Low back pain nos	NR	NR	51.8	13	189 (51)	2	Hydrocodone	Placebo
Katz[63]	2015	389	Low back pain nos	NR	NR	49.6	13	206 (53)	2	Oxycodone	Placebo
Rauck[64,65]	2015	281	Low back pain nos	12.4	10.7	50	12.6	156 (56)	2	Oxycodone + Naltrexone	Placebo
Trenkwalder[66]	2015	202	Parkinson's disease	40.8	34.8	67.1	8.5	94 (47)	2	Oxycodone + Naloxone	Placebo
Wen[67]	2015	588	Low back pain nos	NR	NR	48.6	13.4	338 (57)	2	Hydrocodone	Placebo
Gimbel[68]	2016	511	Low back pain nos	NR	NR	53.55	11.18	278 (54)	2	Buprenorphine	Placebo
Lin[69]	2016	21	Low back pain nos	97.2	92.4	41.9	10	7 (33)	2	Morphine	Placebo
Mayorga[70]	2016	196	Osteoarthritis	NR	NR	59.375	9.25	110 (56)	4	Oxycodone; Fulranumab (two doses, excluded)[b]	Placebo
Rauck[71]	2016	420	Low back pain nos	NR	NR	50.1	12.9	235 (56)	2	Buprenorphine	Placebo

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				Mean/ median	SD or Range	Mean/ median	SD or Range	No. (%)		Opioid(s)	Control
Simpson[72]	2016	186	Painful diabetic neuropathy	NR	NR	62.95	9.45	62 (33)	2	Buprenorphine	Placebo
Tominaga[73] [d]	2016	91	Mixed neuropathic & non-neuropathic conditions	NR	NR	NR	NR	NR	2	Tapentadol	Placebo
Tominaga[73] [d]	2016	91	Postherpetic neuralgia & painful diabetic neuropathy	NR	NR	NR	NR	NR	2	Tapentadol	Placebo
Christoph[74]	2017	641	Mixed neuropathic & non-neuropathic conditions	NR	124.2	NR	11.71	412 (65)	5	Cebranopadol (three doses); Tapentadol	Placebo
Serrie[75]	2017	990	Osteoarthritis	NR	NR	NR	9.4	707 (72)	3	Tapentadol; Oxycodone	Placebo
Opioids vs NSAIDs (11 RCTs)											
Pavelka[76]	1995	60[a]	Osteoarthritis	NR	NR	65.2	7.3	52 (87)	2	Tramadol	Diclofenac

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				Mean/ median	SD or Range	Mean/ median	SD or Range	No. (%)		Opioid(s)	Control
Jamison[77]	1998	36	Mixed neuropathic & non-neuropathic conditions	79.1	79.4	42.6	7	21 (57)	3	Oxycodone alone; Oxycodone + morphine	Naproxen
Pavelka[78]	1998	60[a]	Osteoarthritis	NR	36 to 120	NR	44 to 85	52 (96)	2	Tramadol	Diclofenac
Beaulieu[79]	2008	128	Osteoarthritis	127.8	110.4	62.1	8.2	86 (67)	2	Tramadol	Diclofenac
Liu[80]	2009	120	Postherpetic neuralgia	NR	NR	56.9	4.6	62 (52)	2	Oxycodone + Acetaminophen	Diclofenac
O'Donnell[81 d]	2009	796	Low back pain nos	90.1	0.5 to 689.8	48.5	14.7	450 (56)	2	Tramadol	Celecoxib
O'Donnell[81 d]	2009	802	Low back pain nos	97.3	0.1 to 761.6	47	14.2	462 (58)	2	Tramadol	Celecoxib
Qin[82]	2009	73	Fibromyalgia	NR	NR	42.5	13	NR	2	Tramadol + amitriptyline	Celecoxib + amitriptyline
Kim[83]	2012	48	Osteoarthritis	NR	NR	66.1	NR	31 (65)	2	Tramadol + Acetaminophen	Naproxen
Park[84]	2012	97	Osteoarthritis	NR	NR	60.6	7.5	78 (80)	2	Tramadol + Acetaminophen	NSAIDs (unspecified)

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				Mean/ median	SD or Range	Mean/ median	SD or Range	No. (%)		Opioid(s)	Control
Tetsunaga[85]	2015	70	Low back pain nos	NR	NR	63.9	NR	44 (63)	2	Tramadol + Acetaminophen	Celecoxib
Opioids vs anticonvulsants (2 RCTs)[e]											
Ko[86]	2010	163	Painful diabetic neuropathy	129	91.2	57.9	8.4	91 (56)	2	Tramadol + Acetaminophen	Gabapentin
Sakai[87]	2015	65	Mixed neuropathic & non-neuropathic conditions	NR	NR	72.3	5.7	20 (31)	2	Tramadol + Acetaminophen	Pregabalin
Opioids vs synthetic cannabis (1 RCT)											
Frank[88]	2008	96[a]	Chronic neuropathic pain (unspecified)	NR	NR	50.2	13.6	46 (48)	2	Dihydrocodeine	Nabilone
Multiple comparisons (5 RCTs)[f]											
Raja[89]	2002	76[a]	Postherpetic neuralgia	NR	NR	NR	NR	NR	3	Morphine	Placebo; Nortriptyline

eTable 3: Characteristics of 96 eligible randomized clinical trials

First Author	Year	Total patients randomized	Clinical condition(s)	Duration of chronic pain (months)		Age (years)		Female sex	No. of study arms	Interventions	
				Mean/ median	SD or Range	Mean/ median	SD or Range	No. (%)		Opioid(s)	Control
Khoromi[90]	2007	55[a]	Lumbar radiculopathy	NR	NR	53	NR	25 (45)	4	Morphine; Morphine+ Nortriptyline	Active placebo; Nortriptyline
Gilron[91]	2015	52[a]	Mixed neuropathic pain conditions	NR	NR	66	49 to 80	14 (27)	3	Morphine; Morphine + Nortriptyline	Nortriptyline
Gilron[92]	2005	57[a]	Postherpetic neuralgia & painful diabetic neuropathy	54.5	48	NR	NR	NR	4	Morphine; Morphine+ Gabapentin	Placebo; Gabapentin
DeLemos[93]	2011	1011	Osteoarthritis	96.7	94.1	60.2	10.9	1011 (100)	5	Tramadol (3 doses)	Placebo; Celecoxib
Opioids vs Usual Care (1 RCT)											
Corsinovi[94]	2009	154	Osteoarthritis	NR	NR	78	8.3	154 (100)	3	Oxycodone +Acetaminophen and usual care; Codeine +Acetaminophen and usual care	Usual care

SD: standard deviation; nos: not otherwise specified; NR: not reported

a. cross-over trials. The total sample size at randomization among 96 eligible studies were summarized from all patients randomized at each trial; however, we analyzed cross-over trials as parallel trials, which meant that the sample size as effectively doubled for cross-over trials.
b. comparator excluded from analysis because drug is not used in clinical practice
c. % of female was reported among 53 patients in the per protocol population, not in the full population of 79 patients randomized
d. Each of these 3 studies reported 2 separate trials in one paper: Arai et al. 2015, O'Donnell et al 2009, and Tominaga et al 2016
e. Gilron 2005 randomized one treatment arm to receive the anticonvulsant gabapentin, and is listed under "multiple comparisons"
f. Of the 5 multiple comparison RCTs, Gilron 2005 and Khoromi 2007 are 4-arm RCTs; we used data from each to inform the effect of opioids vs. placebo (with and without gabapentin or nortriptyline add-on)

eTable 4: Summary of baseline pain scores in 23 enrichment trials and 51 non-enrichment trials [a]

Type of trial	No. of studies	No. of patients	Average pain score at time of randomization	Median (IQR) of trials reporting mean pain score at time of randomization
Enrichment trials	23	7,286	4.28	3.15 (2.88 to 5.30)
Non-enrichment trials	51	12,568	6.54	6.38 (5.72 to 6.96)

IQR: interquartile range

Enrichment trials precede randomization with an open-label treatment phase. As such, patients would present with lower pain scores when randomized, versus non-enrichment trials.

[a] Of the 96 trials eligible for our review, 74 reported average baseline pain.

eTable 5: Risk of bias assessment of 96 eligible randomized clinical trials

Author	Year	Adequate randomization sequence generation	Adequate allocation concealment	Blinding of patients	Blinding of health care providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of data analyst	Loss to follow-up (%)
Opioids vs placebo (76 RCTs)									
Vlok[1]	1987	No	No	Yes	Yes	Yes	Yes	No	0.0
Kjaersgaard-Andersen[2]	1990	No	No	Yes	Yes	Yes	Yes	No	38.0
Moran[3]	1991	No	No	Yes	Yes	Yes	Yes	No	25.0
Moulin[4]	1996	No	No	Yes	Yes	Yes	Yes	No	24.6
Harati[5]	1998	Yes	Yes	Yes	Yes	Yes	Yes	No	37.4
Watson[6]	1998	No	Yes	Yes	Yes	Yes	Yes	No	22.0
Caldwell[7]	1999	No	Yes	Yes	Yes	Yes	Yes	No	33.6
Schnitzer[8]	1999	No	No	Yes	Yes	Yes	Yes	No	1.7
Sindrup[9]	1999	No	No	Yes	Yes	Yes	Yes	No	20.0
Peloso[10]	2000	No	No	Yes	Yes	Yes	Yes	No	35.9
Russell[11]	2000	Yes	Yes	Yes	Yes	Yes	Yes	No	1.4
Schnitzer[12]	2000	Yes	Yes	Yes	Yes	Yes	Yes	No	42.5

eTable 5: Risk of bias assessment of 96 eligible randomized clinical trials

Author	Year	Adequate randomization sequence generation	Adequate allocation concealment	Blinding of patients	Blinding of health care providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of data analyst	Loss to follow-up (%)
Fleischmann[13]	2001	Yes	No	Yes	Yes	Yes	Yes	No	71.3
Huse[14]	2001	No	No	No	No	No	No	No	16.7
Caldwell[15]	2002	No	No	Yes	Yes	Yes	Yes	No	37.6
Bennett[16]	2003	Yes	Yes	Yes	Yes	Yes	Yes	No	36.5
Boureau[17]	2003	Yes	No	Yes	Yes	Yes	Yes	No	15.0
Gimbel[18]	2003	Yes	Yes	Yes	Yes	Yes	Yes	No	27.7
Ruoff[19]	2003	Yes	Yes	Yes	Yes	Yes	Yes	No	47.5
Babul[20]	2004	Yes	No	Yes	Yes	Yes	Yes	No	49.6
Brunnmuller[21]	2004	No	No	Yes	Yes	No	No	No	35.0
Emkey[22]	2004	No	No	Yes	Yes	Yes	Yes	No	26.1
Peloso[23]	2004	Yes	Yes	Yes	Yes	Yes	Yes	No	56.5
Matsumoto[24]	2005	Yes	Yes	Yes	Yes	Yes	Yes	No	45.2
Gana[25]	2006	Yes	Yes	Yes	Yes	Yes	Yes	No	45.3

eTable 5: Risk of bias assessment of 96 eligible randomized clinical trials

Author	Year	Adequate randomization sequence generation	Adequate allocation concealment	Blinding of patients	Blinding of health care providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of data analyst	Loss to follow-up (%)
Langford[26]	2006	Yes	Yes	Yes	Yes	Yes	Yes	No	52.2
Webster[27]	2006	Yes	Yes	Yes	Yes	Yes	Yes	No	54.4
Burch[28]	2007	Yes	Yes	Yes	Yes	Yes	Yes	No	24.0
Freeman[29]	2007	No	No	Yes	Yes	Yes	Yes	No	24.6
Fishman[30]	2007	Yes	Yes	Yes	Yes	Yes	Yes	No	43.7
Hale[31]	2007	No	No	Yes	Yes	Yes	Yes	No	53.1
Katz[32]	2007	No	Yes	Yes	Yes	Yes	Yes	No	42.4
Hanna[33]	2008	No	Yes	Yes	Yes	Yes	Yes	No	25.9
Ma[34]	2008	No	No	Yes	Yes	Yes	Yes	No	89.7
Thorne[35]	2008	No	No	Yes	Yes	Yes	Yes	No	25.0
Vondrackova[36]	2008	No	No	Yes	Yes	Yes	Yes	No	13.1
Vorsanger[37]	2008	Yes	Yes	Yes	Yes	Yes	Yes	No	37.6
Norrbrink[38]	2009	No	Yes	Yes	Yes	Yes	Yes	No	36.1

eTable 5: Risk of bias assessment of 96 eligible randomized clinical trials

Author	Year	Adequate randomization sequence generation	Adequate allocation concealment	Blinding of patients	Blinding of health care providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of data analyst	Loss to follow-up (%)
Afilalo[39]	2010	Yes	Yes	Yes	Yes	Yes	Yes	No	51.3
Breivik[40]	2010	Yes	Yes	Yes	Yes	Yes	Yes	No	42.2
Buynak[41]	2010	Yes	Yes	Yes	Yes	Yes	Yes	No	53.4
Gordon ISRCTN 06013881[42]	2010	Yes	No	Yes	Yes	Yes	Yes	No	35.4
Gordon[43]	2010	Yes	Yes	Yes	Yes	Yes	Yes	No	37.2
Hale[44]	2010	Yes	Yes	Yes	Yes	Yes	Yes	No	59.0
Katz[45]	2010	Yes	Yes	Yes	Yes	Yes	Yes	No	39.5
Munera[46]	2010	No	No	Yes	Yes	Yes	Yes	No	50.8
Zin[47]	2010	Yes	No	Yes	Yes	Yes	Yes	No	17.7
Friedmann[48]	2011	No	No	Yes	Yes	Yes	Yes	No	36.2
Schwartz[49]	2011	Yes	Yes	Yes	Yes	Yes	Yes	No	33.2
Steiner[50]	2011	No	No	Yes	Yes	Yes	Yes	No	31.5
Vojtassak[51]	2011	Yes	Yes	Yes	Yes	Yes	Yes	No	30.6

eTable 5: Risk of bias assessment of 96 eligible randomized clinical trials

Author	Year	Adequate randomization sequence generation	Adequate allocation concealment	Blinding of patients	Blinding of health care providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of data analyst	Loss to follow-up (%)
Chu[52]	2012	No	No	Yes	No	Yes	Yes	No	25.9
Sindrup[53]	2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	25.0
Uberall[54]	2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	24.6
Cloutier[55]	2013	Yes	Yes	Yes	Yes	Yes	Yes	No	24.1
Lee[56]	2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	19.8
Rauck[57]	2013	No	No	Yes	Yes	Yes	No	No	51.4
Niesters[58]	2014	Yes	Yes	Yes	Yes	Yes	Yes	No	0.0
Rauck[59]	2014	No	No	Yes	Yes	No	No	No	39.4
Vinik[60]	2014	Yes	Yes	Yes	Yes	Yes	Yes	No	29.1
Arai[61 a]	2015	No	No	Yes	Yes	Yes	Yes	No	49.3
Arai[61 a]	2015	No	No	Yes	Yes	Yes	Yes	No	54.0
Hale[62]	2015	Yes	Yes	Yes	Yes	Yes	Yes	No	19.9
Katz[63]	2015	Yes	Yes	Yes	Yes	Yes	Yes	No	42.9

eTable 5: Risk of bias assessment of 96 eligible randomized clinical trials

Author	Year	Adequate randomization sequence generation	Adequate allocation concealment	Blinding of patients	Blinding of health care providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of data analyst	Loss to follow-up (%)
Rauck[64,65]	2015	No	No	Yes	Yes	Yes	No	No	33.1
Trenkwalder[66]	2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	31.2
Wen[67]	2015	No	No	Yes	Yes	Yes	Yes	No	25.3
Lin[69]	2016	No	No	Yes	Yes	Yes	Yes	No	0.0
Gimbel[68]	2016	No	Yes	Yes	Yes	Yes	Yes	Yes	30.9
Mayorga[70]	2016	Yes	Yes	Yes	Yes	Yes	Yes	No	53.1
Rauck[71]	2016	No	No	Yes	Yes	Yes	Yes	No	9.1
Simpson[72]	2016	Yes	Yes	Yes	Yes	Yes	Yes	No	32.8
Tominaga[73 a]	2016	No	No	Yes	Yes	Yes	Yes	No	13.2
Tominaga[73 a]	2016	No	No	Yes	Yes	Yes	Yes	No	8.8
Christoph[74]	2017	Yes	Yes	Yes	Yes	Yes	Yes	No	43.8
Serrie[75]	2017	Yes	Yes	Yes	Yes	Yes	Yes	No	46.4
Opioids vs NSAIDs (11 RCTs)									

eTable 5: Risk of bias assessment of 96 eligible randomized clinical trials

Author	Year	Adequate randomization sequence generation	Adequate allocation concealment	Blinding of patients	Blinding of health care providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of data analyst	Loss to follow-up (%)
Pavelka[76]	1995	No	No	No	No	No	No	No	10.0
Jamison[77]	1998	No	No	No	No	No	No	No	0
Pavelka[78]	1998	Yes	No	Yes	Yes	Yes	Yes	No	10.0
Beaulieu[79]	2008	Yes	Yes	Yes	Yes	Yes	Yes	No	24.2
Liu[80]	2009	No	No	No	No	No	No	No	0.0
O'Donnell[81 a]	2009	Yes	Yes	Yes	Yes	Yes	Yes	No	20.7
O'Donnell[81 a]	2009	Yes	Yes	Yes	Yes	Yes	Yes	No	22.9
Qin[82]	2009	Yes	No	No	No	No	Yes	No	11.0
Kim[83]	2012	Yes	No	No	No	No	No	No	10.4
Park[84]	2012	No	No	No	No	No	No	No	18.6
Tetsunaga[85]	2015	Yes	No	No	No	No	No	No	0.0
Opioids vs anticonvulsants (2 RCTs)[b]									
Ko[86]	2010	Yes	Yes	No	No	No	No	No	25.2

eTable 5: Risk of bias assessment of 96 eligible randomized clinical trials

Author	Year	Adequate randomization sequence generation	Adequate allocation concealment	Blinding of patients	Blinding of health care providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of data analyst	Loss to follow-up (%)
Sakai[87]	2015	No	No	No	No	No	No	No	7.7
Opioids vs synthetic cannabis (1 RCT)									
Frank[88]	2008	No	No	Yes	Yes	Yes	Yes	No	24.0
Multiple comparisons (5 RCTs)									
Raja[89]	2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	42.1
Khoromi[90] [c]	2007	Yes	No	Yes	Yes	Yes	Yes	No	49.1
Gilron[91]	2015	Yes	Yes	Yes	Yes	Yes	Yes	No	36.5
Gilron[92] [c]	2005	No	Yes	Yes	Yes	Yes	Yes	No	28.1
DeLemos[93]	2011	No	No	Yes	Yes	Yes	Yes	No	45.1
Opioids vs Usual Care (1 RCT)									
Corsinovi[94]	2009	No	No	No	No	No	No	No	27.9

a. Each of these3 studies reported 2 separate trials in one paper: Arai et al. 2015, O'Donnell et al 2009, and Tominaga et al 2016
b. Gilron 2005 used anticonvulsant gabapentin and is listed in the table under the multiple comparisons
c. Of the 5 multiple comparison RCTs, Gilron 2005 and Khoromi 2007 are 4-arm RCTs; each provided two comparisons of opioids vs. placebo (with and without gabapentin or nortriptyline add-on)

eTable 6: Original data for pain relief reported by 80 randomized clinical trials of opioids vs. placebo

First Author	Year	Change score reported or converted	Pain scale		Opioids group			Placebo group		
			Lower limit	Upper limit	Sample size	Mean	SD	Sample size	Mean	SD
Vlok[1]	1987	Change score reported	0	10	28	-3.25	2.39	28	-2.38	2.11
Moran[3]	1991	Change score converted	0	100	7	Not reported		8	Not reported	
Moulin[4]	1996	Change score converted	0	10	46	-1.1	2.66	46	-0.2	2.66
Harati[5]	1998	Change score converted	0	4	63	-1.1	0.79	64	-0.4	0.80
Watson[6]	1998	Change score converted	0	100	38	Not reported		38	Not reported	
Caldwell[7]	1999	Change score reported	0	3	71	0.46	0.62	36	1	0.55
Sindrup[9]	1999	Change score converted	0	10	28	Not reported		28	Not reported	
Peloso[10]	2000	Change score reported	0	100	31	-25.7	23.3	35	-5.4	20.3
Russell[11]	2000	Change score converted	0	10	35	1.9	2.58	34	3.2	2.23
Schnitzer[12]	2000	Change score converted	0	10	127	-3.7	2.40	127	-2.1	2.56
Fleischmann[13]	2001	Change score converted	0	4	63	-0.61	0.92	66	-0.37	0.98
Huse[14]	2001	Change score converted	0	10	9	-1.39	1.39	9	-0.66	1.14
Caldwell[15]	2002	Change score reported	0	100	222	-23.32	28.96	73	-13.7	29.05
Raja[89]	2002	Change score converted	0	10	51	-2.1	2.17	70	-0.2	1.98
Bennett[16]	2003	Change score converted	0	100	156	-19	27.62	157	-7	24.95
Boureau[17]	2003	Change score converted	0	100	63	-35.2	19.89	62	-26.8	21.86
Gimbel[18]	2003	Change score reported	0	10	82	-2.6	2.54	77	-1.5	2.54
Ruoff[19]	2003	Change score reported	0	45	151	-8.4	11.8	142	-4.8	9.9
Babul[20]	2004	Change score reported	0	100	124	-30.4	25.6	122	-17.7	25.6
Brunnmuller[21]	2004	Change score converted	0	10	11	-3.3	2.66	8	-0.6	2.66
Emkey[22]	2004	Change score converted	0	100	153	-27.5	22.38	153	-21.2	22.91

eTable 6: Original data for pain relief reported by 80 randomized clinical trials of opioids vs. placebo

First Author	Year	Change score reported or converted	Pain scale		Opioids group			Placebo group		
			Lower limit	Upper limit	Sample size	Mean	SD	Sample size	Mean	SD
Peloso[23]	2004	Change score reported	0	45	164	-6.1	12	161	-2.5	9.2
Gilron[92 a]	2005	Change score converted	0	10	57	-2.66	1.59	57	-1.57	1.59
Gilron[92 a]	2005	Change score converted	0	10	57	-2.02	1.59	57	-1.23	1.59
Matsumoto[24]	2005	Change score reported	0	500	348	-101	124.6	119	-58.2	85.09
Gana[25]	2006	Change score reported	0	500	806	-107.6	123.4	205	-74.2	121.7
Langford[26]	2006	Change score reported	0	100	202	-23.6	25.58	197	-17.9	26.67
Webster[27]	2006	Change score converted	0	10	608	-3.4	2.177	101	-2.5	2.63
Burch[28]	2007	Change score reported	0	10	393	-3.03	2.12	196	-2.29	1.97
Fishman[30]	2007	Change score reported	0	500	311	-129	133.9	224	-97.1	54.7
Freeman[29]	2007	Change score reported	0	10	150	-2.5	2.61	146	-1.7	2.4
Hale[31]	2007	Change score reported	0	100	49	8.7	21	18	31.6	12.3
Katz[32]	2007	Change score reported	0	100	71	10.9	24.53	47	26	27.88
Khoromi[90 a]	2007	Change score converted	0	10	28	-1.2	2.36	28	-1.1	2.31
Khoromi[90 a]	2007	Change score converted	0	10	28	-1.6	2.36	28	-1.8	2.31
Hanna[33]	2008	Change score reported	0	10	163	-2.1	2.61	165	-1.5	2.38
Ma[34]	2008	Change score converted	0	10	7	-5.54	1.57	5	-3.06	1.20
Thorne[35]	2008	Change score converted	0	100	78	-12.6	20.35	79	-3.1	22.50
Vorsanger[37]	2008	Change score converted	0	100	256	4.15	24.73	126	9.6	25.30
Norrbrink[38]	2009	Change score converted	0	10	23	-1	1.68	12	-0.5	1.75
Afilalo[39]	2010	Change score reported	0	100	686	-15.11	25.6	337	-13.1	25.6
Breivik[40]	2010	Change score reported	0	10	86	-0.9	1.8	91	-0.5	1.5
Buynak[41]	2010	Change score reported	0	10	635	-2.9	2.59	316	-2.1	2.33

eTable 6: Original data for pain relief reported by 80 randomized clinical trials of opioids vs. placebo

First Author	Year	Change score reported or converted	Pain scale		Opioids group			Placebo group		
			Lower limit	Upper limit	Sample size	Mean	SD	Sample size	Mean	SD
Gordon[42]	2010	Change score converted	0	100	52	-15.6	18.88	52	-7.8	21.12
Gordon[43]	2010	Change score converted	0	100	53	-24.1	18.34	53	-18.5	18.97
Hale[44]	2010	Change score reported	0	10	133	0.2	2.61	133	1.6	2.61
Katz[45]	2010	Change score reported	0	10	171	0.1	1.4	173	0.7	1.5
Munera[46]	2010	Change score reported	0	10	149	-1.81	2.69	162	-1.1	2.67
Zin[47]	2010	Change score reported	0	10	26	-3.59	2.35	29	-4.03	2.33
DeLemos[93]	2011	Change score reported	0	100	599	-21.32	25.39	200	-16.5	26.87
Friedmann[48]	2011	Change score reported	0	10	203	-0.7	2.05	207	-0.3	2.48
Schwartz[49]	2011	Change score reported	0	10	196	0	2.61	193	1.4	2.61
Steiner[50]	2011	Change score converted	0	10	257	1.21	2.29	283	1.79	2.20
Vojtassak[51]	2011	Change score reported	0	10	132	-2.4	2.1	143	-2.6	2.3
Chu[52]	2012	Change score reported	0	100	48	-21.1	15.9	55	-12.5	19.2
Sindrup[53]	2012	Change score reported	0	10	56	-2.4	2.1	55	-0.7	1.8
Uberall[54]	2012	Change score reported	0	10	85	-2.03	1.83	96	-1.77	1.59
Cloutier[55]	2013	Change score reported	0	100	54	-12.3	21.8	54	-5.7	23.1
Lee[56]	2013	Change score reported	0	100	83	-19.4	18.99	87	-17.7	14.84
Rauck[57]	2013	Change score reported	0	10	649	-2.25	2.88	331	-1.9	2.91
Niesters[58]	2014	Change score converted	0	10	12	-2.6	2.06	12	-1.7	2.25
Rauck[59]	2014	Change score reported	0	10	151	0.48	1.56	151	0.96	1.55
Vinik[60]	2014	Change score reported	0	10	146	-0.04	1.97	131	1.05	2.31
Arai[61 b]	2015	Change score reported	0	100	84	-0.3	21.28	79	9.6	20.45
Arai[61 b]	2015	Change score reported	0	100	73	-0.2	18.21	77	6.9	20.84

eTable 6: Original data for pain relief reported by 80 randomized clinical trials of opioids vs. placebo

First Author	Year	Change score reported or converted	Pain scale		Opioids group			Placebo group		
			Lower limit	Upper limit	Sample size	Mean	SD	Sample size	Mean	SD
Gilron[91]	2015	Change score converted	0	10	52	-1.9	2.58	52	-1.6	2.58
Hale[62]	2015	Change score reported	0	10	191	-0.03	1.66	179	0.55	1.87
Katz[63]	2015	Change score reported	0	10	122	0.29	1.66	100	1.85	2.2
Rauck[64]	2015	Change score reported	0	10	146	0.6	1.81	134	1.2	1.93
Trenkwalder[66]	2015	Change score converted	0	10	61	-2.3	1.46	73	-1.7	1.44
Wen[67]	2015	Change score converted	0	10	296	-3.69	1.87	292	-3.15	1.87
Gimbel[68]	2016	Change score reported	0	10	254	0.88	1.79	256	1.92	1.87
Lin[69]	2016	Change score reported	0	10	11	-1.52	2.4	10	-1.46	1.39
Mayorga[70]	2016	Change score reported	0	10	50	-1.45	2.55	48	-2.93	2.56
Rauck[71]	2016	Change score reported	0	10	209	0.94	1.85	211	1.59	2.04
Simpson[72]	2016	Change score reported	0	10	89	-3.3	2.16	92	-2.1	2.16
Tominaga[73] [b]	2016	Change score reported	0	10	60	-2.6	2.23	31	-2.6	2.65
Tominaga[73] [b]	2016	Change score reported	0	10	60	-3	1.99	31	-2.9	2.22
Christoph[74]	2017	Change score reported	0	10	123	-3.05	2.55	125	-2.16	2.35
Serrie[75]	2017	Change score reported	0	10	650	Not reported		337	Not reported	

a. Gilron 2005 and Khoromi 2007 are 4-arm RCTs; each contributed twice to our effect estimate of opioids vs. placebo for pain relief (with and without gabapentin or nortriptyline add-on)

b. Arai 2015 and Tominaga 2016 each reported 2 separate trials in one paper

eTable 7: Multiple meta-regression of length of follow-up, clinical condition (neuropathic vs. non-neuropathic conditions) and pain relief

Factor		No. of Studies	Coefficient	95%CI		p-value
				lower limit	upper limit	
neuropathic vs non-neuropathic conditions	Univariable meta-regression	76[a]	-0.076	-0.174	0.022	0.127
	Multivariable meta-regression		-0.050	-0.147	0.046	0.303
length of follow-up (per day)	Univariable meta-regression		0.006	0.002	0.010	0.006
	Multivariable meta-regression		0.005	0.001	0.009	0.014

[a] Four of 80 trials were excluded due to enrolling mixed populations with neuropathic and non-neuropathic conditions

eTable 8: GRADE evidence profile of adverse events for opioids vs. placebo and patients with chronic noncancer pain from 83 randomized clinical trials

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[a]	Indirectness[b]	Imprecision[c]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								placebo	opioids	
Nausea (35 RCTs)										
9 enrichment trials with adequate random sequence generation[d]	3,021	1 to 4	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	105 (7.9%)	275 (16.2%)	**High**
								Difference: +8.3% (95%CI +4.9% to +12.5%)		
								RR 2.04 (95%CI 1.62 to 2.57)		
26 non-enrichment trials with adequate random sequence generation[d]	8,836	1 to 6	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected; Symmetric funnel plot; Begg's test p=0.40	282 (8.2%)	1,398 (25.9%)	**High**
								Difference: +17.7% (95%CI +13.8% to +22.3%)		
								RR 3.17 (95%CI 2.69 to 3.73)		

eTable 8: GRADE evidence profile of adverse events for opioids vs. placebo and patients with chronic noncancer pain from 83 randomized clinical trials

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[a]	Indirectness[b]	Imprecision[c]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								placebo	opioids	
Constipation[e] (63 RCTs)										
52 trials, after excluding studies at risk of publication bias (SE>1)	18,071	1 to 6	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected; Symmetric funnel plot; Begg's test p=0.36	390 (5.3%)	1,727 (16.2%)	**High**
								Difference: +10.9% (95%CI +8.7% to +13.4%)		
								RR 3.08 (95%CI 2.65 to 3.55)		
Dizziness (60 RCTs)										
19 enrichment trials[f]	6,826	1 to 4	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected; Symmetric funnel plot; Begg's test p=0.68	97 (3.1%)	210 (5.7%)	**High**
								Difference: +2.6% (95%CI +1.4% to +4.3%)		

eTable 8: GRADE evidence profile of adverse events for opioids vs. placebo and patients with chronic noncancer pain from 83 randomized clinical trials

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[a]	Indirectness[b]	Imprecision[c]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								placebo	opioids	
								RR 1.86 (95%CI 1.45 to 2.39)		
41 non-enrichment trials[f]	12,843	1 to 6	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected; Symmetric funnel plot; Begg's test p=0.65	281 (5.6%)	1,188 (15.1%)	**High**
								Difference: +9.5% (95%CI +7.5% to +11.9%)		
								RR 2.69 (95%CI 2.33 to 3.11)		
Drowsiness (54 RCTs)										
17 enrichment trials[g]	5,755	1.5 to 3	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected; Symmetric funnel plot; Begg's test p=0.34	49 (1.8%)	96 (3.2%)	**High**
								Difference: +1.5% (95%CI +0.6% to +2.6%)		

eTable 8: GRADE evidence profile of adverse events for opioids vs. placebo and patients with chronic noncancer pain from 83 randomized clinical trials

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[a]	Indirectness[b]	Imprecision[c]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								placebo	opioids	
								RR 1.82 (95%CI 1.35 to 2.45)		
37 non-enrichment trials[g]	12,234	1 to 6	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected; Symmetric funnel plot; Begg's test p=0.12	195 (4.2 %)	1,139 (15.0%)	**High**
								Difference: +10.8 (95%CI +7.9% to +14.5%)		
								RR 3.59 (95%CI 2.88 to 4.47)		
Headache[h] (52 RCTs)										
50 with blinding of outcome assessors [h]	18,412	1 to 6	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[i]	Undetected; Symmetric funnel plot; Begg's test p=0.39	576 (7.8%)	933 (8.6%)	**Moderate**
								Difference: +0.8% (95%CI -0.1% to +1.7%)		

eTable 8: GRADE evidence profile of adverse events for opioids vs. placebo and patients with chronic noncancer pain from 83 randomized clinical trials

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[a]	Indirectness[b]	Imprecision[c]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								placebo	opioids	
								RR 1.10 (95%CI 0.99 to 1.22)		
Pruritis (35 RCTs)										
35	12,761	1 to 6	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected: Symmetric funnel plot; Begg's test p=0.46	186 (3.8%)	759 (9.7%)	**High**
								Difference: +6.1% (95%CI +3.2% to +9.8%		
								RR 2.59 (95%CI 1.86 to 3.62)		
Dry mouth[j] (34 RCTs)										
30, after excluding	11,129	1 to 4	No serious	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected; Symmetric	82 (1.9%)	335 (4.9%)	**High**

eTable 8: GRADE evidence profile of adverse events for opioids vs. placebo and patients with chronic noncancer pain from 83 randomized clinical trials

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[a]	Indirectness[b]	Imprecision[c]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								placebo	opioids	
trials with ≥20% loss to follow-up [j]			risk of bias				funnel plot; Begg's test p=0.64	Difference: +3.0% (95%CI +1.9% to +4.5%)		
								RR 2.57 (95%CI 1.98 to 3.34)		

RR: relative risk; CI: confidence interval; SE: standard error

a. Inconsistency refers to an unexplained heterogeneity of results. An I^2 of 75-100% indicates that heterogeneity may be considerable
b. Indirectness results if the patients, intervention, control or outcomes are different from the research question under investigation
c. In this review, serious imprecision refers to situations in which the confidence interval includes both benefit and harm
d. When restricted to trials with adequate randomization sequence generation (test of interaction p-value = 0.002), compared to placebo, opioids were associated with nausea, but less so for enrichment vs. non-enrichment trials (test of interaction p-value <0.001).
e. Publication bias was detected (p= 0.008), and our pooled analysis excludes 11 trials with evidence of small study effects.
f. Compared to placebo, opioids were associated with dizziness, but less so for enrichment vs. non-enrichment trials (test of interaction p-value = 0.01).
g. Compared to placebo, opioids were associated with drowsiness, but less so for enrichment vs. non-enrichment trials (test of interaction p-value = 0.01).
h. We found a significant subgroup effect for trials reporting blinded outcome assessors vs. not (test of interaction p-value = 0.04).
i. Confidence intervals include benefit and harm
j. We found a significant subgroup effect for trials reporting <20% loss to follow-up vs. ≥20% loss to follow-up (test of interaction p-value = 0.008).

eTable 9: GRADE evidence profile of opioids vs. NSAIDs for patients with chronic noncancer pain from 12 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								NSAIDs	opioids	
Pain: 10 cm VAS for pain; lower is better; the MID = 1 cm										
9	1,431	1-6	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Undetected;	381 (74.2%) achieve the MID	773 (84.3%) achieve the MID	**Moderate**
								Difference: 10.1% (95%CI -6.8% to +19.9%)		
								WMD -0.60 cm (95%CI -1.54 cm to +0.34 cm)		
Physical Functioning: 0 to 100-point SF-36 physical component summary scale; higher is better; the MID = 5-points										
7	1,311	1-4	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Undetected	224 (49.1%) achieve the MID	403 (47.1%) achieve the MID	**Moderate**

eTable 9: GRADE evidence profile of opioids vs. NSAIDs for patients with chronic noncancer pain from 12 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								NSAIDs	opioids	
								Difference: -2.0% (95%CI -6.0% to +2.0%)		
								WMD -0.90 points (95%CI -2.69 to +0.89)		
Emotional Functioning: 0 to 100-point SF-36 mental component summary scale; higher is better; the MID = 5-points										
2	837	3 to 4	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Undetected	90 (42%) achieve the MID	258 (41.4%) achieve the MID	**Moderate**
								Difference: -0.6% (95%CI -3.6% to +2.4%)		
								WMD -0.27 points (95%CI -1.62 to +1.08)		

eTable 9: GRADE evidence profile of opioids vs. NSAIDs for patients with chronic noncancer pain from 12 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								NSAIDs	opioids	
Role Functioning: 0 to 100-point SF-36 physical role functioning subscale; higher is better; the MID = 10-points										
1	70	2	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Undetected	29 (83.7%) achieve the MID	31 (89.3%) achieve the MID	**Moderate**
								Difference: +5.6% (95%CI -5.7% to +11.9%)		
								WMD +12.33 points (95%CI -9.86 to +34.53)		
Sleep Quality: 100 mm VAS for sleep quality (on the SF-36); higher is better; the MID = 10 mm										
2	898	1.5 to 3	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Undetected	134 (52.8%) achieve the MID	316 (49%) achieve the MID	**Moderate**

eTable 9: GRADE evidence profile of opioids vs. NSAIDs for patients with chronic noncancer pain from 12 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								NSAIDs	opioids	
								Difference: -3.8% (95%CI -9.3% to +1.7%)		
								WMD -3.06 mm (95%CI -7.50 to +1.37)		
Vomiting										
5	2,632	1.5 to 4	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	19 (1.7%)	119 (7.9%)	**High**
								Difference: +6.2% (95%CI +3.2% to +11.1%)		
								RR 4.71 (95%CI 2.92 to 7.60)		
Nausea										

eTable 9: GRADE evidence profile of opioids vs. NSAIDs for patients with chronic noncancer pain from 12 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								NSAIDs	opioids	
8	2,829	1.5 to 6	No serious risk of bias	No serious inconsistency	No serious indirectness	No Serious imprecision	Undetected	93 (7.6%)	318 (19.1%)	**High**
								Difference: +11.5% (95%CI +7.6% to +16.4%)		
								RR 2.51 (95%CI 2.00 to 3.15)		
Constipation										
9	2,872	1.5 to 6	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected;	40 (3.2%)	190 (9.0%)	**High**
								Difference: +5.8% (95%CI +2.6% to +11.0%)		
								RR 2.84 (95%CI 1.82 to 4.43)		

eTable 9: GRADE evidence profile of opioids vs. NSAIDs for patients with chronic noncancer pain from 12 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								NSAIDs	opioids	
Dizziness										
8	2,829	1.5 to 4	No serious risk of bias	No serious inconsistency	No serious indirectness	No Serious imprecision	Undetected;	86 (7.0%)	261 (14.0%)	**High**
								Difference: +7.0% (95%CI +3.3% to +11.7%)		
								RR 1.98 (95%CI 1.47 to 2.66)		
Drowsiness										
6	2,618	1.5 to 4	No serious risk of bias	No serious inconsistency	No serious indirectness	No Serious imprecision	Undetected	50 (4.5%)	161 (10.3%)	**High**
								Difference: +5.8% (95%CI +2.3% to +11.1%)		

eTable 9: GRADE evidence profile of opioids vs. NSAIDs for patients with chronic noncancer pain from 12 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								NSAIDs	opioids	
								RR 2.29 (95%CI 1.52 to 3.46)		
Headache										
6	2,668	1.5 to 4	No serious risk of bias	No serious inconsistency	No serious indirectness	No Serious imprecision	Undetected	111 (9.8%)	209 (13.5%)	**High**
								Difference: +3.7% (95%CI +1.0% to +7.0%)		
								RR 1.37 (95%CI 1.10 to 1.69)		
Pruritis										
4	2,420	1.5 to 4	No serious risk of bias	No serious inconsistency	No serious indirectness	No Serious imprecision	Undetected	15 (1.5%)	100 (5.9%)	**High**

eTable 9: GRADE evidence profile of opioids vs. NSAIDs for patients with chronic noncancer pain from 12 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								NSAIDs	opioids	
								Difference: +4.4% (95%CI +2.0% to +8.7%)		
								RR 4.01 (95%CI 2.33 to 6.89)		
Dry mouth										
3	1,629	1.5 to 4	No serious risk of bias	No serious inconsistency	No serious indirectness	No Serious imprecision	Undetected	10 (1.6%)	69 (5.6%)	**High**
								Difference: +4% (95%CI +1.2% to +9.5%)		
								RR 3.42 (95%CI 1.73 to 6.77)		

WMD: weighted mean difference. RR: relative risk; CI: confidence interval; VAS: visual analogue scale; MID: minimally important difference; NSAIDs: nonsteroidal anti-inflammatory drugs

a. No study reported social functioning when comparing opioids with NSAIDs
b. Inconsistency refers to an unexplained heterogeneity of results. An I^2 of 75-100% indicates that heterogeneity may be considerable

[c] Indirectness results if the intervention, patients or outcomes are different from the research question under investigation
[d] In this review, serious imprecision refers to situations in which the confidence interval includes both benefit and harm
[e] Wide confidence intervals which include benefit and harm

eTable 10: GRADE evidence profile of opioids vs. tricyclic antidepressants for patients with chronic noncancer pain from 3 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								antidepressants	opioids	
Emotional Functioning: 0 to 100-point SF-36 mental component summary scale; higher is better; the MID = 5-points										
2	158	1.25-2 (5-8 weeks)	Serious risk of bias[e]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	38 (48.7%) achieve the MID	26 (32.6%) achieve the MID	**Moderate**
								Difference: -16.1% (95%CI -3.8% to -27.0%)		
								WMD -6.22 points (95%CI -11.06 to -1.38)		

eTable 10: GRADE evidence profile of opioids vs. tricyclic antidepressants for patients with chronic noncancer pain from 3 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								antidepressants	opioids	
Role Functioning: 0 to 100-point SF-36 physical role functioning subscale; higher is better; the MID = 10-points[g]										
2	158	1.25-2 (5-8 weeks)	Serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious imprecision[f]	Undetected	WMD -5.15 points (95%CI -19.92 to +9.62)		**Low**
Social Functioning: 0 to 100-point SF-36 social role functioning subscale; higher is better; the MID = 10-points[g]										
2	158	1.25-2 (5-8 weeks)	Serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious imprecision[f]	Undetected	WMD -4.42 points (95%CI -12.23 to +3.40)		**Low**
Nausea										

eTable 10: GRADE evidence profile of opioids vs. tricyclic antidepressants for patients with chronic noncancer pain from 3 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								antidepressants	opioids	
1	56	1.25 (5 weeks)	Serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious imprecision[f]	Not applicable	0 (0%)	2 (7.1%)	**Low**
								Difference: +7.1% (95%CI -4.5% to +18.8%)		
								RR 5.00 (95%CI 0.25 to 99.67)		
Constipation										
1	56 (1 RCT)	1.25 (5 weeks)		No serious inconsistency	No serious indirectness	No serious imprecision		7 (25%)	18 (64.3%)	**Moderate**

eTable 10: GRADE evidence profile of opioids vs. tricyclic antidepressants for patients with chronic noncancer pain from 3 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								antidepressants	opioids	
	Follow-up:		Serious risk of bias[e]				Not applicable	Difference: +39.3% (95%CI +15.4% to +63.2%)		
								RR 2.57 (95%CI 1.28 to 5.17)		
Dizziness										
1	56	1.25 (5 weeks)	Serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious imprecision[f]	Not applicable	2 (7.1%)	4 (14.3%)	**Low**
								Difference: +7.2% (95%C-9% to +23.2%)		

eTable 10: GRADE evidence profile of opioids vs. tricyclic antidepressants for patients with chronic noncancer pain from 3 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								antidepressants	opioids	
								RR 2.00 (95%CI 0.40 to 10.05)		
Drowsiness										
1	56	1.25 (5 weeks)	Serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious imprecision[f]	Not applicable	2 (7.1%)	7 (25%)	**Low**
								Difference: +17.9% (95%CI-0.8% to +36.5%)		
								RR 3.50 (95%CI 0.80 to 15.40)		

eTable 10: GRADE evidence profile of opioids vs. tricyclic antidepressants for patients with chronic noncancer pain from 3 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								antidepressants	opioids	
Headache										
1	56	1.25 months (5 weeks)	Serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious imprecision[f]	Not applicable	2 (7.1%)	4 (14.3%)	**Low**
								Difference: +7.2% (95%CI-9% to +23.2%)		
								RR 2.00 (95%CI 0.40 to 10.05)		
Dry mouth										

eTable 10: GRADE evidence profile of opioids vs. tricyclic antidepressants for patients with chronic noncancer pain from 3 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								antidepressants	opioids	
1	56	1.25 (5 weeks)	Serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious imprecision[f]	Not applicable	10 (35.7%)	6 (21.4%)	**Low**
								Difference: +14.3% (95%CI-37.7% to +9.1%)		
								RR 0.60 (95%CI 0.25 to 1.43)		

WMD: weighted mean difference. RR: relative risk; CI: confidence interval; VAS: visual analogue scale; MID: minimally important difference

a. Pain and physical functioning were reported in The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain, Section Four Initiation and Dosing of Opioids in Patients with Chronic Noncancer Pain, Recommendation 1, When considering therapy for patients with chronic non-cancer pain, we recommend optimization of non-opioid pharmacotherapy and non-pharmacological therapy, rather than a trial of opioids. Available at https://app.magicapp.org/app#/guideline/2182 ; none of three trials reported incidence of vomiting

b. Inconsistency refers to an unexplained heterogeneity of results. An I^2 of 75-100% indicates that heterogeneity may be considerable

c. Indirectness results if the patients, intervention, control or outcomes are different from the research question under investigation

d. In this review, serious imprecision refers to situations in which the confidence interval includes both benefit and harm

e. High loss to follow up in all studies (>35%).
f. Confidence interval includes benefit and harm
g. Only an end-of-study score was reported, without a baseline score, so the change score cannot be calculated. Thus, there is no baseline risk available to estimate the risk difference between groups

eTable 11: GRADE evidence profile of opioids vs. anticonvulsants for patients with chronic noncancer pain from 3 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								anticonvulsants	opioids	
Emotional Functioning: 0 to 100-point SF-36 mental component summary scale; higher is better; the MID = 5-points										
2	243	1-1.5	Serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious imprecision[g]	Undetected	65 (52.1%) achieve the MID	55 (46.0%) achieve the MID	**Low**
								Difference: -6.1% (95%CI -17.1% to +5.2%)		
								WMD -2.58 points (95%CI -7.34 to +2.18)		

eTable 11: GRADE evidence profile of opioids vs. anticonvulsants for patients with chronic noncancer pain from 3 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								anticonvulsants	opioids	
Role Functioning: 0 to 100-point SF-36 physical role functioning subscale; higher is better; the MID = 10-points										
2	243	1-1.5	Serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious imprecision[g]	Undetected	65 (52.4%) achieve the MID	62 (52.5%) achieve the MID	**Low**
								Difference: +0.1% (95%CI -9.6% to +9.6%)		
								WMD +0.03 points (95%CI -11.74 to +11.81)		

eTable 11: GRADE evidence profile of opioids vs. anticonvulsants for patients with chronic noncancer pain from 3 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								anticonvulsants	opioids	
Social Functioning: 0 to 100-point SF-36 social role functioning subscale; higher is better; the MID = 10-points										
2	243	1-1.5	Serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious imprecision[g]	Undetected	59 (47.2%) achieve the MID	57 (48.1%) achieve the MID	**Low**
								Difference: +0.9% (95%CI -8.8% to +10.8%)		
								WMD +0.63 points (95%CI -6.06 to +7.33)		

eTable 11: GRADE evidence profile of opioids vs. anticonvulsants for patients with chronic noncancer pain from 3 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								anticonvulsants	opioids	
Sleep Quality: 100 mm VAS for sleep quality (on the SF-36); higher is better; the MID = 10 mm										
2	243	1-1.5	Serious risk of bias[e]	No serious inconsistency	No serious indirectness	Serious imprecision[g]	Undetected	82 (66%) achieve the MID	77 (64.9%) achieve the MID	**Low**
								Difference: -1.1% (95%CI -11.1% to +7.9%)		
								WMD -1.00 mm (95%CI -9.80 to +7.80)		

eTable 11: GRADE evidence profile of opioids vs. anticonvulsants for patients with chronic noncancer pain from 3 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								anticonvulsants	opioids	
Nausea										
2	179	1-1.5	Serious risk of bias[e]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	0 (0%)	13 (14.4%)	**Moderate**
								Difference: +14.4% (95%CI +7% to +21.7%)		
								RR 13.74 (95%CI 1.85 to 102.24)		
Constipation										

eTable 11: GRADE evidence profile of opioids vs. anticonvulsants for patients with chronic noncancer pain from 3 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								anticonvulsants	opioids	
3	342	1-1.5	Serious risk of bias[e]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	2 (1.2%)	15 (9.0%)	**Moderate**
								Difference: +7.8% (95%CI +0.3% to +56%)		
								RR 7.77 (95%CI 1.22 to 49.43)		
Dizziness										
2	277	1-1.5		No serious inconsistency	No serious indirectness	Serious imprecision[g]	Undetected	8 (5.7%)	9 (6.7%)	**Low**

eTable 11: GRADE evidence profile of opioids vs. anticonvulsants for patients with chronic noncancer pain from 3 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								anticonvulsants	opioids	
			Serious risk of bias[f]					Difference: +1.0% (95%CI -2.9% to +10.5%) RR 1.18 (95%CI 0.49 to 2.85)		
Drowsiness										
2	228	1-1.5		No serious inconsistency	No serious indirectness	Serious imprecision[g]	Undetected	13 (11.2%)	8 (6.8%)	**Low**

eTable 11: GRADE evidence profile of opioids vs. anticonvulsants for patients with chronic noncancer pain from 3 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								anticonvulsants	opioids	
			Serious risk of bias[e]					Difference: -4.4% (95%CI -8.1% to +6.0%) RR 0.61 (95%CI 0.28 to 1.36)		
Headache										
1	114	1-1.5	No serious	No serious inconsistency	No serious indirectness	Serious imprecision[g]	Not applicable	0 (0%)	1 (1.8%)	**Moderate**

eTable 11: GRADE evidence profile of opioids vs. anticonvulsants for patients with chronic noncancer pain from 3 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								anticonvulsants	opioids	
			risk of bias					Difference: +1.8% (95%CI -3.1% to +6.6%)		
								RR 3.00 (95%CI 0.12 to 72.13)		
Pruritus										
1	114	1-1.5	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[g]	Not applicable	1 (1.8%)	4 (7%)	**Moderate**
								Difference: +5.2% (95%CI -0.9% to +59.1%)		

eTable 11: GRADE evidence profile of opioids vs. anticonvulsants for patients with chronic noncancer pain from 3 randomized clinical trials [a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								anticonvulsants	opioids	
								RR 4.00 (95%CI 0.46 to 34.70)		
Dry mouth										
1	114	1-1.5	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[g]	Not applicable	4 (7%)	3 (5.3%)	**Moderate**
								Difference: -1.7% (95%CI -5.8% to +15.4%)		
								RR 0.75 (95%CI 0.18 to 3.20)		

WMD: weighted mean difference. RR: relative risk; CI: confidence interval; VAS: visual analogue scale; MID: minimally important difference

a. Pain and physical functioning were reported in The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain, Section Four Initiation and Dosing of Opioids in Patients with Chronic Noncancer Pain, Recommendation 1, When considering therapy for patients with chronic non-cancer pain, we recommend optimization of non-opioid pharmacotherapy and non-pharmacological therapy, rather than a trial of opioids. Available at https://app.magicapp.org/app#/guideline/2182; zero events for vomiting was reported in both groups in one trial (Gilron 2005)
b. Inconsistency refers to an unexplained heterogeneity of results. An I^2 of 75-100% indicates that heterogeneity may be considerable
c. Indirectness results if the intervention, patients or outcomes are different from the research question under investigation
d. In this review, serious imprecision refers to situations in which the confidence interval includes both benefit and harm
e. Two (Sakai et al 2015, Ko et al 2010) out of three studies had no allocation concealment and no blinding; and one study (Ko et al., 2010) had high loss to follow-up (25%)
f. One out of two studies (Sakai et al 2015 or Ko et al 2010) had no allocation concealment and no blinding; and one study (Ko et al., 2010) had high loss to follow-up (25%)
g. Wide confidence intervals which include benefit and harm

eTable 12: GRADE evidence profile of opioids vs. nabilone for patients with chronic noncancer pain from 1 randomized clinical trial[a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								nabilone	opioids	
Emotional Functioning: 0 to 100-point SF-36 mental component summary scale; higher is better; the MID = 5-points[e]										
1	71	1.5 (6 weeks)	Serious risk of bias[f]	No serious inconsistency	No serious indirectness	Serious imprecision[g]	Not applicable	WMD +2.50 point (95%CI -2.70 to +7.60)		**Low**
Role Functioning: 0 to 100-point SF-36 physical role functioning subscale; higher is better; the MID = 10-points[e]										
1	71	1.5 (6 weeks)	Serious risk of bias[f]	No serious inconsistency	No serious indirectness	No serious imprecision	Not applicable	WMD +8.9 point (95%CI +1.1 to +16.7)		**Moderate**
Social Functioning: 0 to 100-point SF-36 social role functioning subscale; higher is better; the MID = 10-points[e]										

eTable 12: GRADE evidence profile of opioids vs. nabilone for patients with chronic noncancer pain from 1 randomized clinical trial[a]

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								nabilone	opioids	
1	71	1.5 (6 weeks)	Serious risk of bias[f]	No serious inconsistency	No serious indirectness	Serious imprecision[g]	Not applicable	WMD +3.4 point (95%CI -4.1 to +10.8)		**Low**

WMD: weighted mean difference. RR: relative risk; CI: confidence interval; VAS: visual analogue scale; MID: minimally important difference

a. Pain and physical functioning were reported in The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain, Section Four Initiation and Dosing of Opioids in Patients with Chronic Noncancer Pain, Recommendation 1, When considering therapy for patients with chronic non-cancer pain, we recommend optimization of non-opioid pharmacotherapy and non-pharmacological therapy, rather than a trial of opioids. Available at https://app.magicapp.org/app#/guideline/2182

b. Inconsistency refers to an unexplained heterogeneity of results. An I^2 of 75-100% indicates that heterogeneity may be considerable

c. Indirectness results if the patients, intervention, control or outcomes are different from the research question under investigation

d. A In this review, serious imprecision refers to situations in which the confidence interval includes both benefit and harm

e. Only mean & 95%CI were reported - there is no baseline risk available to estimate the risk difference between groups

f. Did not report randomization or allocation; loss to follow-up was 24%; the trial reported a benefit for pain relief in favor of opioids (mean difference 0.6 cm on the 10 cm VAS for pain (95%CI 0.14 to 1.05); however, it is not clear how this result was calculated. When we calculated the effect on pain, based on change scores reported for the 10 cm VAS for pain, we found no significant effect (and this is what we have reported). Contact with the lead author of the trial was unable to resolve this issue.

g. Confidence interval includes benefit and harm

eTable 13: GRADE evidence profile of opioids vs. usual care for patients with chronic noncancer pain from 1 randomized clinical trial

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[a]	Indirectness[b]	Imprecision[c]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								Usual care	opioids	
Pain: 10 cm VAS for pain; lower is better; the MID = 1 cm										
1	111	1.5	Very serious risk of bias[d]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected;	26 (77.4%) achieve the MID	77 (98.5%) achieve the MID	**Low**
								Difference: 21.1% (95%CI 18.7% to 22.1%)		
								WMD -2.06 cm (95%CI -2.65 to -1.48)		

eTable 13: GRADE evidence profile of opioids vs. usual care for patients with chronic noncancer pain from 1 randomized clinical trial

# of Trials	# of patients	Duration of follow-up (months)	Risk of bias	Inconsistency[a]	Indirectness[b]	Imprecision[c]	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								Usual care	opioids	
Role Functioning: 0 to 100-point SF-36 role functioning subscale; higher is better; the MID = 10-points										
1	111	1.5	Very serious risk of bias[d]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected;	14 (43.7%) achieve the MID	51 (65.4%) achieve the MID	**Low**
								Difference: 21.7% (95%CI 5.7% to 35.4%)		
								WMD +11.67 points (95%CI +3.00 to +20.34)		

WMD: weighted mean difference. RR: relative risk; CI: confidence interval; VAS: visual analogue scale; MID: minimally important difference

a. Inconsistency refers to an unexplained heterogeneity of results. An I^2 of 75-100% indicates that heterogeneity may be considerable
b. Indirectness results if the intervention, patients or outcomes are different from the research question under investigation
c. In this review, serious imprecision refers to situations in which the confidence interval includes both benefit and harm
d. Did not report how their randomization sequence was generated, or if allocation was concealed, healthcare providers, outcome assessors, and adjudicators were unblinded, and there was 28% loss to follow-up

eTable 14: Results of within-trial comparisons of different opioid doses

Study, Clinical condition	Interventions and Outcomes					
	Treatment arm, (no. of patients)	Pain	Physical Function	Gastrointestinal adverse events, no. of patients (%)		
				nausea	vomiting	constipation
Fishman 2007 [30], Osteoarthritis	Placebo (224)	204.5[a]	27%[b]	13 (5.7%)	1 (0.4%)	3 (1.3%)
	Tramadol Contramid OAD 100 mg (103)	166.9[a]	48%[b]	12 (11.3%)	4 (3.8%)	12 (11.3%)
	Tramadol Contramid OAD 200 mg (107)	161.8[a]	45%[b]	22 (19.8%)	6 (5.4%)	16 (14.4%)
	Tramadol Contramid OAD 300 mg (105)	169.8[a]	46%[b]	28 (25.9%)	16 (14.8%)	11 (10.2%)
Vorsanger 2008 [37], Low back pain not otherwise specified	Placebo	+12.2[c]	9.8[d]	36 (27.9%)	9 (7.0%)	25 (19.1%)
	Tramadol ER 200 mg (128)	+7.8[c]	8.5[d]	35 (27.1%)	10 (7.8%)	33 (25.6%)
	Tramadol ER 300 mg (129)	+5.2[c]	8.2[d]	37 (28.9%)	9 (7.0%)	30 (23.4%)
Gana 2006 [25], Osteoarthritis	Placebo (205)	74.2 ± 8.5[e]	2.4 ± 0.6[f]	15 (7.3%)	6 (2.9%)	12 (5.9%)
	Tramadol ER 100 mg (202)	107.2 ± 8.6[e]	3.6 ± 0.6[f]	30 (14.9%)	11 (5.4%)	26 (12.9%)
	Tramadol ER 200 mg (201)	111.5 ± 8.7[e]	3.9 ± 0.6[f]	47 (23.4%)	15 (7.5%)	33 (16.4%)
	Tramadol ER 300 mg (201)	103.9 ± 8.7[e]	3.6 ± 0.6[f]	49 (24.4%)	14 (7.0%)	45 (22.4%)

eTable 14: Results of within-trial comparisons of different opioid doses

Study, Clinical condition	Interventions and Outcomes					
	Treatment arm, (no. of patients)	Pain	Physical Function	Gastrointestinal adverse events, no. of patients (%)		
				nausea	vomiting	constipation
	Tramadol ER 400 mg (202)	107.8 ± 8.7[e]	3.2 ± 0.6[f]	52 (25.7%)	19 (9.4%)	60 (29.7%)
Rauck 2013 [57], Osteoarthritis	Placebo (332)	-1.9 ±0.16[g]	1.3 ± 0.11[h]	32 (9.6%)	7 (2.1%)	39 (11.7%)
	Hydromorphone ER 8 mg (319)	-2.0 ±0.16[g]	-1.6 ± 0.11[h]	96 (30.1%)	29 (9.1%)	131 (41.1%)
	Hydromorphone ER16 mg (330)	-2.5 ±0.16[g]	-1.7 ±0.11[h]	120 (36.4%)	38 (11.5%)	155 (47.0%)
DeLemos 2011 [93], Osteoarthritis	Placebo (200)	16.5 ±1.9[i]	3.0 ± 0.6[j]	17 (8.5%)	5 (2.5%)	5 (2.5%)
	Tramadol ER 100 mg (201)	16.7 ±1.8[i]	2.8 ± 0.6[j]	31 (15.4%)	9 (4.5%)	23 (11.4%)
	Tramadol ER 200 mg (199)	21.6 ±1.8[i]	3.1 ± 0.6[j]	41 (20.6%)	14 (7.0%)	35 (17.6%)
	Tramadol ER 300 mg (199)	25.7 ±1.8[i]	3.5 ± 0.6[j]	52 (26.1%)	20 (10.1%)	40 (20.1%)
Christoph 2017 [74], Chronic low back pain of mixed presentation	Placebo (126)	-2.16 (95%CI -2.58 to -1.74)[k]	-12.8 ± 16.2[l]	2 (1.5%)	5 (3.8%)	5 (4.1%)
	Cebranopadol 200 µg (131)	-2.95 (95%CI -3.41 to -2.50)[k]	-17.7 ± 19.3[l]	12 (9.1%)	8 (6.2%)	10 (7.7%)
	Cebranopadol 400 µg (128)	-2.95 (95%CI -3.44 to -2.47)[k]	-14.9 ± 17.4[l]	7(5.6%)	10 (7.7%)	10 (7.7%)

eTable 14: Results of within-trial comparisons of different opioid doses

Study, Clinical condition	Interventions and Outcomes					
	Treatment arm, (no. of patients)	Pain	Physical Function	Gastrointestinal adverse events, no. of patients (%)		
				nausea	vomiting	constipation
	Cebranopadol 600 µg (130)	-3.18 (95%CI -3.70 to -2.66)[k]	-17.6 ± 14.5[l]	7(5.6%)	6 (5.0%)	12 (9.4%)

ER: extended release; NRS: numerical rating scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

[a] Pain measured on the 0 - 500 WOMAC pain subscale at week 12

[b] Physical functioning measured on the 0 – 1700 WOMAC physical function subscale at week 12

[c] Pain Measured as pain increase at 12 weeks from baseline on the 100mm VAS (no difference between tramadol ER 300mg and 200mg; p = 0.481) No standard deviation was provided

[d] Physical functioning measured with Roland Disability index scores (no difference between tramadol ER 300 mg and 200mg; p = 0.125) No standard deviation was provided

[e] Pain measured at week 12 on the WOMAC pain 0-500 scale (no significant difference between different tramadol ER doses)

[f] Physical functioning measured using the SF-36 physical component score (no significant difference between different doses of tramadol; p= 0.403)

[g] Pain measured as reduction at 12 weeks from baseline on the 11-point NRS pain scale

[h] Physical function measured on the WOMAC physical function score

[i] Pain reduction at 12 weeks from baseline on the 100mm VAS

[j] SF-36 Physical component score (no significant difference between treatment groups)

[k] Mean change from baseline pain to week 14 with the 11-point NRS for pain

[l] Mean change from baseline to week 14 with the Oswestry Disability Index

eTable 15a: Subgroup analyses for pain, physical and emotional functioning for randomized clinical trials of opioids vs. placebo

Subgroup factors		Pain					Physical functioning					Emotional functioning				
		No. of studies	WMD	95%CI		Inter-action test p	No. of studies	WMD	95%CI		Inter-action test p	No. of studies	WMD	95%CI		Inter-action test p
Treatment effect	Change score reported	50	-0.73	-0.86	-0.59	0.11	36	1.74	0.99	2.48	0.23	23	-0.44	-1.09	0.20	**0.01**
	Change score converted	30	-0.93	-1.12	-0.75		15	2.75	1.61	3.89		14	1.70	-0.06	3.46	
Length of follow-up	< 3 months	38	-0.97	-1.16	-0.78	**0.04**	22	2.34	1.21	3.47	0.61	20	0.43	-1.04	1.89	0.72
	≥ 3 months	42	-0.69	-0.82	-0.56		29	1.92	1.13	2.70		17	0.05	-0.79	0.89	
Clinical condition category 1[a]	Objective	49	-0.77	-0.93	-0.61	0.45	30	1.73	0.95	2.52	0.42	21	-0.64	-1.33	0.04	0.05 [b]
	Subjective	27	-0.85	-1.01	-0.69		19	2.51	1.48	3.55		15	1.17	-0.16	2.49	
Clinical condition category 2 [a]	Neuropathic	24	-0.97	-1.19	-0.75	0.18	12	1.87	1.16	2.58	0.37	12	0.14	-1.11	1.40	0.05 [b]
	Nociceptive	25	-0.61	-0.80	-0.42		18	1.72	0.65	2.79		9	-0.83	-1.63	-0.04	
	Central sensitization	27	-0.85	-1.01	-0.69		19	2.51	1.48	3.55		15	1.17	-0.16	2.49	
Clinical condition category 3 [a]	Neuropathic	24	-0.97	-1.19	-0.75	0.13	12	1.87	1.16	2.58	0.98	12	0.14	-1.11	1.40	0.62
	Non-neuropathic	52	-0.74	-0.87	-0.61		37	2.15	1.36	2.94		24	0.25	-0.59	1.10	
Randomization	Adequate randomization	44	-0.75	-0.90	-0.59	0.37	34	1.98	1.22	2.75	0.93	24	-0.51	-1.29	0.28	0.15 [b]
	Inadequate randomization	36	-0.83	-0.99	-0.68		17	2.18	1.02	3.34		13	1.34	0.00	2.68	
Allocation concealment	Adequate concealment	49	-0.80	-0.93	-0.66	0.99	33	1.67	1.00	2.35	0.17	24	-0.34	-1.09	0.41	0.12
	Inadequate concealment	31	-0.78	-0.97	-0.60		18	3.13	1.67	4.58		13	1.00	-0.50	2.49	

eTable 15a: Subgroup analyses for pain, physical and emotional functioning for randomized clinical trials of opioids vs. placebo

Subgroup factors		Pain					Physical functioning					Emotional functioning				
		No. of studies	WMD	95%CI		Inter-action test p	No. of studies	WMD	95%CI		Inter-action test p	No. of studies	WMD	95%CI		Inter-action test p
Blinding of patients	Yes	79				NA	51				NA	37				NA
	No	1					0					0				
Blinding of health care providers	Yes	78	-0.79	-0.91	-0.68	0.96	50				NA	37				NA
	No	2	-0.83	-1.42	-0.24		1					0				
Blinding of data collectors	Yes	77	-0.80	-0.91	-0.68	0.83	51				NA	37				NA
	No	3	-0.74	-1.50	0.02		0					0				
Blinding of outcome assessors	Yes	75	-0.81	-0.93	-0.69	0.38	49	2.05	1.39	2.71	1.00	36				NA
	No	5	-0.50	-0.72	-0.27		2	2.04	-0.34	4.42		1				
Blinding of data analyst	Yes	5	-1.03	-1.57	-0.49	0.36	3	2.29	-5.68	10.25	0.48	1				NA
	No	75	-0.77	-0.89	-0.66		48	2.07	1.45	2.69		36				
Trial design	Parallel trials	64	-0.76	-0.88	-0.64	0.24	42	2.27	1.53	3.01	0.29	27	0.11	-0.71	0.92	0.80
	Cross-over trials	16	-0.97	-1.25	-0.69		9	1.29	0.53	2.04		10	0.57	-1.03	2.17	
Enrichment trial	Yes	23	-0.84	-1.02	-0.67	0.52	13	2.20	1.04	3.36	0.94	8	-0.01	-1.85	1.83	0.85
	No	57	-0.77	-0.91	-0.62		38	2.01	1.27	2.75		29	0.14	-0.65	0.93	
Type of opioid intervention	Opioids alone	67	-0.79	-0.91	-0.67	0.73	45	2.05	1.33	2.78	0.93	31	-0.17	-0.98	0.65	0.12
	Combination	7	-0.72	-0.96	-0.48		6	2.17	1.21	3.13		6	1.31	0.33	2.29	

WMD: Weighted mean difference; 95%CI: 95% confidence interval; NA: not applicable as no subgroup analysis was conducted for less than 2 studies in a given subgroup.

[a] We excluded one to four trials with mixed clinical conditions from subgroup analysis for different clinical conditions.
[b] p-value from multivariable meta-regression.

Significant subgroup effects are **bolded.**

eTable 15b: Subgroup analyses for role and social functioning, and sleep quality for randomized clinical trials of opioids vs. placebo

Subgroup factors		Role functioning					Social functioning					Sleep quality				
		No. of studies	WMD	95%CI		Inter-action test p	No. of studies	WMD	95%CI		Inter-action test p	No. of studies	WMD	95%CI		Inter-action test p
Treatment effect	Change score reported	16	0.87	-0.54	2.28	**0.007**	17	1.00	-0.08	2.08	0.09	20	3.86	2.13	5.59	0.15
	Change score converted	16	5.79	2.69	8.88		12	3.28	0.71	5.85		11	7.14	2.86	11.42	
Length of follow-up	< 3 months	19	3.15	0.21	6.09	0.90	17	3.01	0.75	5.28	0.07	16	7.51	4.89	10.12	**0.03** [b]
	≥ 3 months	13	2.45	0.28	4.63		12	0.85	-0.16	1.85		15	3.42	1.58	5.26	
Clinical condition category 1 [a]	Objective	18	1.51	0.12	2.89	0.19	17	0.49	-0.72	1.70	0.06	22	5.11	3.33	6.89	0.10 [b]
	Subjective	11	4.59	0.95	8.22		11	2.91	1.14	4.68		7	0.65	-0.74	2.05	
Clinical condition category 2 [a]	Neuropathic	12	1.80	0.20	3.39	0.22	11	2.03	0.35	3.71	**0.01**[c]	10	5.07	1.54	8.60	0.07 [b]
	Nociceptive	6	2.04	-2.57	6.65		6	-1.03	-2.69	0.63		12	5.20	3.04	7.35	
	Central sensitization	11	4.59	0.95	8.22		11	2.91	1.14	4.68		7	0.65	-0.74	2.05	
Clinical condition category 3 [a]	Neuropathic	12	1.80	0.20	3.39	0.37	11	2.03	0.35	3.71	0.46	10	5.07	1.54	8.60	0.58
	Non-neuropathic	17	3.74	0.95	6.53		17	1.43	-0.06	2.92		19	3.96	2.06	5.86	
Randomization	Adequate randomization	18	2.20	-0.12	4.52	0.52	20	0.68	-0.43	1.79	0.09	17	4.65	2.91	6.39	0.71
	Inadequate randomization	14	3.61	0.41	6.82		9	3.26	0.96	5.56		14	4.56	1.62	7.49	
Allocation concealment	Adequate concealment	18	2.57	0.26	4.88	0.86	19	0.95	-0.22	2.12	0.26	22	4.12	2.16	6.09	0.38
	Inadequate concealment	14	3.04	-0.27	6.35		10	2.80	0.31	5.29		9	5.82	2.56	9.07	
	Yes	32				NA	29				NA	31				NA

eTable 15b: Subgroup analyses for role and social functioning, and sleep quality for randomized clinical trials of opioids vs. placebo

Subgroup factors		Role functioning					Social functioning					Sleep quality				
		No. of studies	WMD	95%CI		Inter-action test p	No. of studies	WMD	95%CI		Inter-action test p	No. of studies	WMD	95%CI		Inter-action test p
Blinding of patients	No	0					0					0				
Blinding of health care providers	Yes	31				NA	29				NA	31				NA
	No	1					0					0				
Blinding of data collectors	Yes	31				NA	29				NA	30				NA
	No	1					0					1				
Blinding of outcome assessors	Yes	30	2.77	0.83	4.71	0.81	28				NA	29	4.43	2.69	6.16	0.48
	No	2	5.02	-6.34	16.37		1					2	6.81	2.13	11.50	
Blinding of data analyst	Yes	1				NA	1				NA	2	2.25	-0.76	5.26	0.43
	No	31					28					29	4.84	3.00	6.69	
Trial design	Parallel trials	22	3.15	1.05	5.25	0.45	20	1.79	0.43	3.15	0.70	24	4.60	2.79	6.41	0.98
	Cross-over trials	10	0.79	-2.78	4.35		9	1.19	-1.98	4.36		7	4.41	-0.32	9.13	
Enrichment trial	Yes	8	1.12	-0.15	2.40	0.39	6	1.52	0.21	2.82	1.00	7	1.58	-0.31	3.47	0.54 [b]
	No	24	3.44	0.66	6.22		23	1.76	0.11	3.40		24	5.60	3.72	7.49	
Type of opioid intervention	Opioids alone	25	1.33	-0.29	2.95	**0.002** [d]	23	1.14	-0.14	2.42	0.11	29	4.03	2.46	5.61	0.06 [b]
	Combination	7	8.35	4.27	12.43		6	3.65	1.20	6.09		2	16.14	1.57	30.72	

WMD: Weighted mean difference; RR: relative risk; 95%CI: 95% confidence interval; NA: not applicable as no subgroup analysis was conducted for less than 2 studies in a given subgroup.

[a] We excluded one to four trials with mixed clinical conditions from subgroup analysis for different clinical conditions.
[b] p-value from multivariable meta-regression.
[c] Although there is significant subgroup effect based on clinical condition and social functioning, this finding had low credibility as only 3 of 11 criteria for establishing trustworthiness of subgroup effects (eTable2) are met: (1) characteristic measured at baseline, (2) hypothesis specified a priori, and (3) p-value 0.01 for interaction test suggests a low likelihood that chance explains effect

[d] Although there is significant subgroup effect based on combination products vs. opioids alone and role functioning, this finding had low credibility as only 2 of 11 criteria for establishing trustworthiness of subgroup effects (eTable 2) are met: (1) characteristic measured at baseline, and (2) p-value 0.002 for interaction test suggests a low likelihood that chance explains effect.

Significant subgroup effects are **bolded.**

eTable 15c: Subgroup analyses for vomiting, nausea and constipation for randomized clinical trials of opioids vs. placebo

Subgroup factors		Vomiting					Nausea					Constipation				
		No. studies	RR	95%CI		Inter-action test p	No. studies	RR	95%CI		Inter-action test p	No. studies	RR	95%CI		Inter-action test p
Length of follow-up	< 3 months	17	4.37	2.92	6.52	0.22	24	2.56	2.02	3.24	0.44	24	3.44	2.54	4.66	0.72
	≥ 3 months	34	3.26	2.69	3.96		39	2.28	1.94	2.69		39	3.30	2.86	3.81	
Clinical condition category 1 [a]	Objective	30	3.87	3.14	4.78	0.12	39	2.64	2.27	3.08	0.27 [b]	39	3.65	3.04	4.39	0.14
	Subjective	17	3.01	2.03	4.47		20	1.95	1.52	2.49		20	2.85	2.28	3.56	
Clinical condition category 2 [a]	Neuropathic	13	3.08	2.05	4.63	0.06	17	2.33	1.89	2.86	0.21 [b]	16	3.59	2.50	5.17	0.12
	Nociceptive	17	4.25	3.32	5.45		22	2.75	2.26	3.35		23	3.73	3.01	4.62	
	Central sensitization	17	3.01	2.03	4.47		20	1.95	1.52	2.49		20	2.85	2.28	3.56	
Clinical condition category 3 [a]	Neuropathic	13	3.08	2.05	4.63	0.56	17	2.33	1.89	2.86	0.84	16	3.59	2.50	5.17	0.97
	Non-neuropathic	34	3.62	2.89	4.53		42	2.36	2.01	2.77		43	3.33	2.85	3.89	
Randomization	Adequate randomization	26	3.73	2.86	4.86	0.36	35	2.80	2.41	3.25	**0.003**	33	3.26	2.78	3.81	0.70
	Inadequate randomization	25	3.11	2.41	4.02		28	1.88	1.53	2.30		30	3.25	2.49	4.24	
Allocation concealment	Adequate concealment	29	3.49	2.71	4.49	0.91	35	2.56	2.13	3.07	0.18	34	3.29	2.73	3.96	0.79
	Inadequate concealment	22	3.37	2.55	4.44		28	2.11	1.76	2.51		29	3.20	2.53	4.06	
Blinding of patients	Yes	51				NA	63				NA	63				NA
	No	0					0					0				
	Yes	51				NA	63				NA	63				NA

eTable 15c: Subgroup analyses for vomiting, nausea and constipation for randomized clinical trials of opioids vs. placebo

Subgroup factors		Vomiting					Nausea					Constipation				
		No. studies	RR	95%CI		Inter-action test p	No. studies	RR	95%CI		Inter-action test p	No. studies	RR	95%CI		Inter-action test p
Blinding of health care providers	No	0					0					0				
Blinding of data collectors	Yes	50				NA	62				NA	62				NA
	No	1					1					1				
Blinding of outcome assessors	Yes	48	3.41	2.83	4.10	0.70	60	2.33	2.03	2.68	0.30	60	3.24	2.78	3.76	0.75
	No	3	3.97	2.15	7.30		3	3.36	2.46	4.57		3	3.52	1.45	8.59	
Blinding of data analyst	Yes	3	2.77	1.32	5.81	0.60	4	2.01	1.15	3.51	0.49	3	3.93	1.90	8.10	0.57
	No	48	3.48	2.90	4.19		59	2.40	2.09	2.76		60	3.23	2.78	3.74	
Trial design	Parallel trials	43	3.48	2.90	4.18	0.70	52	2.40	2.07	2.79	0.62	51	3.18	2.73	3.69	0.57
	Cross-over trials	8	3.08	1.64	5.77		11	2.10	1.67	2.65		12	4.04	2.51	6.53	
Enrichment trial	Yes	18	2.50	1.89	3.30	**0.007**	21	1.67	1.41	1.99	**<0.001**	20	2.52	1.98	3.20	0.05
	No	33	4.12	3.34	5.07		42	2.85	2.45	3.31		43	3.55	2.99	4.22	
Type of opioid intervention	Opioids alone	48	3.39	2.82	4.08	0.43	55	2.35	2.05	2.69	0.15	56	3.37	2.91	3.90	0.66
	Combination	2	5.17	1.92	13.96		7	3.08	2.29	4.15		6	2.98	2.05	4.34	

RR: relative risk; 95%CI: 95% confidence interval; NA: not applicable as no subgroup analysis was conducted for less than 2 studies in a given subgroup.

[a] We excluded four trials with mixed clinical conditions from subgroup analysis for different clinical conditions.
[b] p-value from multivariable meta-regression.

Significant subgroup effects are **bolded.**

eTable 15d: Subgroup analyses for dizziness, drowsiness, and headache for randomized clinical trials of opioids vs. placebo

Subgroup factors		Dizziness					Drowsiness					Headache				
		No. studies	RR	95%CI		Interaction test p	No. studies	RR	95%CI		Interaction test p	No. studies	RR	95%CI		Interaction test p
Length of follow-up	< 3 months	25	2.57	1.91	3.45	0.98	19	3.02	2.17	4.20	0.65	19	1.14	0.91	1.42	0.64
	≥ 3 months	35	2.51	2.20	2.86		35	3.27	2.56	4.17		33	1.07	0.95	1.21	
Clinical condition category 1 [a]	Objective	38	2.47	2.10	2.91	0.79	34	3.15	2.47	4.03	0.87	30	1.02	0.90	1.16	0.13
	Subjective	19	2.37	1.79	3.14		16	3.13	2.13	4.59		19	1.20	1.00	1.44	
Clinical condition category 2 [a]	Neuropathic	16	2.16	1.61	2.90	0.58	12	2.78	1.75	4.41	0.65	13	0.94	0.70	1.27	0.19
	Nociceptive	22	2.62	2.17	3.15		22	3.37	2.53	4.50		17	1.05	0.91	1.21	
	Central sensitization	19	2.37	1.79	3.14		16	3.13	2.13	4.59		19	1.20	1.00	1.44	
Clinical condition category 3 [a]	Neuropathic	16	2.16	1.61	2.90	0.38	12	2.78	1.75	4.41	0.41	13	1.11	0.99	1.25	0.29
	Non-neuropathic	41	2.52	2.16	2.95		38	3.25	2.58	4.09		36	0.94	0.70	1.27	
Randomization	Adequate randomization	34	2.63	2.23	3.09	0.14	28	3.54	2.63	4.76	0.30	32	1.15	1.00	1.32	0.16
	Inadequate randomization	26	2.11	1.65	2.70		26	2.71	2.12	3.47		20	0.97	0.79	1.18	
Allocation concealment	Adequate concealment	35	2.56	2.13	3.07	0.37	28	3.50	2.63	4.65	0.30	31	1.14	0.99	1.30	0.27
	Inadequate concealment	25	2.13	1.78	2.54		26	2.71	2.08	3.52		21	0.99	0.82	1.21	
Blinding of patients	Yes	60				NA	54				NA	52				NA
	No	0					0					0				
Blinding of health care providers	Yes	60				NA	54				NA	52				NA
	No	0					0					0				

eTable 15d: Subgroup analyses for dizziness, drowsiness, and headache for randomized clinical trials of opioids vs. placebo

Subgroup factors		Dizziness					Drowsiness					Headache				
		No. studies	**RR**	**95%CI**		**Inter-action test p**	**No. studies**	**RR**	**95%CI**		**Inter-action test p**	**No. studies**	**RR**	**95%CI**		**Inter-action test p**
Blinding of data collectors	Yes	59				NA	53				NA	51				NA
	No	1					1					1				
Blinding of outcome assessors	Yes	57	2.46	2.13	2.84	0.89	51	3.19	2.58	3.93	0.82	50	1.10	0.99	1.22	**0.04**
	No	3	2.22	1.42	3.49		3	3.12	1.90	5.13		2	0.25	0.06	0.99	
Blinding of data analyst	Yes	4	1.97	1.08	3.60	0.45	2	0.95	0.49	1.85	**0.01** [b]	4	1.17	0.69	2.01	0.79
	No	56	2.49	2.16	2.87		52	3.29	2.72	4.00		48	1.09	0.97	1.21	
Trial design	Parallel trials	49	2.44	2.12	2.81	0.83	48	3.31	2.66	4.11	0.28	43	1.08	0.96	1.21	0.43
	Cross-over trials	11	2.54	1.47	4.37		6	2.33	1.49	3.64		9	1.31	0.83	2.06	
Enrichment trial	Yes	19	1.86	1.45	2.39	**0.01**	17	1.82	1.35	2.45	**0.01**	19	0.97	0.77	1.22	0.28
	No	41	2.69	2.33	3.11		37	3.59	2.88	4.47		33	1.13	0.99	1.28	
Type of opioid intervention	Opioids alone	52	2.50	2.17	2.87	0.58	47	3.13	2.55	3.86	0.95	47	1.06	0.94	1.18	0.13
	Combination	7	2.79	1.97	3.95		6	4.32	1.89	9.85		5	1.33	1.02	1.75	

RR: relative risk; 95%CI: 95% confidence interval; NA: not applicable as no subgroup analysis was conducted for less than 2 studies in a given subgroup.

[a] We excluded one to four trials with mixed clinical conditions from subgroup analysis for different clinical conditions.
[b] Although there is a significant subgroup effect based on blinding of data analysts and drowsiness, this finding had low credibility as only 4 of 11 criteria for establishing trustworthiness of subgroup effects (eTable 2) are met: (1) characteristic measured at baseline, (2) hypothesis specified a priori, (3) direction of effect specified a priori, and (4) p-value 0.01 for interaction test suggest a low likelihood that chance explains effect

Significant subgroup effects are **bolded.**

eTable 15e: Subgroup analyses for pruritus and dry mouth for randomized clinical trials of opioids vs. placebo

Subgroup factors		Pruritus					Dry mouth				
		No. studies	RR	95%CI		Inter-action test p	No. studies	RR	95%CI		Inter-action test p
Length of follow-up	< 3 months	13	1.78	1.21	2.62	0.24	17	1.98	1.35	2.93	0.10
	≥ 3 months	22	3.14	1.95	5.05		17	2.69	1.99	3.64	
Clinical condition category 1[a]	Objective	23	3.15	2.02	4.90	0.34	22	2.30	1.69	3.14	0.88
	Subjective	11	2.15	1.16	3.96		11	2.20	1.29	3.75	
Clinical condition category 2[a]	Neuropathic	6	2.91	1.56	5.42	0.36	9	1.79	1.09	2.94	0.55
	Nociceptive	17	3.21	1.90	5.44		13	2.70	1.82	4.01	
	Central sensitization	11	2.15	1.16	3.96		11	2.20	1.29	3.75	
Clinical condition category 3[a]	Neuropathic	6	2.91	1.56	5.42	0.75	9	1.79	1.09	2.94	0.24
	Non-neuropathic	28	2.71	1.84	4.00		24	2.50	1.84	3.40	
Randomization	Adequate randomization	19	3.04	1.94	4.75	0.30	19	2.53	1.71	3.73	0.49
	Inadequate randomization	16	1.97	1.22	3.20		15	1.86	1.36	2.54	
Allocation concealment	Adequate concealment	20	2.94	1.92	4.52	0.37	21	2.63	1.90	3.64	0.11
	Inadequate concealment	15	2.06	1.26	3.38		13	1.61	1.11	2.35	
Blinding of patients	Yes	35				NA	34				NA
	No	0					0				
Blinding of health care providers	Yes	35				NA	34				NA
	No	0					0				
	Yes	34				NA	33				NA

eTable 15e: Subgroup analyses for pruritus and dry mouth for randomized clinical trials of opioids vs. placebo

Subgroup factors		Pruritus					Dry mouth				
		No. studies	RR	95%CI		Inter-action test p	No. studies	RR	95%CI		Inter-action test p
Blinding of data collectors	No	1					1				
Blinding of outcome assessors	Yes	32	2.57	1.81	3.64	0.85	32	2.31	1.78	3.01	0.27
	No	3	3.60	1.86	6.97		2	1.00	0.26	3.82	
Blinding of data analyst	Yes	1				NA	3	1.25	0.49	3.18	0.26
	No	34					31	2.34	1.79	3.07	
Trial design	Parallel trials	28	2.94	1.97	4.39	0.24	25	2.59	1.96	3.41	0.89
	Cross-over trials	7	1.30	0.91	1.87		9	1.47	0.92	2.34	
Enrichment trial	Yes	9	1.01	0.61	1.67	0.07	6	1.43	0.57	3.57	0.36
	No	26	3.04	2.08	4.45		28	2.34	1.78	3.09	
Type of opioid intervention	Opioids alone	32	2.65	1.83	3.83	0.89	31	2.19	1.68	2.85	0.79
	Combination	3	2.35	1.02	5.41		3	3.08	0.99	9.57	
Proportion of loss to follow-up [b]	< 20%	NA[b]				NA[b]	4	1.09	0.69	1.74	**0.008[b]**
	≥ 20%	NA[b]					30	2.57	1.98	3.34	

RR: relative risk; 95%CI: 95% confidence interval; NA: not applicable as no subgroup analysis was conducted for less than 2 studies in a given subgroup.

[a] We excluded one trial with mixed clinical conditions from subgroup analysis for different clinical conditions.
[b] subgroup analysis for loss to follow-up was only performed for the outcome dry month, as meta-regression of loss to follow-up and incidence of dry mouth was significant

Significant subgroup effects are **bolded.**

eTable 16a: Subgroup analyses for pain, physical functioning and vomiting for randomized clinical trials of opioids vs. NSAIDs

Subgroup factors		Pain					Physical functioning					Vomiting				
		No. studies	WMD	95%CI		Inter-action test p	No. studies	WMD	95%CI		Inter-action test p	No. studies	RR	95%CI		Inter-action test p
Treatment effect	Change score reported	3	0.38	-0.16	0.93	0.08	4	-1.45	-2.92	0.02	0.29	NA[a]				NA[a]
	Change score converted	6	-1.07	-2.08	-0.05		3	2.52	-3.36	8.41		NA[a]				
Length of follow-up	< 3 months	6	-0.68	-1.85	0.49	0.77	5	0.41	-1.96	2.78	0.13	4				NA
	≥ 3 months	3	-0.43	-1.86	1.01		2	-2.06	-3.41	-0.70		1				
Clinical condition category 1 [b]	Objective	2	-0.35	-1.62	0.93	0.50	5				NA	3	4.06	1.79	9.24	0.69
	Subjective	6	-1.04	-1.55	-0.52		1					2	5.08	2.83	9.15	
Clinical condition category 2 [b,c]	Neuropathic	1				0.21	0				NA	0				0.69
	Nociceptive	5	0.12	-0.56	0.80		1					3	4.06	1.79	9.24	
	Central sensitization	2	-1.04	-1.55	-0.52		5					2	5.08	2.83	9.15	
Clinical condition category 3 [b]	Neuropathic	1				NA	0				NA	0				NA
	Non-neuropathic	7					6					5				
Randomization	Adequate randomization	4	-0.81	-1.14	-0.48	0.71	3	1.62	-1.46	4.70	0.08	3	4.68	2.75	7.97	0.96
	Inadequate randomization	5	-0.47	-2.12	1.19		4	-2.03	-3.31	-0.74		2	4.86	1.65	14.3	
Allocation concealment	Adequate concealment	2	0.46	-0.39	1.30	0.17	2	-2.00	-3.34	-0.66	0.15	3	4.68	2.75	7.97	0.96
	Inadequate concealment	7	-0.88	-1.85	0.09		5	0.40	-2.05	2.84		2	4.86	1.65	14.3	
	Yes	2	0.46	-0.39	1.30		3	-0.95	-3.23	1.33		4				

eTable 16a: Subgroup analyses for pain, physical functioning and vomiting for randomized clinical trials of opioids vs. NSAIDs

Subgroup factors		Pain					Physical functioning					Vomiting				
		No. studies	WMD	95%CI		Inter-action test p	No. studies	WMD	95%CI		Inter-action test p	No. studies	RR	95%CI		Inter-action test p
Blinding of patients [d]	No	7	-0.88	-1.85	0.09	0.17	4	0.13	-4.35	4.60	0.77	1				NA
Blinding of health care providers [d]	Yes	2	0.46	-0.39	1.30	0.17	3	-0.95	-3.23	1.33	0.77	4				NA
	No	7	-0.88	-1.85	0.09		4	0.13	-4.35	4.60		1				
Blinding of data collectors [d]	Yes	2	0.46	-0.39	1.30	0.17	3	-0.95	-3.23	1.33	0.77	4				NA
	No	7	-0.88	-1.85	0.09		4	0.13	-4.35	4.60		1				
Blinding of outcome assessors [d]	Yes	2	0.46	-0.39	1.30	0.17	3	-0.95	-3.23	1.33	0.77	4				NA
	No	7	-0.88	-1.85	0.09		4	0.13	-4.35	4.60		1				
Blinding of data analyst	Yes	0				NA	0				NA	0				NA
	No	9					7					5				
Trial design	Parallel trials	8				NA	5	-0.93	-3.59	1.72	0.87	4				NA
	Cross-over trials	1					2	-0.22	-3.43	2.99		1				
Enrichment trial	Yes	1				NA	1				NA	0				NA
	No	8					6					5				

eTable 16a: Subgroup analyses for pain, physical functioning and vomiting for randomized clinical trials of opioids vs. NSAIDs

Subgroup factors		Pain					Physical functioning					Vomiting				
		No. studies	WMD	95%CI		Inter-action test p	No. studies	WMD	95%CI		Inter-action test p	No. studies	RR	95%CI		Inter-action test p
Type of opioid intervention	Opioids alone	5	-0.21	-1.02	0.59	0.31	5	-1.61	-2.80	-0.41	0.29	5				NA
	Combination	4	-1.04	-2.50	0.43		2	3.46	-5.45	12.37		0				

WMD: Weighted mean difference; 95%CI: 95% confidence interval; RR: relative risk; NA: not applicable as no subgroup analysis was conducted for less than 2 studies in a given subgroup.

[a] Subgroup analysis for change score reported vs converted is only applicable for continuous outcomes, not for binary outcomes, e.g. vomiting.
[b] We excluded one trial with mixed clinical conditions from subgroup analysis for different clinical conditions.
[c] This analysis was restricted to the 2 clinical subgroups that provided sufficient trials (≥2 trials in each subgroup) for analysis.
[d] Results are the same for subgroup analyses of blinding of patients, health care providers, data collectors or outcome assessors.

eTable 16b: Subgroup analyses for nausea, constipation and dizziness for randomized clinical trials of opioids vs. NSAIDs

Subgroup factors		Nausea					Constipation					Dizziness				
		No. studies	RR	95%CI		Inter-action test p	No. studies	RR	95%CI		Inter-action test p	No. studies	RR	95%CI		Inter-action test p
Length of follow-up	< 3 months	6	0.10	0.05	0.15	0.83	7	0.05	0.03	0.07	0.15	6	0.05	0.00	0.09	0.68
	≥ 3 months	2	0.13	0.08	0.18		2	0.14	0.10	0.18		2	0.08	0.03	0.14	
Clinical condition category 1 [a]	Objective	4	2.07	1.12	3.81	0.57	5	3.07	1.28	7.33	0.80	4	1.58	1.13	2.21	0.09
	Subjective	3	2.66	2.02	3.49		3	2.73	1.44	5.18		3	2.49	1.50	4.14	
Clinical condition category 2 [a,b]	Neuropathic	0				0.57	0				0.80	0				0.09
	Nociceptive	4	2.07	1.12	3.81		5	3.07	1.28	7.33		4	1.58	1.13	2.21	
	Central sensitization	3	2.66	2.02	3.49		3	2.73	1.44	5.18		3	2.49	1.50	4.14	
Clinical condition category 3 [a]	Neuropathic	0				NA	0				NA	0				NA
	Non-neuropathic	7					8					7				
Randomization	Adequate randomization	4	2.62	2.02	3.39	0.59	5	2.36	1.41	3.94	0.18	4	2.07	1.25	3.41	0.40
	Inadequate randomization	4	1.99	0.88	4.51		4	5.22	2.49	10.95		4	1.67	1.14	2.44	
Allocation concealment	Adequate concealment	3	2.66	2.03	3.47	0.50	3	2.54	1.37	4.72	0.66	3	2.30	1.51	3.49	0.19
	Inadequate concealment	5	2.07	1.21	3.56		6	3.27	1.62	6.58		5	1.59	1.09	2.32	
Blinding of patients [c]	Yes	4	2.65	2.09	3.35	0.22	4	3.16	1.66	6.02	0.53	4	2.11	1.53	2.93	0.21
	No	4	1.59	0.70	3.64		5	2.12	0.96	4.68		4	1.01	0.39	2.63	
	Yes	4	2.65	2.09	3.35	0.22	4	3.16	1.66	6.02	0.53	4	2.11	1.53	2.93	0.21

eTable 16b: Subgroup analyses for nausea, constipation and dizziness for randomized clinical trials of opioids vs. NSAIDs

Subgroup factors		Nausea					Constipation					Dizziness				
		No. studies	RR	95%CI		Inter-action test p	No. studies	RR	95%CI		Inter-action test p	No. studies	RR	95%CI		Inter-action test p
Blinding of health care providers [c]	No	4	1.59	0.70	3.64		5	2.12	0.96	4.68		4	1.01	0.39	2.63	
Blinding of data collectors [c]	Yes	4	2.65	2.09	3.35	0.22	4	3.16	1.66	6.02	0.53	4	2.11	1.53	2.93	0.21
	No	4	1.59	0.70	3.64		5	2.12	0.96	4.68		4	1.01	0.39	2.63	
Blinding of outcome assessors [c]	Yes	4	2.65	2.09	3.35	0.22	4	3.16	1.66	6.02	0.53	4	2.11	1.53	2.93	0.21
	No	4	1.59	0.70	3.64		5	2.12	0.96	4.68		4	1.01	0.39	2.63	
Blinding of data analyst	Yes	0				NA	0				NA	0				NA
	No	8					9					8				
Trial design	Parallel trials	7				NA	8				NA	7				NA
	Cross-over trials	1					1					1				
Enrichment trial	Yes	1				NA	1				NA	1				NA
	No	7					8					7				
Type of opioid intervention	Opioids alone	6	2.67	2.11	3.37	0.13	6	3.17	1.87	5.37	0.40	6	2.12	1.64	2.73	0.16
	Combination	2	1.23	0.45	3.37		3	1.83	0.75	4.49		2	0.79	0.25	2.45	

RR: relative risk; 95% confidence interval; NA: not applicable as no subgroup analysis was conducted for less than 2 studies in a given subgroup.

[a] We excluded one trial with mixed clinical conditions from subgroup analysis for different clinical conditions.
[b] This analysis was restricted to the 2 clinical subgroups that provided sufficient trials (≥2 trials in each subgroup) for analysis.
[c] Results are the same for subgroup analyses of blinding of patients, health care providers, data collectors or outcome assessors.

eTable 16c: Subgroup analyses for drowsiness, headache and pruritus for randomized clinical trials of opioids vs. NSAIDs

Subgroup factors		Drowsiness					Headache					Pruritus				
		No. of studies	RR	95%CI		Inter-action test p	No. of studies	RR	95%CI		Inter-action test p	No. of studies	RR	95%CI		Inter-action test p
Length of follow-up	< 3 months	4	2.19	1.57	3.05	0.48	4	1.43	0.97	2.10	0.83	2	5.67	1.98	16.26	0.45
	≥ 3 months	2	5.07	0.37	69.09		2	1.45	0.91	2.30		2	2.94	1.28	6.77	
Clinical condition category 1 [a]	Objective	2	5.55	0.56	54.80	0.50	3	2.89	0.78	10.71	0.49	1				NA
	Subjective	3	2.17	1.53	3.08		2	1.30	1.01	1.68		2				
Clinical condition category 2 [a,b]	Neuropathic	0				0.50	0				0.49	0				NA
	Nociceptive	2	5.55	0.56	54.80		3	2.89	0.78	10.71		1				
	Central sensitization	3	2.17	1.53	3.08		2	1.30	1.01	1.68		2				
Clinical condition category 3 [a]	Neuropathic	0				NA	0				NA	0				NA
	Non-neuropathic	5					5					3				
Randomization	Adequate randomization	4	2.19	1.57	3.05	0.48	3	1.36	0.98	1.90	0.67	2	5.67	1.98	16.26	0.45
	Inadequate randomization	2	5.07	0.37	69.09		3	1.52	0.96	2.39		2	2.94	1.28	6.77	
Allocation concealment	Adequate concealment	*3*	2.39	1.67	3.42	0.66	3	1.36	0.98	1.90	0.67	3				NA
	Inadequate concealment	*3*	2.88	0.56	14.84		3	1.52	0.96	2.39		1				
Blinding of patients [c]	Yes	4	2.39	1.67	3.42	0.23	4	1.36	1.08	1.70	0.53	3				NA
	No	2	2.88	0.56	14.84		2	2.42	0.47	12.34		1				
	Yes	4	2.39	1.67	3.42	0.23	4	1.36	1.08	1.70	0.53	3				NA

Subgroup factors		Drowsiness					Headache					Pruritus				
		No. of studies	RR	95%CI		Inter-action test p	No. of studies	RR	95%CI		Inter-action test p	No. of studies	RR	95%CI		Inter-action test p
Blinding of health care providers [c]	No	2	2.88	0.56	14.84		2	2.42	0.47	12.34		1				
Blinding of data collectors [c]	Yes	4	2.39	1.67	3.42	0.23	4	1.36	1.08	1.70	0.53	3				NA
	No	2	2.88	0.56	14.84		2	2.42	0.47	12.34		1				
Blinding of outcome assessors [c]	Yes	4	2.39	1.67	3.42	0.23	4	1.36	1.08	1.70	0.53	3				NA
	No	2	2.88	0.56	14.84		2	2.42	0.47	12.34		1				
Blinding of data analyst	Yes	0				NA	0				NA	0				NA
	No	6					6					4				
Trial design	Parallel trials	6				NA	5				NA	4				NA
	Cross-over trials	0					1					0				
Enrichment trial	Yes	0				NA	0				NA	0				NA
	No	6					6					4				
Type of opioid intervention	Opioids alone	5				NA	6				NA	4				NA
	Combination	1					0					0				

RR: relative risk; 95% confidence interval; NA: not applicable as no subgroup analysis was conducted for less than 2 studies in a given subgroup.

[a] We excluded one trial with mixed clinical conditions from subgroup analysis for different clinical conditions.
[b] This analysis was restricted to the 2 clinical subgroups that provided sufficient trials (≥2 trials in each subgroup) for analysis.
[c] Results are the same for subgroup analyses of blinding of patients, health care providers, data collectors or outcome assessors.

eTable 17: Meta-regressions of length of follow-up and proportion of loss to follow-up for randomized clinical trials of opioids vs. placebo

Outcomes	Length of follow-up (days)					Proportion of loss to follow-up (%)			
	No. studies	Coef.	95%CI		p-value	Coef.	95%CI		p-value
Pain	80	0.005	0.002	0.01	**0.01**	-0.001	-0.01	0.01	0.88
Physical functioning	51	-0.01	-0.03	0.02	0.60	0.04	-0.01	0.09	0.09
Emotional functioning	37	-0.01	-0.04	0.02	0.64	0.03	-0.03	0.09	0.36
Role functioning	32	-0.02	-0.09	0.05	0.61	0.05	-0.07	0.17	0.43
Social functioning	29	-0.04	-0.09	0.001	0.06	0.05	-0.03	0.14	0.21
Sleep quality	31	-0.06	-0.11	-0.002	**0.03**	0.11	-0.01	0.23	0.07
Vomiting	51	1.00	0.99	1.01	0.97	1.03	0.98	1.08	0.28
Nausea	63	1.00	1.00	1.00	0.89	1.00	0.97	1.02	0.72
Constipation	63	1.00	1.00	1.01	0.45	1.00	0.99	1.02	0.60
Dizziness	60	1.00	1.00	1.01	0.62	1.00	0.98	1.03	0.67
Drowsiness	54	1.00	1.00	1.01	0.45	0.99	0.97	1.01	0.44
Headache	52	1.00	1.00	1.00	0.70	1.01	0.99	1.03	0.35
Pruritus	35	1.00	0.99	1.01	0.84	0.98	0.92	1.04	0.48
Dry mouth	34	1.00	1.00	1.01	0.26	0.98	0.96	0.99	**0.005**

Coef.: coefficient

Significant meta-regressions are **bolded.**

eTable 18: Sensitivity analysis by excluding studies with data imputed for non-significant results

Outcomes	Sensitivity analysis	No. of studies	Sample size	WMD	95%CI	
Pain[a]	Primary analysis	42	16,617	-0.69	-0.82	-0.56
	Analysis excluding imputation for non-significant results	42	16,617	-0.69	-0.82	-0.56
Physical functioning	Primary analysis	51	15,754	2.04	1.41	2.68
	Analysis excluding imputation for non-significant results	48	15,026	2.14	1.49	2.80
Emotional functioning	Primary analysis	23	8,962	-0.44	-1.09	0.20
	Analysis excluding imputation for non-significant results	17	5,885	-0.55	-1.38	0.29
Role functioning	Primary analysis	16	5,329	0.87	-0.54	2.28
	Analysis excluding imputation for non-significant results	12	4,370	0.53	-0.57	1.64
Social functioning	Primary analysis	29	7,623	1.58	0.45	2.70
	Analysis excluding imputation for non-significant results	26	6,746	1.80	0.54	3.05
Sleep quality	Primary analysis	15	6,585	3.42	1.58	5.26
	Analysis excluding imputation for non-significant results	11	5,340	4.10	1.96	6.23

WMD: Weighted mean difference; 95%CI: 95% confidence interval

[a.] No imputation was needed for pain relief

eTable 19: Sensitivity analysis by using DerSimonian-Laird method vs. Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis

Outcomes		DL method			HKSJ method		
		WMD/RR	95%CI		WMD/RR	95%CI	
Opioids vs placebo							
Pain		-0.69	-0.82	-0.56	-0.69	-0.84	-0.54
Physical functioning		2.04	1.41	2.68	2.04	1.32	2.86
Emotional functioning		-0.44	-1.09	0.20	-0.44	-1.16	0.28
Role functioning		0.87	-0.54	2.28	0.87	-0.56	2.26
Social functioning		1.58	0.45	2.70	1.58	0.38	2.97
Sleep quality		3.42	1.58	5.26	3.42	1.43	5.36
Vomiting	Enrichment trials	2.50	1.89	3.30	2.50	1.85	3.37
	Non-enrichment trials	4.12	3.34	5.07	4.12	3.32	5.11
Nausea	Enrichment trials with randomization reported	2.04	1.62	2.57	2.04	1.55	2.68
	Non-enrichment trials with randomization reported	3.17	2.69	3.73	3.17	2.67	3.76
Constipation		3.08	2.65	3.55	3.08	2.67	3.55
Dizziness	Enrichment trials	1.67	1.34	2.10	1.67	1.41	2.47
	Non-enrichment trials	2.63	2.21	3.13	2.63	2.32	3.12
Drowsiness	Enrichment trials	1.82	1.35	2.45	1.82	1.28	2.79
	Non-enrichment trials	3.59	2.88	4.47	3.59	2.86	4.48
Headache among trials that blinded outcome assessors		1.10	0.99	1.22	1.10	0.99	1.22
Pruritus		2.59	1.86	3.62	2.59	1.83	3.71
Dry mouth for trials with loss to follow-up<20%		2.57	1.98	3.34	2.57	1.96	3.41
Opioids vs NSAIDs							
Pain		-0.60	-1.54	0.34	-0.60	-1.47	0.28
Physical functioning		-0.90	-2.69	0.89	-0.90	-3.23	1.73
Emotional functioning [a]		-0.27	-1.62	1.08	-0.27	-61.06	67.39
Sleep quality [a]		-3.06	-7.50	1.37	-3.06	-31.83	25.70

eTable 19: Sensitivity analysis by using DerSimonian-Laird method vs. Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis

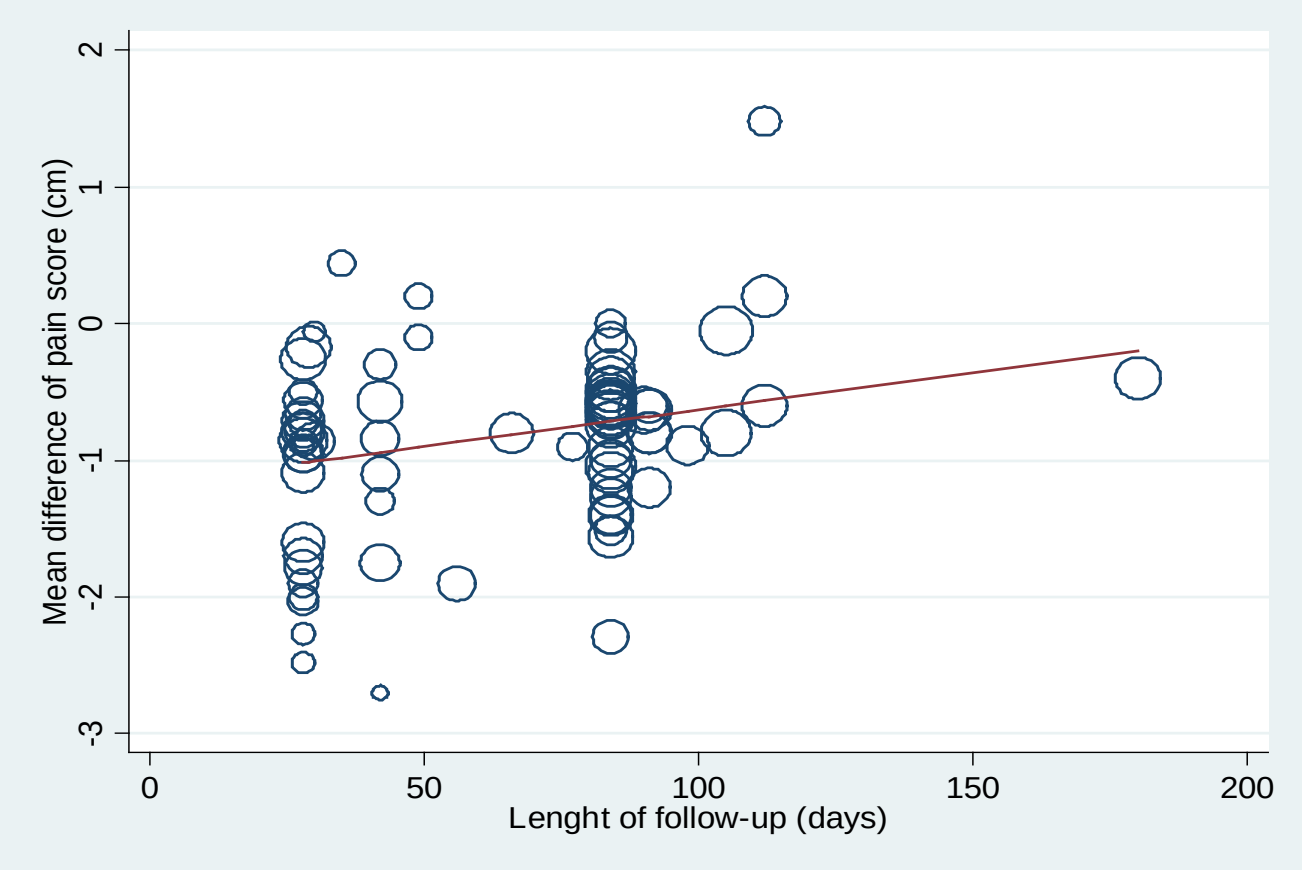
Outcomes		DL method			HKSJ method		
		WMD/RR	95%CI		WMD/RR	95%CI	
Vomiting		4.71	2.92	7.60	4.71	2.40	9.27
Nausea		2.51	2.00	3.15	2.51	1.92	3.30
Constipation		2.84	1.82	4.43	2.84	1.62	4.95
Dizziness		1.98	1.47	2.66	1.98	1.35	2.86
Drowsiness		2.29	1.52	3.46	2.29	1.44	3.62
Headache		1.38	1.10	1.72	1.38	1.03	1.84
Pruritus		4.01	2.33	6.89	4.01	1.66	9.66
Dry Mouth		3.42	1.73	6.77	**3.42**	**0.79**	**14.83**
Opioids vs anticonvulsants							
Pain		-0.90	-1.65	-0.14	**-0.90**	**-2.75**	**0.94**
Physical functioning		0.45	-5.77	6.66	0.45	-14.11	15.17
Emotional functioning [a]		-2.58	-7.34	2.18	-2.58	-33.43	28.27
Role functioning [a]		0.03	-11.74	11.81	0.03	-76.29	76.35
Social functioning [a]		0.63	-6.06	7.33	0.32	-54.48	55.12
Sleep quality [a]		-1.00	-9.80	7.80	-1.00	-58.04	56.04
Nausea [a]		13.74	1.85	102.24	**12.27**	**0.00002**	**6226242.0**
Constipation		7.77	1.22	49.43	**7.84**	**0.15**	**409.54**
Dizziness [a]		1.18	0.49	2.85	1.22	0.004	418.34
Drowsiness [a]		0.61	0.28	1.36	0.67	0.0003	1409.89
Opioids vs antidepressants							
Pain		-0.15	-1.04	0.74	-0.15	-2.09	1.79
Physical functioning [a]		-5.29	-13.70	3.12	-5.29	-59.81	49.22
Emotional functioning [a]		-6.19	-11.00	-1.38	-6.76	-51.02	37.49
Role functioning [a]		-5.14	-19.82	9.55	-5.14	-100.36	90.09
Social functioning [a]		-4.39	-12.15	3.37	-4.39	-54.71	45.92

WMD: Weighted mean difference; RR: relative risk; 95%CI: 95% confidence interval; DL: DerSimonian-Laird; HKSJ: Hartung-Knapp-Sidik-Jonkman

[a.] Fixed-effects model was used when only two trials contributed to a meta-analysis

Treatment effects that changed from significant to non-significant with the HKSJ approach are **bolded**.

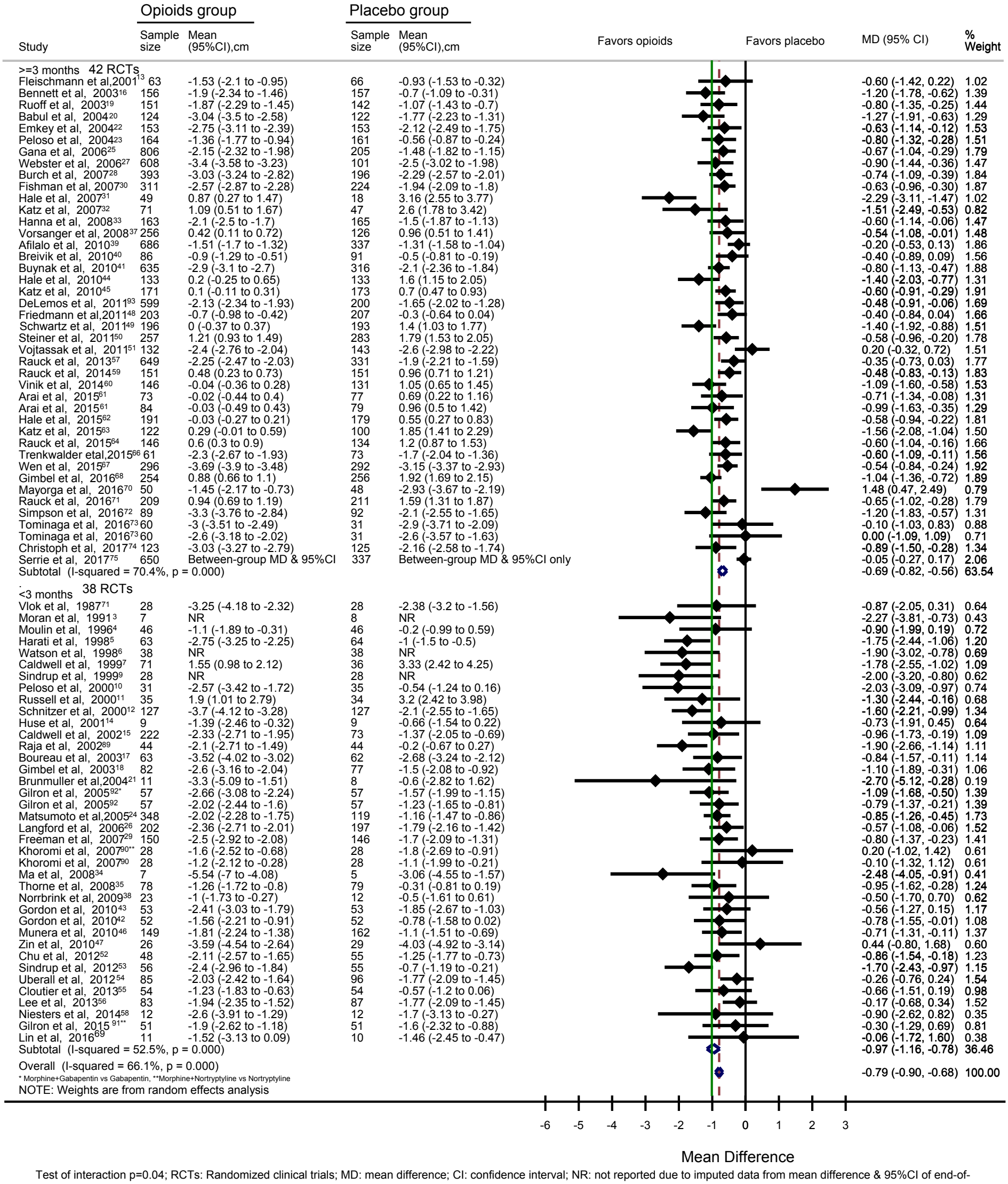
eFigure 1: Meta-regression for pain relief and length of follow-up for 80 randomized clinical trials of opioids vs. placebo



p-value = 0.007 for the slope among 80 trials

The size of circle represents the weight of each study in the fitted random-effects meta-regression model (i.e. the inverse of its total variance)

eFigure 2: Subgroup analysis for pain relief and length of follow-up (<3 months vs. ≥3 months) from 80 randomized clinical trials of opioids vs. placebo

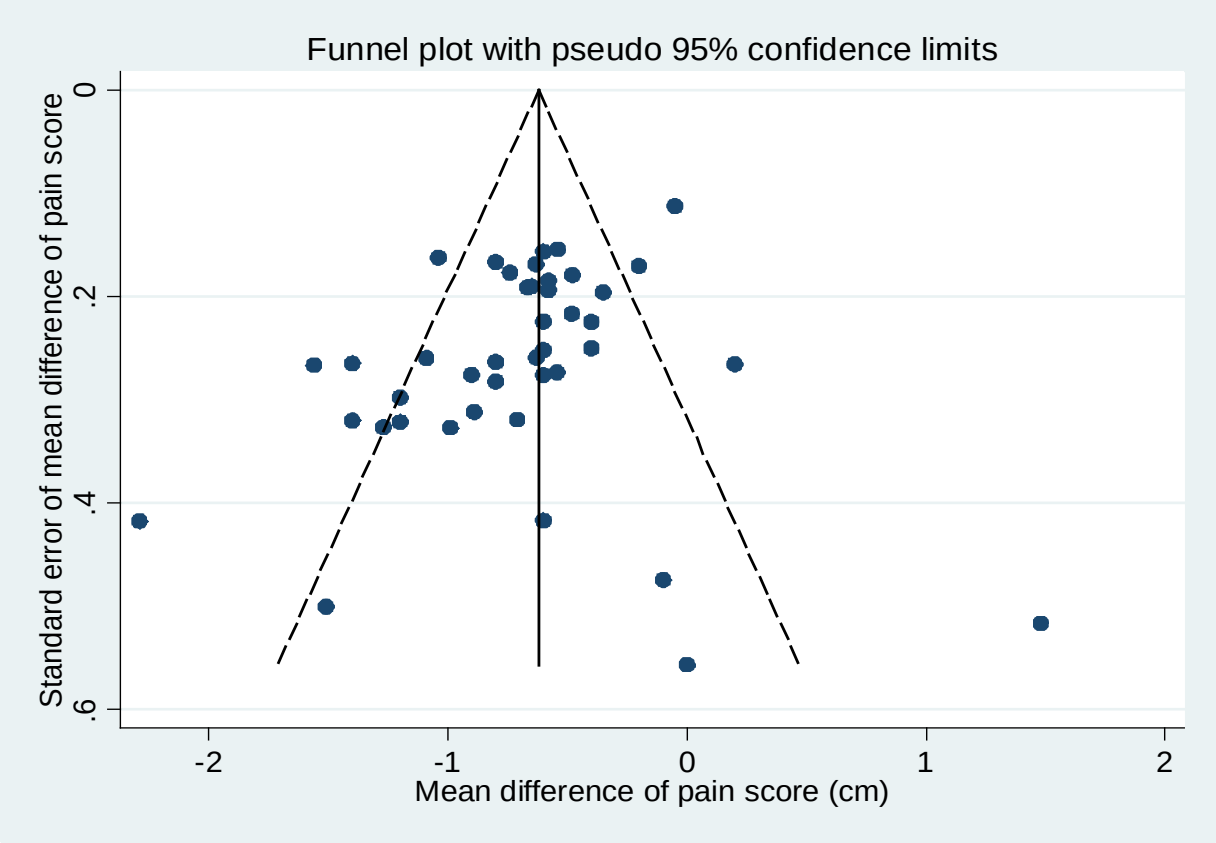


* Morphine+Gabapentin vs Gabapentin, **Morphine+Nortryptyline vs Nortryptyline

NOTE: Weights are from random effects analysis

Test of interaction p=0.04; RCTs: Randomized clinical trials; MD: mean difference; CI: confidence interval; NR: not reported due to imputed data from mean difference & 95%CI of end-of-study score; the green line represents the minimally important difference. The mean and 95%CI in each group are within-group change from baseline data, and the mean difference (MD) and 95%CI are between-group differences in change from baseline data.

eFigure 3: Funnel plot for pain relief at ≥ 3 months follow-up for 42 randomized clinical trials of opioids vs. placebo



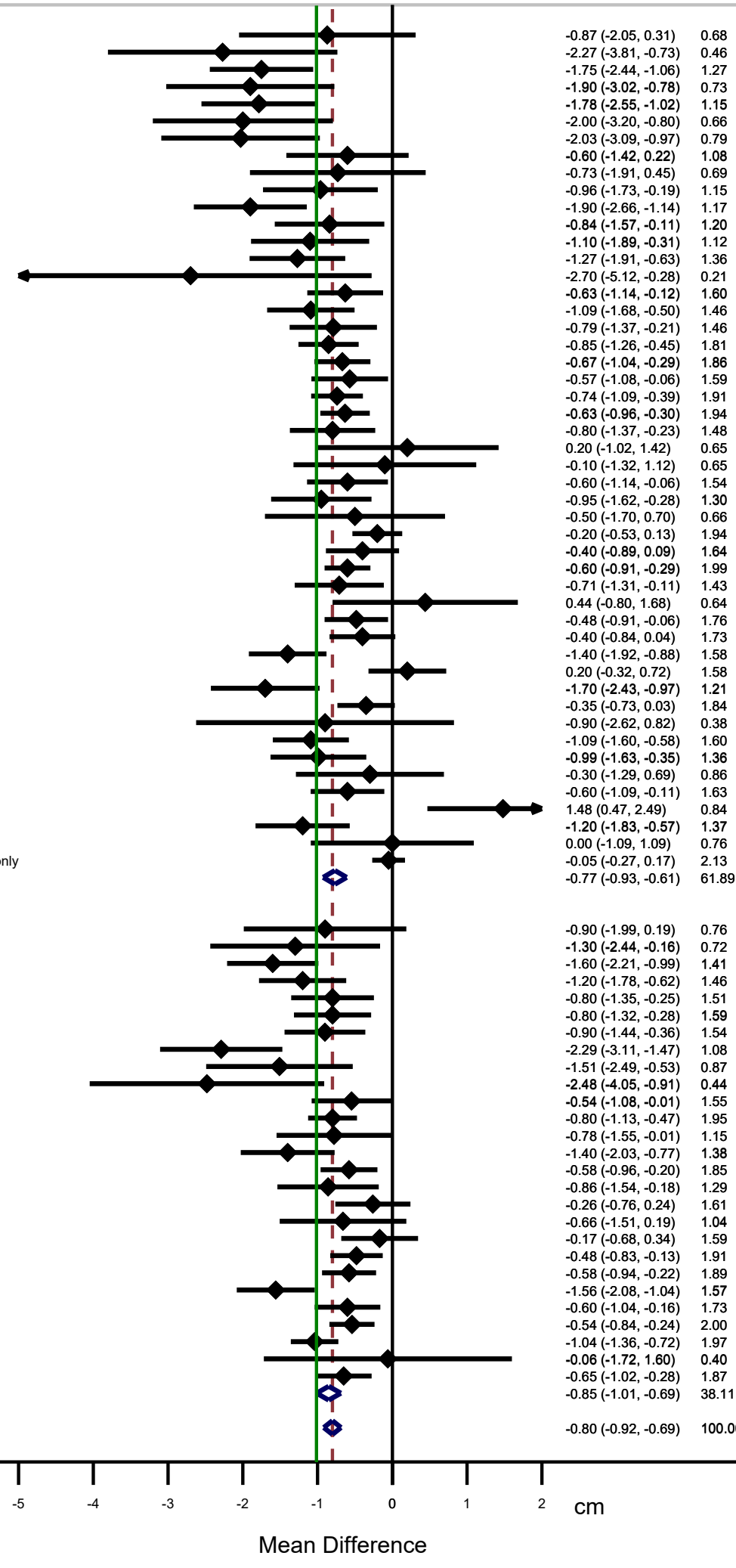
Begg's test p-value = 0.07 among 42 trials with pain relief at ≥ 3 months follow-up

eFigure 4: Subgroup analysis for pain relief and objective vs. subjective conditions from 76 randomized clinical trials of opioids vs. placebo

Study	Opioids group: Sample size	Opioids group: Mean (95%CI),cm	Placebo group: Sample size	Placebo group: Mean (95%CI),cm	MD (95% CI)	% Weight
Objective conditions 49 RCTs						
Vlok et al, 1987[1]	28	-3.25 (-4.18 to -2.32)	28	-2.38 (-3.2 to -1.56)	-0.87 (-2.05, 0.31)	0.68
Moran et al, 1991[3]	7	NR	8	NR	-2.27 (-3.81, -0.73)	0.46
Harati et al, 1998[5]	63	-2.75 (-3.25 to -2.25)	64	-1 (-1.5 to -0.5)	-1.75 (-2.44, -1.06)	1.27
Watson et al, 1998[6]	38	NR	38	NR	-1.90 (-3.02, -0.78)	0.73
Caldwell et al, 1999[7]	71	1.55 (0.98 to 2.12)	36	3.33 (2.42 to 4.25)	-1.78 (-2.55, -1.02)	1.15
Sindrup et al, 1999[9]	28	NR	28	NR	-2.00 (-3.20, -0.80)	0.66
Peloso et al, 2000[10]	31	-2.57 (-3.42 to -1.72)	35	-0.54 (-1.24 to 0.16)	-2.03 (-3.09, -0.97)	0.79
Fleischmann et al, 2001[13]	63	-1.53 (-2.1 to -0.95)	66	-0.93 (-1.53 to -0.32)	-0.60 (-1.42, 0.22)	1.08
Huse et al, 2001[13]	9	-1.39 (-2.46 to -0.32)	9	-0.66 (-1.54 to 0.22)	-0.73 (-1.91, 0.45)	0.69
Caldwell et al, 2002[15]	222	-2.33 (-2.71 to -1.95)	73	-1.37 (-2.05 to -0.69)	-0.96 (-1.73, -0.19)	1.15
Raja et al, 2002[89]	44	-2.1 (-2.71 to -1.49)	44	-0.2 (-0.67 to 0.27)	-1.90 (-2.66, -1.14)	1.17
Boureau et al, 2003[17]	63	-3.52 (-4.02 to -3.02)	62	-2.68 (-3.24 to -2.12)	-0.84 (-1.57, -0.11)	1.20
Gimbel et al, 2003[18]	82	-2.6 (-3.16 to -2.04)	77	-1.5 (-2.08 to -0.92)	-1.10 (-1.89, -0.31)	1.12
Babul et al, 2004[20]	124	-3.04 (-3.5 to -2.58)	122	-1.77 (-2.23 to -1.31)	-1.27 (-1.91, -0.63)	1.36
Brunmuller et al, 2004[21]	11	-3.3 (-5.09 to -1.51)	8	-0.6 (-2.82 to 1.62)	-2.70 (-5.12, -0.28)	0.21
Emkey et al, 2004[22]	153	-2.75 (-3.11 to -2.39)	153	-2.12 (-2.49 to -1.75)	-0.63 (-1.14, -0.12)	1.60
Gilron et al, 2005[91*]	57	-2.66 (-3.08 to -2.24)	57	-1.57 (-1.99 to -1.15)	-1.09 (-1.68, -0.50)	1.46
Gilron et al, 2005[91]	57	-2.02 (-2.44 to -1.6)	57	-1.23 (-1.65 to -0.81)	-0.79 (-1.37, -0.21)	1.46
Matsumoto et al, 2005[24]	348	-2.02 (-2.28 to -1.75)	119	-1.16 (-1.47 to -0.86)	-0.85 (-1.26, -0.45)	1.81
Gana et al, 2006[25]	806	-2.15 (-2.32 to -1.98)	205	-1.48 (-1.82 to -1.15)	-0.67 (-1.04, -0.29)	1.86
Langford et al, 2006[26]	202	-2.36 (-2.71 to -2.01)	197	-1.79 (-2.16 to -1.42)	-0.57 (-1.08, -0.06)	1.59
Burch et al, 2007[28]	393	-3.03 (-3.24 to -2.82)	196	-2.29 (-2.57 to -2.01)	-0.74 (-1.09, -0.39)	1.91
Fishman et al, 2007[30]	311	-2.57 (-2.87 to -2.28)	224	-1.94 (-2.09 to -1.8)	-0.63 (-0.96, -0.30)	1.94
Freeman et al, 2007[29]	150	-2.5 (-2.92 to -2.08)	146	-1.7 (-2.09 to -1.31)	-0.80 (-1.37, -0.23)	1.48
Khoromi et al, 2007[90**]	28	-1.6 (-2.52 to -0.68)	28	-1.8 (-2.69 to -0.91)	0.20 (-1.02, 1.42)	0.65
Khoromi et al, 2007[90]	28	-1.2 (-2.12 to -0.28)	28	-1.1 (-1.99 to -0.21)	-0.10 (-1.32, 1.12)	0.65
Hanna et al, 2008[33]	163	-2.1 (-2.5 to -1.7)	165	-1.5 (-1.87 to -1.13)	-0.60 (-1.14, -0.06)	1.54
Thorne et al, 2008[35]	78	-1.26 (-1.72 to -0.8)	79	-0.31 (-0.81 to 0.19)	-0.95 (-1.62, -0.28)	1.30
Norrbrink et al, 2009[38]	23	-1 (-1.73 to -0.27)	12	-0.5 (-1.61 to 0.61)	-0.50 (-1.70, 0.70)	0.66
Afilalo et al, 2010[39]	686	-1.51 (-1.7 to -1.32)	337	-1.31 (-1.58 to -1.04)	-0.20 (-0.53, 0.13)	1.94
Breivik et al, 2010[40]	86	-0.9 (-1.29 to -0.51)	91	-0.5 (-0.81 to -0.19)	-0.40 (-0.89, 0.09)	1.64
Katz et al, 2010[45]	171	0.1 (-0.11 to 0.31)	173	0.7 (0.47 to 0.93)	-0.60 (-0.91, -0.29)	1.99
Munera et al, 2010[46]	149	-1.81 (-2.24 to -1.38)	162	-1.1 (-1.51 to -0.69)	-0.71 (-1.31, -0.11)	1.43
Zin et al, 2010[47]	26	-3.59 (-4.54 to -2.64)	29	-4.03 (-4.92 to -3.14)	0.44 (-0.80, 1.68)	0.64
DeLemos et al, 2011[93]	599	-2.13 (-2.34 to -1.93)	200	-1.65 (-2.02 to -1.28)	-0.48 (-0.91, -0.06)	1.76
Friedmann et al, 2011[48]	203	-0.7 (-0.98 to -0.42)	207	-0.3 (-0.64 to 0.04)	-0.40 (-0.84, 0.04)	1.73
Schwartz et al, 2011[49]	196	0 (-0.37 to 0.37)	193	1.4 (1.03 to 1.77)	-1.40 (-1.92, -0.88)	1.58
Vojtassak et al, 2011[51]	132	-2.4 (-2.76 to -2.04)	143	-2.6 (-2.98 to -2.22)	0.20 (-0.32, 0.72)	1.58
Sindrup et al, 2012[53]	56	-2.4 (-2.96 to -1.84)	55	-0.7 (-1.19 to -0.21)	-1.70 (-2.43, -0.97)	1.21
Rauck et al, 2013[57]	649	-2.25 (-2.47 to -2.03)	331	-1.9 (-2.21 to -1.59)	-0.35 (-0.73, 0.03)	1.84
Niesters et al, 2014[58]	12	-2.6 (-3.91 to -1.29)	12	-1.7 (-3.13 to -0.27)	-0.90 (-2.62, 0.82)	0.38
Vinik et al, 2014[60]	146	-0.04 (-0.36 to 0.28)	131	1.05 (0.65 to 1.45)	-1.09 (-1.60, -0.58)	1.60
Arai et al, 2015[61]	84	-0.03 (-0.49 to 0.43)	79	0.96 (0.5 to 1.42)	-0.99 (-1.63, -0.35)	1.36
Gilron et al, 2015[91**]	51	-1.9 (-2.62 to -1.18)	51	-1.6 (-2.32 to -0.88)	-0.30 (-1.29, 0.69)	0.86
Trenkwalder et al, 2015[66]	61	-2.3 (-2.67 to -1.93)	73	-1.7 (-2.04 to -1.36)	-0.60 (-1.09, -0.11)	1.63
Mayorga et al, 2016[70]	50	-1.45 (-2.17 to -0.73)	48	-2.93 (-3.67 to -2.19)	1.48 (0.47, 2.49)	0.84
Simpson et al, 2016[72]	89	-3.3 (-3.76 to -2.84)	92	-2.1 (-2.55 to -1.65)	-1.20 (-1.83, -0.57)	1.37
Tominaga et al, 2016[73]	60	-2.6 (-3.18 to -2.02)	31	-2.6 (-3.57 to -1.63)	0.00 (-1.09, 1.09)	0.76
Serrie et al, 2017[75]	650	Between-group MD & 95%CI only	337	Between-group MD & 95%CI only	-0.05 (-0.27, 0.17)	2.13
Subtotal (I-squared = 70.2%, p = 0.000)					-0.77 (-0.93, -0.61)	61.89
.						
Subjective conditions 27 RCTs						
Moulin et al, 1996[4]	46	-1.1 (-1.89 to -0.31)	46	-0.2 (-0.99 to 0.59)	-0.90 (-1.99, 0.19)	0.76
Russell et al, 2000[11]	35	1.9 (1.01 to 2.79)	34	3.2 (2.42 to 3.98)	-1.30 (-2.44, -0.16)	0.72
Schnitzer et al, 2000[8]	127	-3.7 (-4.12 to -3.28)	127	-2.1 (-2.55 to -1.65)	-1.60 (-2.21, -0.99)	1.41
Bennett et al, 2003[16]	156	-1.9 (-2.34 to -1.46)	157	-0.7 (-1.09 to -0.31)	-1.20 (-1.78, -0.62)	1.46
Ruoff et al, 2003[19]	151	-1.87 (-2.29 to -1.45)	142	-1.07 (-1.43 to -0.7)	-0.80 (-1.35, -0.25)	1.51
Peloso et al, 2004[23]	164	-1.36 (-1.77 to -0.94)	161	-0.56 (-0.87 to -0.24)	-0.80 (-1.32, -0.28)	1.59
Webster et al, 2006[27]	608	-3.4 (-3.58 to -3.23)	101	-2.5 (-3.02 to -1.98)	-0.90 (-1.44, -0.36)	1.54
Hale et al, 2007[31]	49	0.87 (0.27 to 1.47)	18	3.16 (2.55 to 3.77)	-2.29 (-3.11, -1.47)	1.08
Katz et al, 2007[32]	71	1.09 (0.51 to 1.67)	47	2.6 (1.78 to 3.42)	-1.51 (-2.49, -0.53)	0.87
Ma et al, 2008[34]	7	-5.54 (-7 to -4.08)	5	-3.06 (-4.55 to -1.57)	-2.48 (-4.05, -0.91)	0.44
Vorsanger et al, 2008[37]	256	0.42 (0.11 to 0.72)	126	0.96 (0.51 to 1.41)	-0.54 (-1.08, -0.01)	1.55
Buynak et al, 2010[41]	635	-2.9 (-3.1 to -2.7)	316	-2.1 (-2.36 to -1.84)	-0.80 (-1.13, -0.47)	1.95
Gordon et al, 2010[42]	52	-1.56 (-2.21 to -0.91)	52	-0.78 (-1.58 to 0.02)	-0.78 (-1.55, -0.01)	1.15
Hale et al, 2010[44]	133	0.2 (-0.25 to 0.65)	133	1.6 (1.15 to 2.05)	-1.40 (-2.03, -0.77)	1.38
Steiner et al, 2011[50]	257	1.21 (0.93 to 1.49)	283	1.79 (1.53 to 2.05)	-0.58 (-0.96, -0.20)	1.85
Chu et al, 2012[52]	48	-2.11 (-2.57 to -1.65)	55	-1.25 (-1.77 to -0.73)	-0.86 (-1.54, -0.18)	1.29
Uberall et al, 2012[54]	85	-2.03 (-2.42 to -1.64)	96	-1.77 (-2.09 to -1.45)	-0.26 (-0.76, 0.24)	1.61
Cloutier et al, 2013[55]	54	-1.23 (-1.83 to -0.63)	54	-0.57 (-1.2 to 0.06)	-0.66 (-1.51, 0.19)	1.04
Lee et al, 2013[56]	83	-1.94 (-2.35 to -1.52)	87	-1.77 (-2.09 to -1.45)	-0.17 (-0.68, 0.34)	1.59
Rauck et al, 2014[59]	151	0.48 (0.23 to 0.73)	151	0.96 (0.71 to 1.21)	-0.48 (-0.83, -0.13)	1.91
Hale et al, 2015[62]	191	-0.03 (-0.27 to 0.21)	179	0.55 (0.27 to 0.83)	-0.58 (-0.94, -0.22)	1.89
Katz et al, 2015[63]	122	0.29 (-0.01 to 0.59)	100	1.85 (1.41 to 2.29)	-1.56 (-2.08, -1.04)	1.57
Rauck et al, 2015[64]	146	0.6 (0.3 to 0.9)	134	1.2 (0.87 to 1.53)	-0.60 (-1.04, -0.16)	1.73
Wen et al, 2015[67]	296	-3.69 (-3.9 to -3.48)	292	-3.15 (-3.37 to -2.93)	-0.54 (-0.84, -0.24)	2.00
Gimbel et al, 2016[68]	254	0.88 (0.66 to 1.1)	256	1.92 (1.69 to 2.15)	-1.04 (-1.36, -0.72)	1.97
Lin et al, 2016[69]	11	-1.52 (-3.13 to 0.09)	10	-1.46 (-2.45 to -0.47)	-0.06 (-1.72, 1.60)	0.40
Rauck et al, 2016[71]	209	0.94 (0.69 to 1.19)	211	1.59 (1.31 to 1.87)	-0.65 (-1.02, -0.28)	1.87
Subtotal (I-squared = 59.6%, p = 0.000)					-0.85 (-1.01, -0.69)	38.11
Overall (I-squared = 67.5%, p = 0.000)					-0.80 (-0.92, -0.69)	100.00

*Morphine + Gabapentin vs Gabapentin, **Morphine + Nortryptyline vs Nortryptyline

NOTE: Weights are from random effects analysis



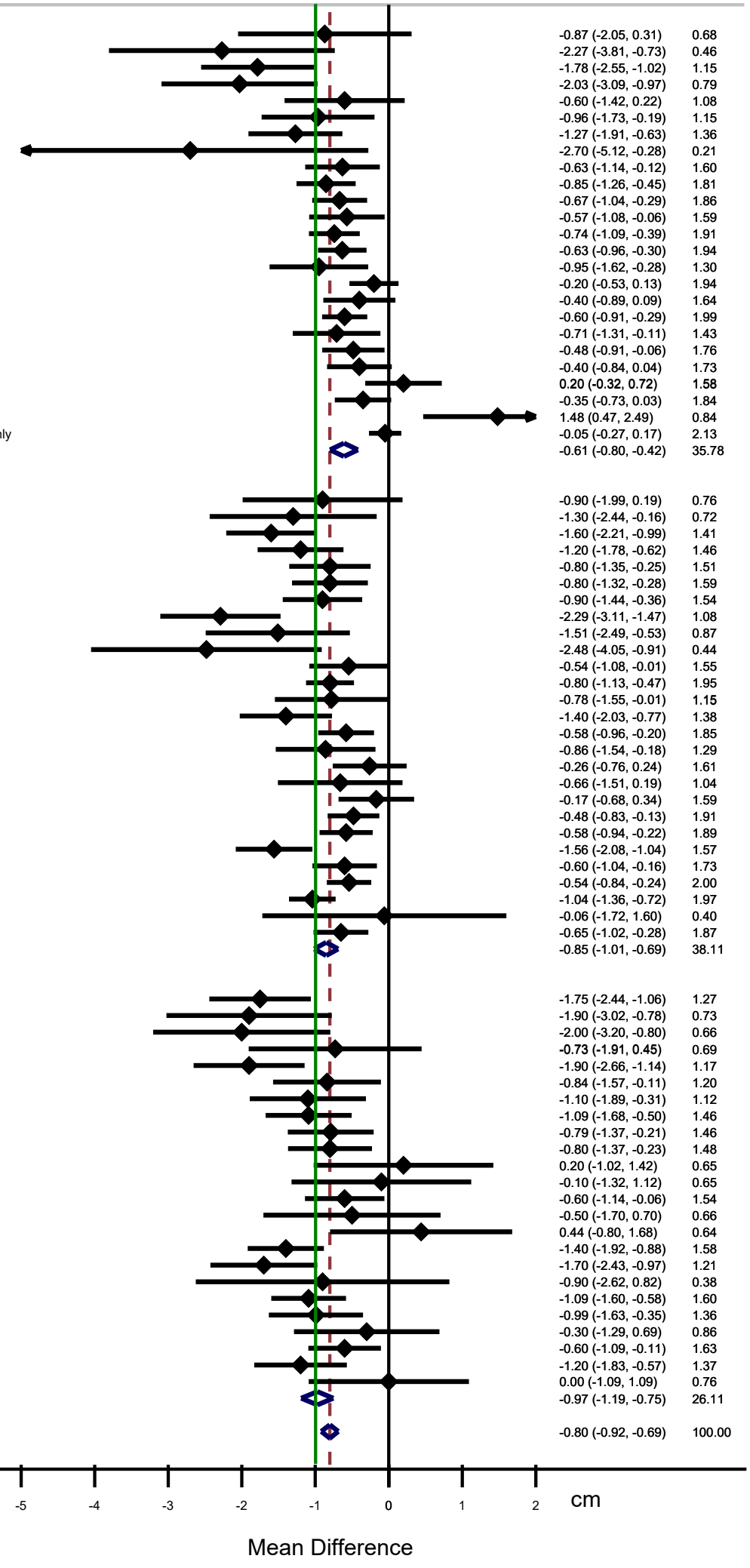
Test of interaction p-value = 0.45; RCTs: Randomized clinical trials; NR: not reported due to imputed data from mean difference & 95%CI of end-of-study score; Four studies were excluded from this subgroup analysis due to mixed conditions; the green line represents the minimally important difference. The mean and 95%CI in each group are within-group change from baseline data, and the mean difference (MD) and 95%CI are between-group differences in change from baseline data.

eFigure 5: Subgroup analysis for pain relief and neuropathic vs. nociceptive vs. central sensitization from 76 randomized clinical trials of opioids vs. placebo

Study	Opioids group: Sample size	Opioids group: Mean (95%CI),cm	Placebo group: Sample size	Placebo group: Mean (95%CI),cm	MD (95% CI)	% Weight
Nociceptive 25 RCTs						
Vlok et al, 1987 [1]	28	-3.25 (-4.18 to -2.32)	28	-2.38 (-3.2 to -1.56)	-0.87 (-2.05, 0.31)	0.68
Moran et al, 1991 [3]	7	NR	8	NR	-2.27 (-3.81, -0.73)	0.46
Caldwell et al, 1999 [7]	71	1.55 (0.98 to 2.12)	36	3.33 (2.42 to 4.25)	-1.78 (-2.55, -1.02)	1.15
Peloso et al, 2000 [10]	31	-2.57 (-3.42 to -1.72)	35	-0.54 (-1.24 to 0.16)	-2.03 (-3.09, -0.97)	0.79
Fleischmann et al, 2001 [13]	63	-1.53 (-2.1 to -0.95)	66	-0.93 (-1.53 to -0.32)	-0.60 (-1.42, 0.22)	1.08
Caldwell et al, 2002 [15]	222	-2.33 (-2.71 to -1.95)	73	-1.37 (-2.05 to -0.69)	-0.96 (-1.73, -0.19)	1.15
Babul et al, 2004 [20]	124	-3.04 (-3.5 to -2.58)	122	-1.77 (-2.23 to -1.31)	-1.27 (-1.91, -0.63)	1.36
Brunmuller et al, 2004 [21]	11	-3.3 (-5.09 to -1.51)	8	-0.6 (-2.82 to 1.62)	-2.70 (-5.12, -0.28)	0.21
Emkey et al, 2004 [22]	153	-2.75 (-3.11 to -2.39)	153	-2.12 (-2.49 to -1.75)	-0.63 (-1.14, -0.12)	1.60
Matsumoto et al, 2005 [24]	348	-2.02 (-2.28 to -1.75)	119	-1.16 (-1.47 to -0.86)	-0.85 (-1.26, -0.45)	1.81
Gana et al, 2006 [25]	806	-2.15 (-2.32 to -1.98)	205	-1.48 (-1.82 to -1.15)	-0.67 (-1.04, -0.29)	1.86
Langford et al, 2006 [26]	202	-2.36 (-2.71 to -2.01)	197	-1.79 (-2.16 to -1.42)	-0.57 (-1.08, -0.06)	1.59
Burch et al, 2007 [28]	393	-3.03 (-3.24 to -2.82)	196	-2.29 (-2.57 to -2.01)	-0.74 (-1.09, -0.39)	1.91
Fishman et al, 2007 [30]	311	-2.57 (-2.87 to -2.28)	224	-1.94 (-2.09 to -1.8)	-0.63 (-0.96, -0.30)	1.94
Thorne et al, 2008 [35]	78	-1.26 (-1.72 to -0.8)	79	-0.31 (-0.81 to 0.19)	-0.95 (-1.62, -0.28)	1.30
Afilalo et al, 2010 [39]	686	-1.51 (-1.7 to -1.32)	337	-1.31 (-1.58 to -1.04)	-0.20 (-0.53, 0.13)	1.94
Breivik et al, 2010 [40]	86	-0.9 (-1.29 to -0.51)	91	-0.5 (-0.81 to -0.19)	-0.40 (-0.89, 0.09)	1.64
Katz et al, 2010 [45]	171	0.1 (-0.11 to 0.31)	173	0.7 (0.47 to 0.93)	-0.60 (-0.91, -0.29)	1.99
Munera et al, 2010 [46]	149	-1.81 (-2.24 to -1.38)	162	-1.1 (-1.51 to -0.69)	-0.71 (-1.31, -0.11)	1.43
DeLemos et al, 2011 [93]	599	-2.13 (-2.34 to -1.93)	200	-1.65 (-2.02 to -1.28)	-0.48 (-0.91, -0.06)	1.76
Friedmann et al, 2011 [48]	203	-0.7 (-0.98 to -0.42)	207	-0.3 (-0.64 to 0.04)	-0.40 (-0.84, 0.04)	1.73
Vojtassak et al, 2011 [51]	132	-2.4 (-2.76 to -2.04)	143	-2.6 (-2.98 to -2.22)	0.20 (-0.32, 0.72)	1.58
Rauck et al, 2013 [57]	649	-2.25 (-2.47 to -2.03)	331	-1.9 (-2.21 to -1.59)	-0.35 (-0.73, 0.03)	1.84
Mayorga et al, 2016 [70]	50	-1.45 (-2.17 to -0.73)	48	-2.93 (-3.67 to -2.19)	1.48 (0.47, 2.49)	0.84
Serrie et al, 2017 [75]	650	Between-group MD & 95%CI only	337	Between-group MD & 95%CI only	-0.05 (-0.27, 0.17)	2.13
Subtotal (I-squared = 71.9%, p = 0.000)					-0.61 (-0.80, -0.42)	35.78
Central sensitization 27 RCTs						
Moulin et al, 1996 [4]	46	-1.1 (-1.89 to -0.31)	46	-0.2 (-0.99 to 0.59)	-0.90 (-1.99, 0.19)	0.76
Russell et al, 2000 [11]	35	1.9 (1.01 to 2.79)	34	3.2 (2.42 to 3.98)	-1.30 (-2.44, -0.16)	0.72
Schnitzer et al, 2000 [12]	127	-3.7 (-4.12 to -3.28)	127	-2.1 (-2.55 to -1.65)	-1.60 (-2.21, -0.99)	1.41
Bennett et al, 2003 [16]	156	-1.9 (-2.34 to -1.46)	157	-0.7 (-1.09 to -0.31)	-1.20 (-1.78, -0.62)	1.46
Ruoff et al, 2003 [19]	151	-1.87 (-2.29 to -1.45)	142	-1.07 (-1.43 to -0.7)	-0.80 (-1.35, -0.25)	1.51
Peloso et al, 2004 [23]	164	-1.36 (-1.77 to -0.94)	161	-0.56 (-0.87 to -0.24)	-0.80 (-1.32, -0.28)	1.59
Webster et al, 2006 [27]	608	-3.4 (-3.58 to -3.23)	101	-2.5 (-3.02 to -1.98)	-0.90 (-1.44, -0.36)	1.54
Hale et al, 2007 [31]	49	0.87 (0.27 to 1.47)	18	3.16 (2.55 to 3.77)	-2.29 (-3.11, -1.47)	1.08
Katz et al, 2007 [32]	71	1.09 (0.51 to 1.67)	47	2.6 (1.78 to 3.42)	-1.51 (-2.49, -0.53)	0.87
Ma et al, 2008 [34]	7	-5.54 (-7 to -4.08)	5	-3.06 (-4.55 to -1.57)	-2.48 (-4.05, -0.91)	0.44
Vorsanger et al, 2008 [37]	256	0.42 (0.11 to 0.72)	126	0.96 (0.51 to 1.41)	-0.54 (-1.08, -0.01)	1.55
Buynak et al, 2010 [41]	635	-2.9 (-3.1 to -2.7)	316	-2.1 (-2.36 to -1.84)	-0.80 (-1.13, -0.47)	1.95
Gordon et al, 2010 [42]	52	-1.56 (-2.21 to -0.91)	52	-0.78 (-1.58 to 0.02)	-0.78 (-1.55, -0.01)	1.15
Hale et al, 2010 [44]	133	0.2 (-0.25 to 0.65)	133	1.6 (1.15 to 2.05)	-1.40 (-2.03, -0.77)	1.38
Steiner et al, 2011 [50]	257	1.21 (0.93 to 1.49)	283	1.79 (1.53 to 2.05)	-0.58 (-0.96, -0.20)	1.85
Chu et al, 2012 [52]	48	-2.11 (-2.57 to -1.65)	55	-1.25 (-1.77 to -0.73)	-0.86 (-1.54, -0.18)	1.29
Uberall et al, 2012 [54]	85	-2.03 (-2.42 to -1.64)	96	-1.77 (-2.09 to -1.45)	-0.26 (-0.76, 0.24)	1.61
Cloutier et al, 2013 [55]	54	-1.23 (-1.83 to -0.63)	54	-0.57 (-1.2 to 0.06)	-0.66 (-1.51, 0.19)	1.04
Lee et al, 2013 [56]	83	-1.94 (-2.35 to -1.52)	87	-1.77 (-2.09 to -1.45)	-0.17 (-0.68, 0.34)	1.59
Rauck et al, 2014 [57]	151	0.48 (0.23 to 0.73)	151	0.96 (0.71 to 1.21)	-0.48 (-0.83, -0.13)	1.91
Hale et al, 2015 [62]	191	-0.03 (-0.27 to 0.21)	179	0.55 (0.27 to 0.83)	-0.58 (-0.94, -0.22)	1.89
Katz et al, 2015 [63]	122	0.29 (-0.01 to 0.59)	100	1.85 (1.41 to 2.29)	-1.56 (-2.08, -1.04)	1.57
Rauck et al, 2015 [64]	146	0.6 (0.3 to 0.9)	134	1.2 (0.87 to 1.53)	-0.60 (-1.04, -0.16)	1.73
Wen et al, 2015 [67]	296	-3.69 (-3.9 to -3.48)	292	-3.15 (-3.37 to -2.93)	-0.54 (-0.84, -0.24)	2.00
Gimbel et al, 2016 [68]	254	0.88 (0.66 to 1.1)	256	1.92 (1.69 to 2.15)	-1.04 (-1.36, -0.72)	1.97
Lin et al, 2016 [69]	11	-1.52 (-3.13 to 0.09)	10	-1.46 (-2.45 to -0.47)	-0.06 (-1.72, 1.60)	0.40
Rauck et al, 2016 [71]	209	0.94 (0.69 to 1.19)	211	1.59 (1.31 to 1.87)	-0.65 (-1.02, -0.28)	1.87
Subtotal (I-squared = 59.6%, p = 0.000)					-0.85 (-1.01, -0.69)	38.11
Neuropathic pain 24 RCTs						
Harati et al, 1998 [5]	63	-2.75 (-3.25 to -2.25)	64	-1 (-1.5 to -0.5)	-1.75 (-2.44, -1.06)	1.27
Watson et al, 1998 [6]	38	NR	38	NR	-1.90 (-3.02, -0.78)	0.73
Sindrup et al, 1999 [9]	28	NR	28	NR	-2.00 (-3.20, -0.80)	0.66
Huse et al, 2001 [14]	9	-1.39 (-2.46 to -0.32)	9	-0.66 (-1.54 to 0.22)	-0.73 (-1.91, 0.45)	0.69
Raja et al, 2002 [89]	44	-2.1 (-2.71 to -1.49)	44	-0.2 (-0.67 to 0.27)	-1.90 (-2.66, -1.14)	1.17
Boureau et al, 2003 [17]	63	-3.52 (-4.02 to -3.02)	62	-2.68 (-3.24 to -2.12)	-0.84 (-1.57, -0.11)	1.20
Gimbel et al, 2003 [18]	82	-2.6 (-3.16 to -2.04)	77	-1.5 (-2.08 to -0.92)	-1.10 (-1.89, -0.31)	1.12
Gilron et al, 2005 [92*]	57	-2.66 (-3.08 to -2.24)	57	-1.57 (-1.99 to -1.15)	-1.09 (-1.68, -0.50)	1.46
Gilron et al, 2005 [92]	57	-2.02 (-2.44 to -1.6)	57	-1.23 (-1.65 to -0.81)	-0.79 (-1.37, -0.21)	1.46
Freeman et al, 2007 [29]	150	-2.5 (-2.92 to -2.08)	146	-1.7 (-2.09 to -1.31)	-0.80 (-1.37, -0.23)	1.48
Khoromi et al, 2007 [90**]	28	-1.6 (-2.52 to -0.68)	28	-1.8 (-2.69 to -0.91)	0.20 (-1.02, 1.42)	0.65
Khoromi et al, 2007 [90]	28	-1.2 (-2.12 to -0.28)	28	-1.1 (-1.99 to -0.21)	-0.10 (-1.32, 1.12)	0.65
Hanna et al, 2008 [33]	163	-2.1 (-2.5 to -1.7)	165	-1.5 (-1.87 to -1.13)	-0.60 (-1.14, -0.06)	1.54
Norrbrink et al, 2009 [38]	23	-1 (-1.73 to -0.27)	12	-0.5 (-1.61 to 0.61)	-0.50 (-1.70, 0.70)	0.66
Zin et al, 2010 [47]	26	-3.59 (-4.54 to -2.64)	29	-4.03 (-4.92 to -3.14)	0.44 (-0.80, 1.68)	0.64
Schwartz et al, 2011 [49]	196	0 (-0.37 to 0.37)	193	1.4 (1.03 to 1.77)	-1.40 (-1.92, -0.88)	1.58
Sindrup et al, 2012 [53]	56	-2.4 (-2.96 to -1.84)	55	-0.7 (-1.19 to -0.21)	-1.70 (-2.43, -0.97)	1.21
Niesters et al, 2014 [58]	12	-2.6 (-3.91 to -1.29)	12	-1.7 (-3.13 to -0.27)	-0.90 (-2.62, 0.82)	0.38
Vinik et al, 2014 [60]	146	-0.04 (-0.36 to 0.28)	131	1.05 (0.65 to 1.45)	-1.09 (-1.60, -0.58)	1.60
Arai et al, 2015 [61]	84	-0.03 (-0.49 to 0.43)	79	0.96 (0.5 to 1.42)	-0.99 (-1.63, -0.35)	1.36
Gilron et al, 2015 [91*]	51	-1.9 (-2.62 to -1.18)	51	-1.6 (-2.32 to -0.88)	-0.30 (-1.29, 0.69)	0.86
Trenkwalder et al, 2015 [66]	61	-2.3 (-2.67 to -1.93)	73	-1.7 (-2.04 to -1.36)	-0.60 (-1.09, -0.11)	1.63
Simpson et al, 2016 [72]	89	-3.3 (-3.76 to -2.84)	92	-2.1 (-2.55 to -1.65)	-1.20 (-1.83, -0.57)	1.37
Tominaga et al, 2016 [73]	60	-2.6 (-3.18 to -2.02)	31	-2.6 (-3.57 to -1.63)	0.00 (-1.09, 1.09)	0.76
Subtotal (I-squared = 48.1%, p = 0.005)					-0.97 (-1.19, -0.75)	26.11
Overall (I-squared = 67.5%, p = 0.000)					-0.80 (-0.92, -0.69)	100.00

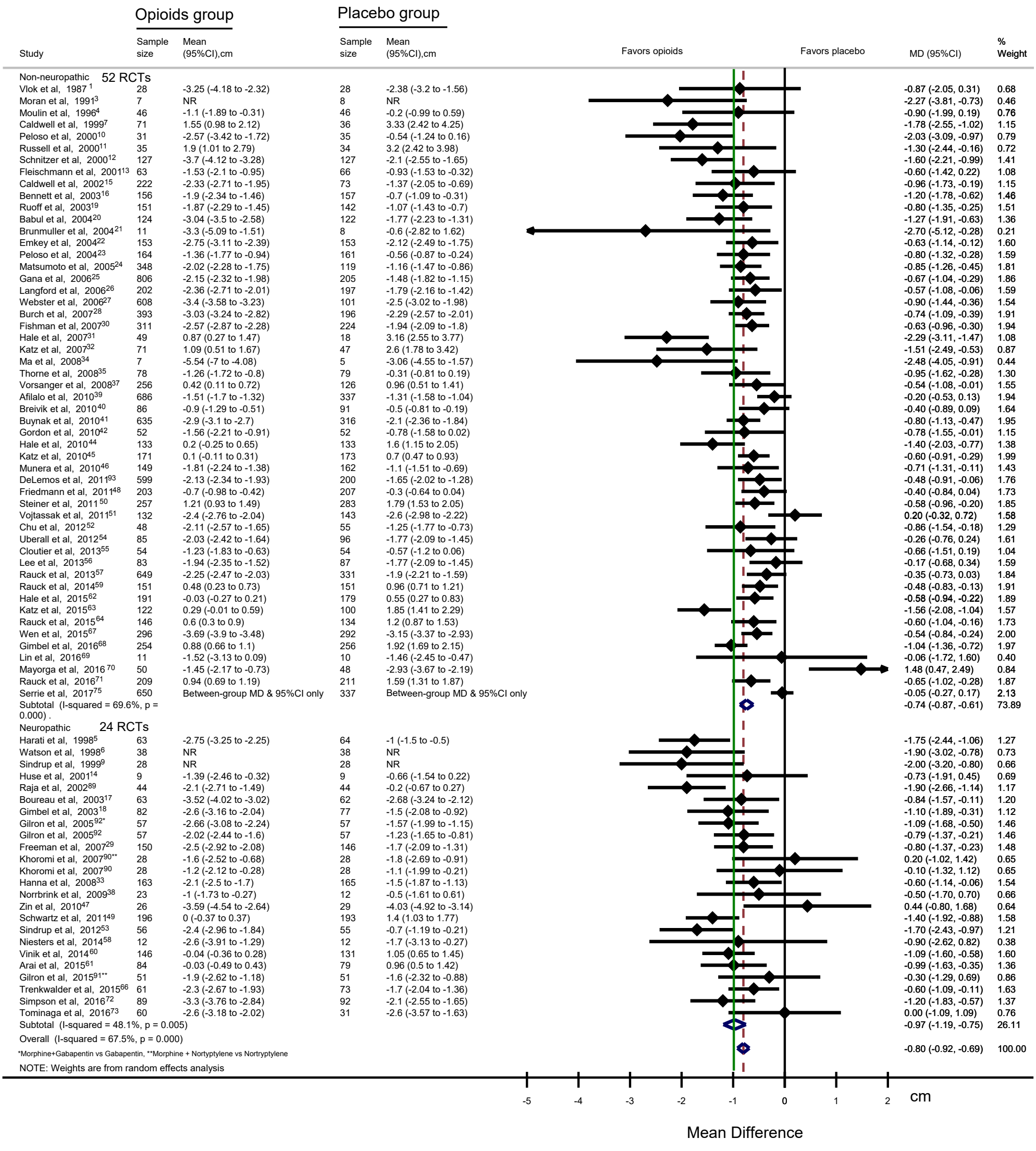
*Morphine+Gabapentin vs Gabapentin, **Morphine+Nortryptyline vs Nortryptyline

NOTE: Weights are from random effects analysis



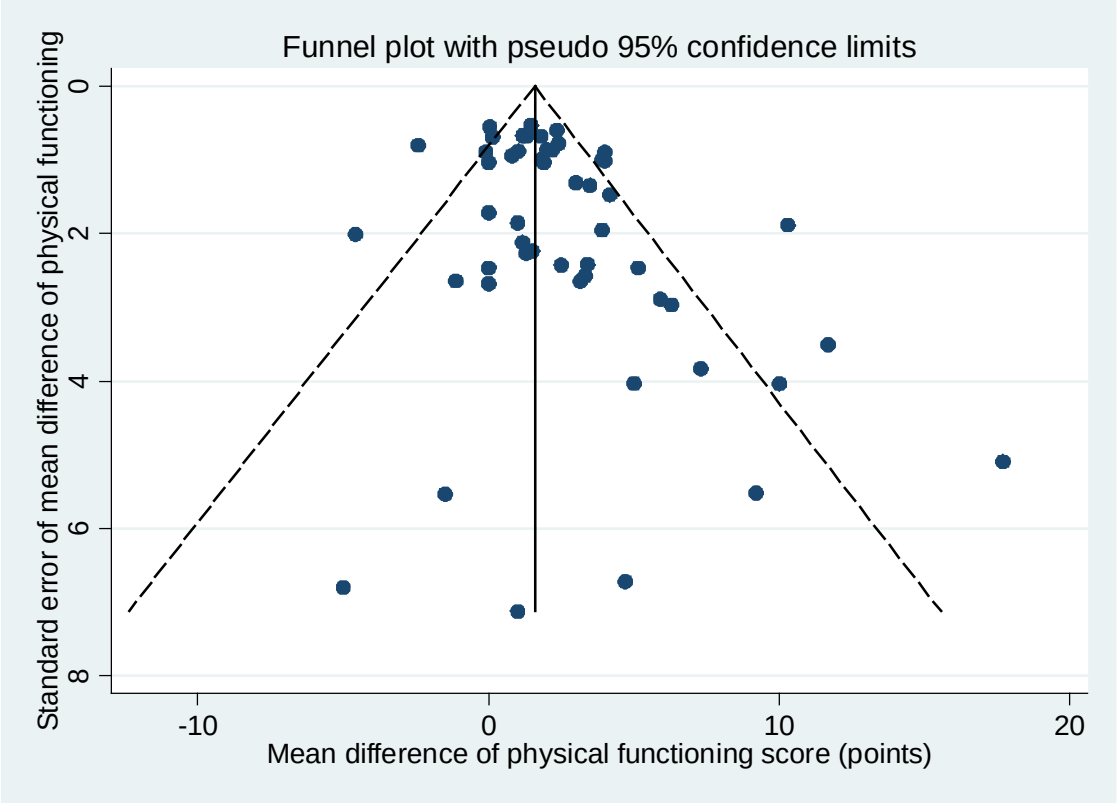
Test of interaction p-value = 0.18; RCTs: Randomized clinical trials; NR: not reported due to imputed data from mean difference & 95%CI of end-of-study score; Four studies were excluded from this subgroup analysis due to mixed conditions; the green line represents the minimally important difference. The mean and 95%CI in each group are within-group change from baseline data, and the mean difference (MD) and 95%CI are between-group differences in change from baseline data.

eFigure 6: Subgroup analysis for pain relief and neuropathic vs. non-neuropathic conditions from 76 randomized clinical trials of opioids vs. placebo



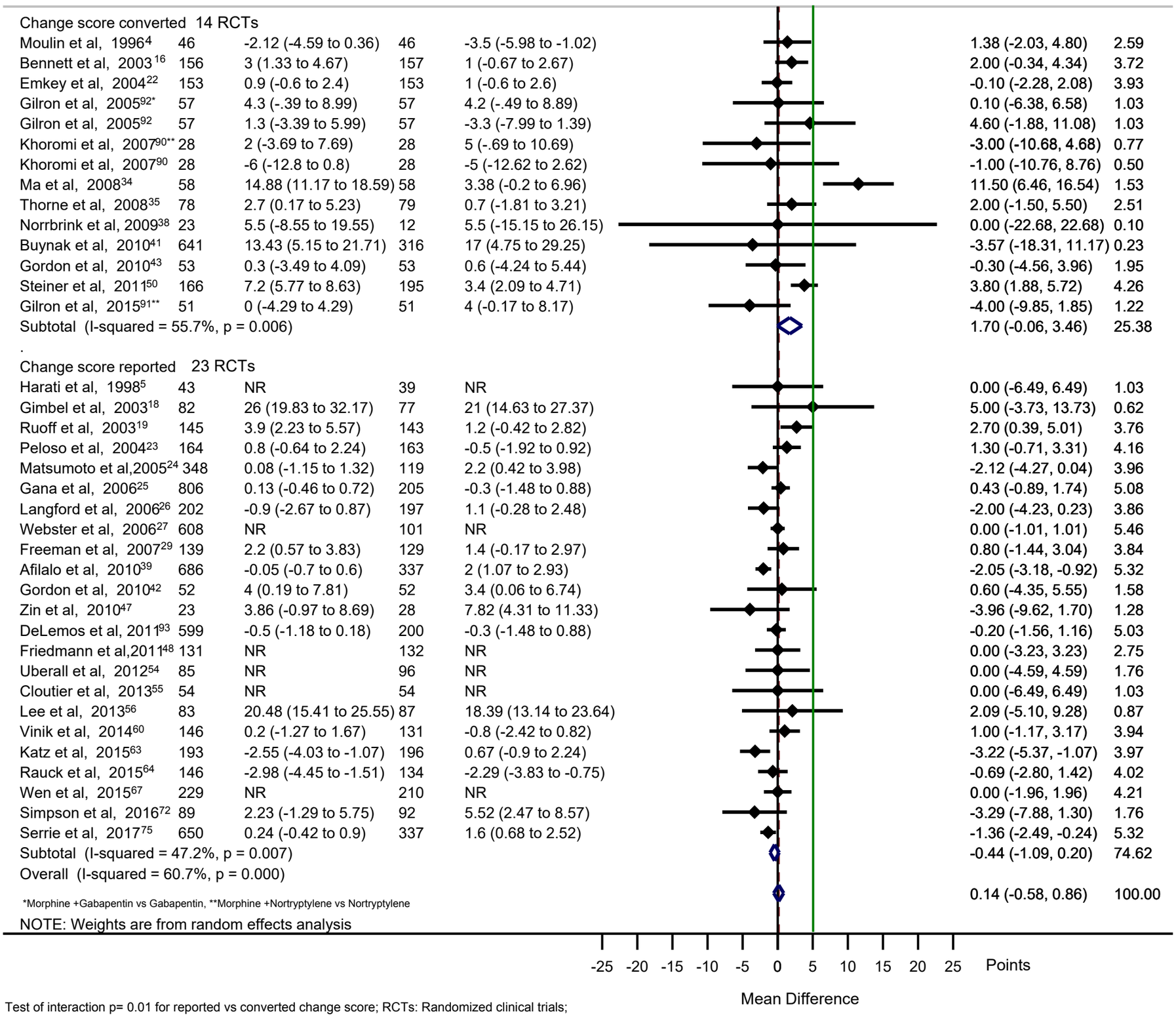
Test of interaction p-value = 0.13; RCTs: Randomized clinical trials; NR: not reported due to imputed data from mean difference & 95%CI of end-of-study score; Four studies were excluded from this subgroup analysis due to mixed conditions; the green line represents the minimally important difference. The mean and 95%CI in each group are within-group change from baseline data, and the mean difference (MD) and 95%CI are between-group differences in change from baseline data.

eFigure 7: Funnel plot for physical function for 51 randomized clinical trials of opioids vs. placebo



Begg's test p-value = 0.06 among 51 trials

eFigure 8: Emotional functioning on the SF-36 mental component summary scale among chronic noncancer pain patients receiving opioids vs. placebo from 37 randomized clinical trials



Test of interaction p= 0.01 for reported vs converted change score; RCTs: Randomized clinical trials;

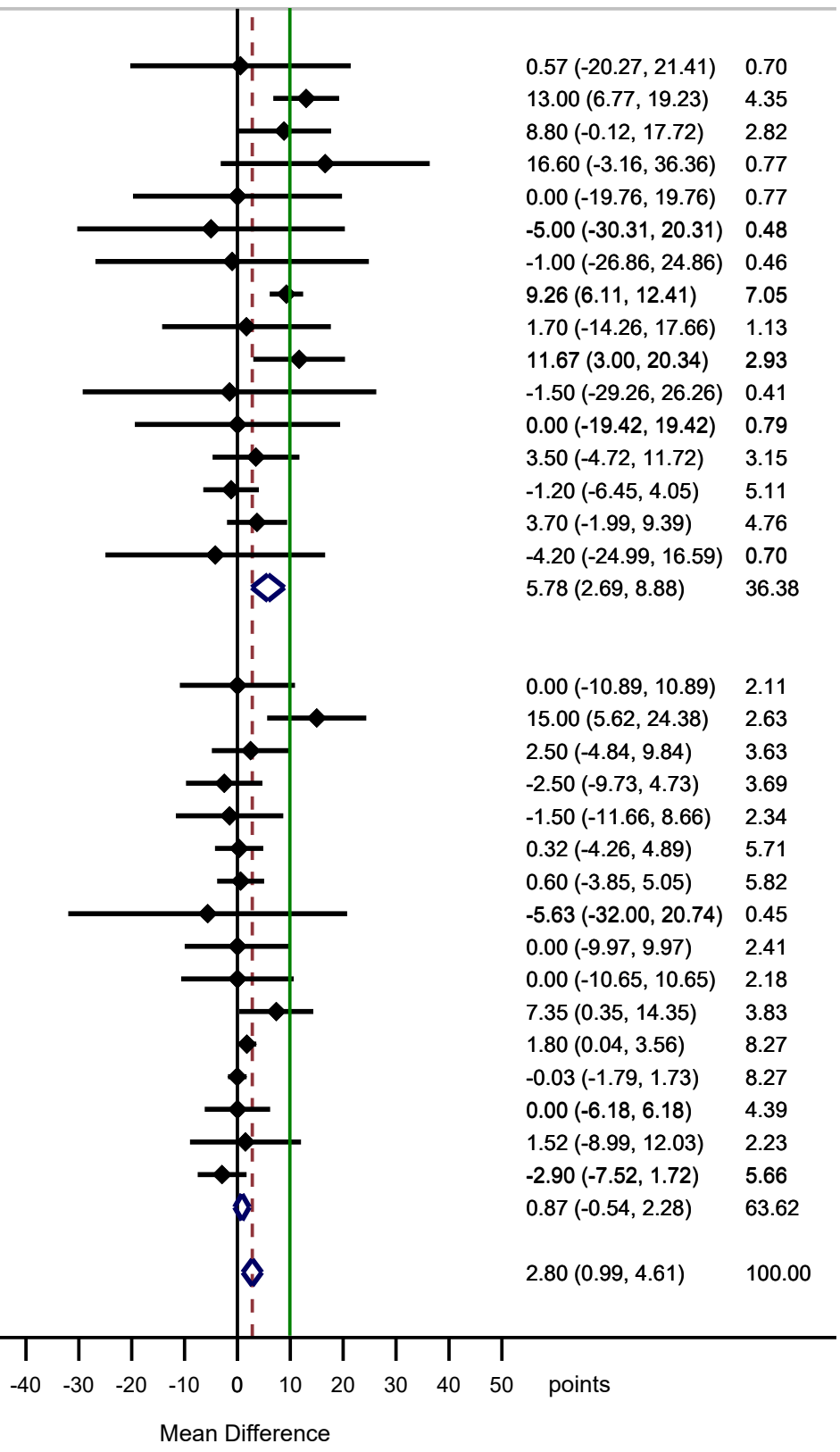
NR: not reported due to imputed data for "not-significant" results; the green line represents the minimally important difference. Change score converted means the change score was not reported directly, but converted from baseline and end-of-study scores. The mean and 95%CI in each group are within-group change from baseline data, and the mean difference (MD) and 95%CI are between-group differences in change from baseline data.

eFigure 9: Role functioning on the SF-36 role limitations due to physical problems sub-scale among chronic noncancer pain patients receiving opioids vs. placebo from 32 randomized clinical trials

Study	Opioids group: Sample size	Opioids group: Mean (95%CI),points	Placebo group: Sample size	Placebo group: Mean (95%CI),points	MD (95% CI)	% Weight
Change score converted 16 RCTs						
Moulin et al, 1996[3]	46	-0.71 (-15.86 to 14.43)	46	-1.29 (-16.43 to 13.86)	0.57 (-20.27, 21.41)	0.70
Bennett et al, 2003[15]	156	18 (13.83 to 22.17)	157	5 (0.31 to 9.69)	13.00 (6.77, 19.23)	4.35
Emkey et al, 2004[22]	153	22.4 (15.86 to 28.94)	153	13.6 (7.43 to 19.77)	8.80 (-0.12, 17.72)	2.82
Gilron et al, 2005[92]	57	10.5 (-3.78 to 24.78)	57	-6.1 (-20.38 to 8.18)	16.60 (-3.16, 36.36)	0.77
Gilron et al, 2005[92*]	57	14.9 (0.52 to 29.28)	57	14.9 (0.72 to 29.08)	0.00 (-19.76, 19.76)	0.77
Khoromi et al, 2007[90**]	28	14 (-4.55 to 32.55)	28	19 (0.07 to 37.93)	-5.00 (-30.31, 20.31)	0.48
Khoromi et al, 2007[90]	28	12 (-6.73 to 30.73)	28	13 (-6.54 to 32.54)	-1.00 (-26.86, 24.86)	0.46
Ma et al, 2008[34]	58	15.21 (12.79 to 17.63)	58	5.95 (3.83 to 8.07)	9.26 (6.11, 12.41)	7.05
Thorne et al, 2008[35]	78	5.1 (-6.4 to 16.6)	79	3.4 (-8.02 to 14.82)	1.70 (-14.26, 17.66)	1.13
Corsinovi et al, 2009[94]	78	18.33 (13.39 to 23.27)	33	6.67 (-0.79 to 14.13)	11.67 (3.00, 20.34)	2.93
Norrbrink et al, 2009[38]	23	-1.5 (-14.77 to 11.77)	12	0 (-27.81 to 27.81)	-1.50 (-29.26, 26.26)	0.41
Gordon et al, 2010[43]	53	2.7 (-11.36 to 16.76)	53	2.7 (-11.36 to 16.76)	0.00 (-19.42, 19.42)	0.79
Steiner et al, 2011[50]	170	NR	199	NR	3.50 (-4.72, 11.72)	3.15
Arai et al, 2015[61]	73	-1.5 (-5.45 to 2.45)	77	-0.3 (-3.9 to 3.3)	-1.20 (-6.45, 4.05)	5.11
Arai et al, 2015[61]	84	1.9 (-2.18 to 5.98)	79	-1.8 (-5.88 to 2.28)	3.70 (-1.99, 9.39)	4.76
Gilron et al, 2015[91**]	51	3.8 (-11.56 to 19.16)	51	8 (-6.75 to 22.75)	-4.20 (-24.99, 16.59)	0.70
Subtotal (I-squared = 35.9%, p = 0.076)					5.78 (2.69, 8.88)	36.38
.						
Change score reported 16 RCTs						
Harati et al, 1998[5]	43	NR	39	NR	0.00 (-10.89, 10.89)	2.11
Ruoff et al, 2003[19]	149	29 (22.23 to 35.77)	146	14 (7.39 to 20.61)	15.00 (5.62, 24.38)	2.63
Peloso et al, 2004[23]	164	8.8 (3.31 to 14.29)	163	6.3 (1.35 to 11.25)	2.50 (-4.84, 9.84)	3.63
Langford et al, 2006[26]	202	5.3 (-0.22 to 10.82)	197	7.8 (3.07 to 12.53)	-2.50 (-9.73, 4.73)	3.69
Freeman et al, 2007[29]	143	19.6 (12.59 to 26.61)	133	21.1 (13.62 to 28.58)	-1.50 (-11.66, 8.66)	2.34
Afilalo et al, 2010[39]	686	12.42 (9.79 to 15.05)	337	12.1 (8.34 to 15.86)	0.32 (-4.26, 4.89)	5.71
Gordon et al, 2010[42]	52	4.4 (0.98 to 7.82)	52	3.8 (0.79 to 6.81)	0.60 (-3.85, 5.05)	5.82
Zin et al, 2010[47]	23	18.47 (-3.69 to 40.63)	28	24.1 (7.31 to 40.89)	-5.63 (-32.00, 20.74)	0.45
Uberall et al, 2012[53]	85	NR	96	NR	0.00 (-9.97, 9.97)	2.41
Cloutier et al, 2013[55]	54	NR	54	NR	0.00 (-10.65, 10.65)	2.18
Lee et al, 2013[56]	83	16.04 (10.82 to 21.26)	87	8.69 (3.87 to 13.51)	7.35 (0.35, 14.35)	3.83
Vinik et al, 2014[60]	146	0.1 (-1.13 to 1.33)	131	-1.7 (-2.99 to -0.41)	1.80 (0.04, 3.56)	8.27
Rauck et al, 2015[64]	146	-2.59 (-3.82 to -1.36)	134	-2.56 (-3.84 to -1.28)	-0.03 (-1.79, 1.73)	8.27
Wen et al, 2015[67]	296	NR	292	NR	0.00 (-6.18, 6.18)	4.39
Simpson et al, 2016[72]	89	6.45 (-1.35 to 14.25)	92	4.93 (-2.32 to 12.18)	1.52 (-8.99, 12.03)	2.23
Serrie et al, 2017[75]	650	12.3 (9.6 to 15)	337	15.2 (11.44 to 18.96)	-2.90 (-7.52, 1.72)	5.66
Subtotal (I-squared = 18.3%, p = 0.244)					0.87 (-0.54, 2.28)	63.62
Overall (I-squared = 54.0%, p = 0.000)					2.80 (0.99, 4.61)	100.00

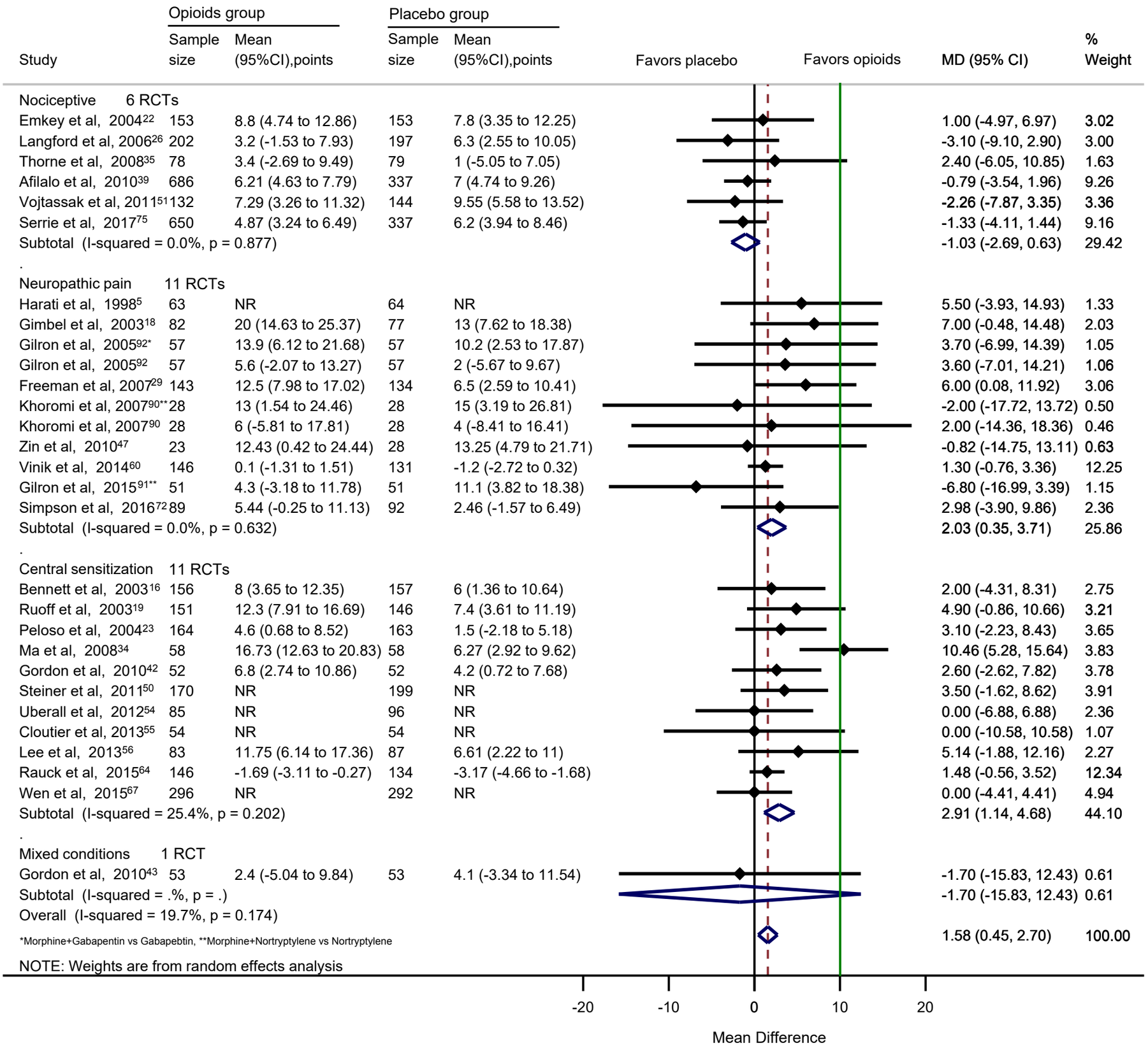
*Morphine+Gabapentin vs Gabapentin, **Morphine+Nortryptylene vs Nortryptylene

NOTE: Weights are from random effects analysis



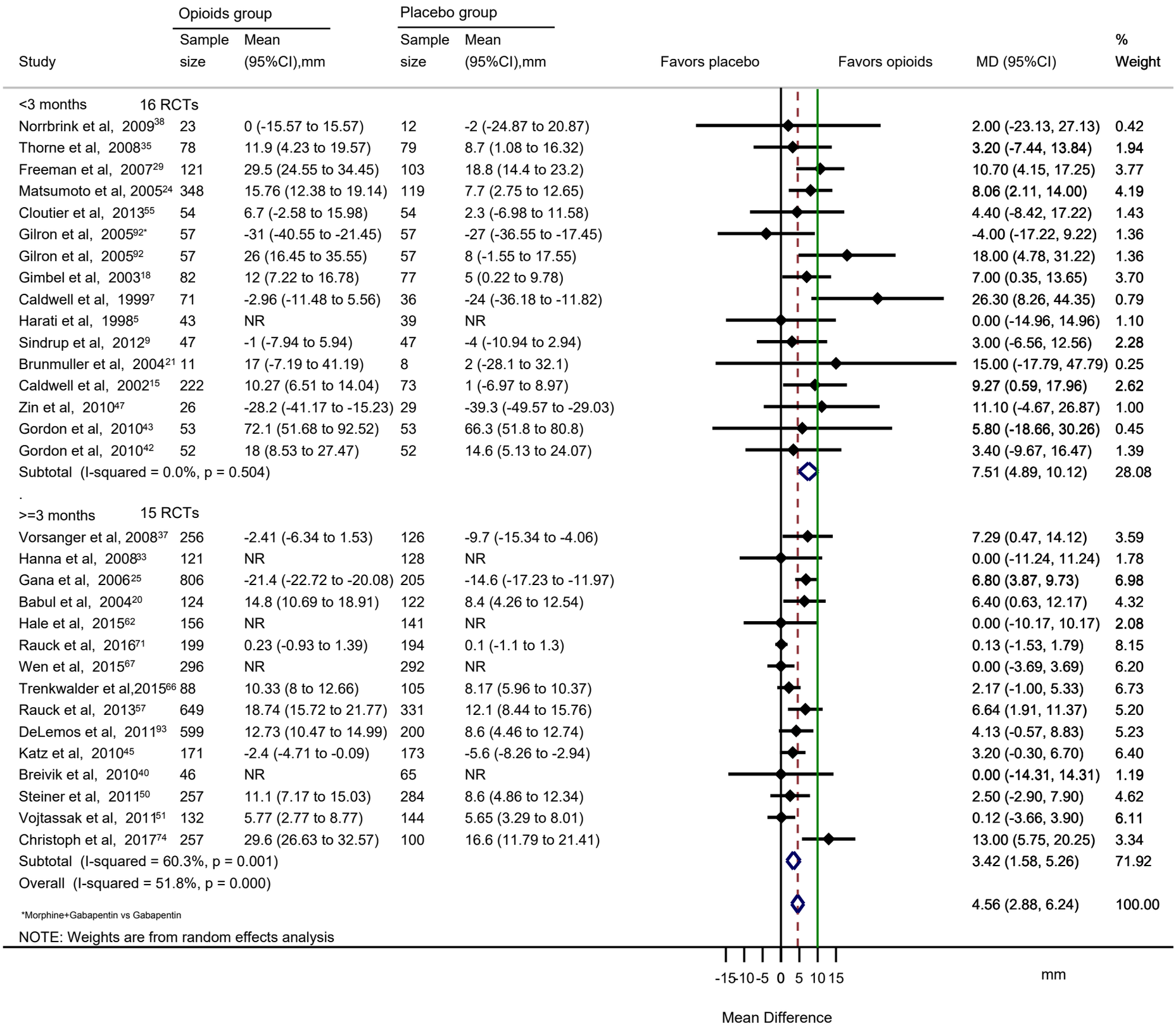
Test of interaction p = 0.007 for reported vs converted change score; RCTs: Randomized clinical trials;
NR: not reported due to imputed data from mean difference & 95%CI of end-of-study score or for non-significant results; the green line represents the minimally important difference. Change score converted means the change score was not reported directly, but converted from baseline and end-of-study scores. The mean and 95%CI in each group are within-group change from baseline data, and the mean difference (MD) and 95%CI are between-group differences in change from baseline data.

eFigure 10: Social functioning on the SF-36 social functioning sub-scale among chronic noncancer pain patients receiving opioids vs. placebo from 29 randomized clinical trials



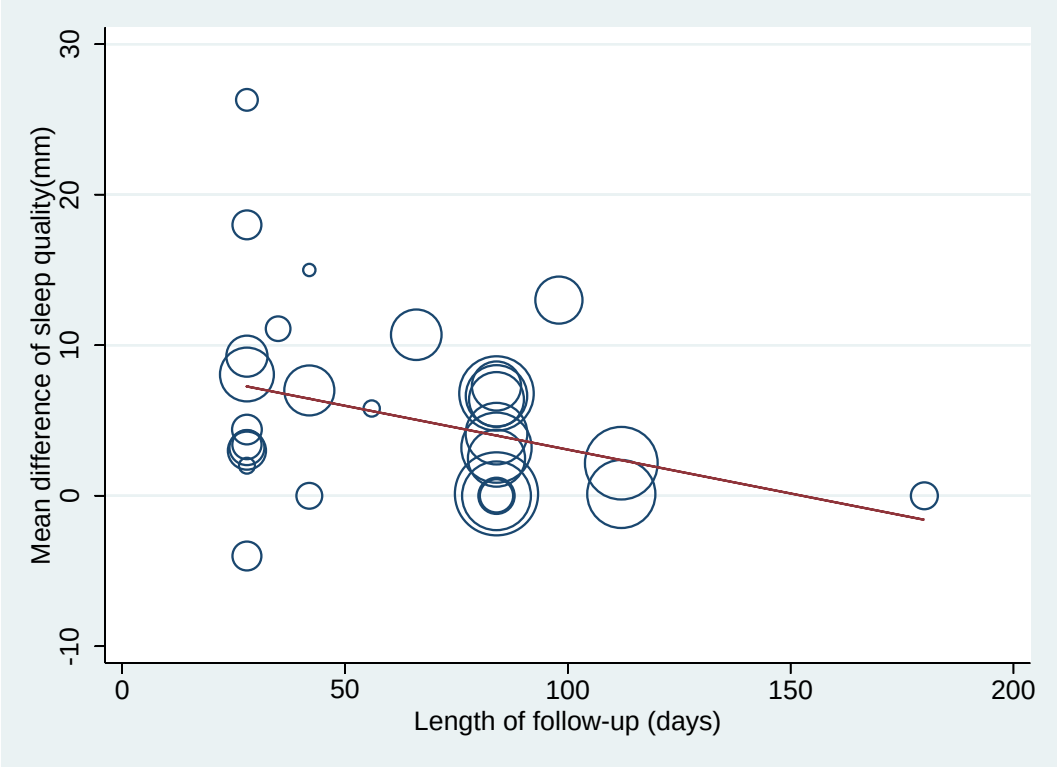
Test of interaction p = 0.01 for Neuropathic vs. Nociceptive vs. Central Sensitization; RCTs: Randomized clinical trials; NR: not reported due imputed data from mean difference & 95%CI of end-of-study score or for non-significant results; the green line represents the minimally important difference. Change score converted means the change score was not reported directly, but converted from baseline and end-of-study scores. The mean and 95%CI in each group are within-group change from baseline data, and the mean difference (MD) and 95%CI are between-group differences in change from baseline data.

eFigure 11: Sleep quality on a 100 mm VAS among chronic noncancer pain patients receiving opioids vs. placebo from 31 randomized clinical trials



Test of interaction p=0.03. RCTs: Randomized clinical trials; NR: not reported due to imputed data for non-significant results; VAS: visual analog scale; the green line represents the minimally important difference. The mean and 95%CI in each group are within-group change from baseline data, and the mean difference (MD) and 95%CI are between-group differences in change from baseline data.

eFigure 12: Meta-regression for sleep quality and length of follow-up for 31 randomized clinical trials of opioids vs. placebo

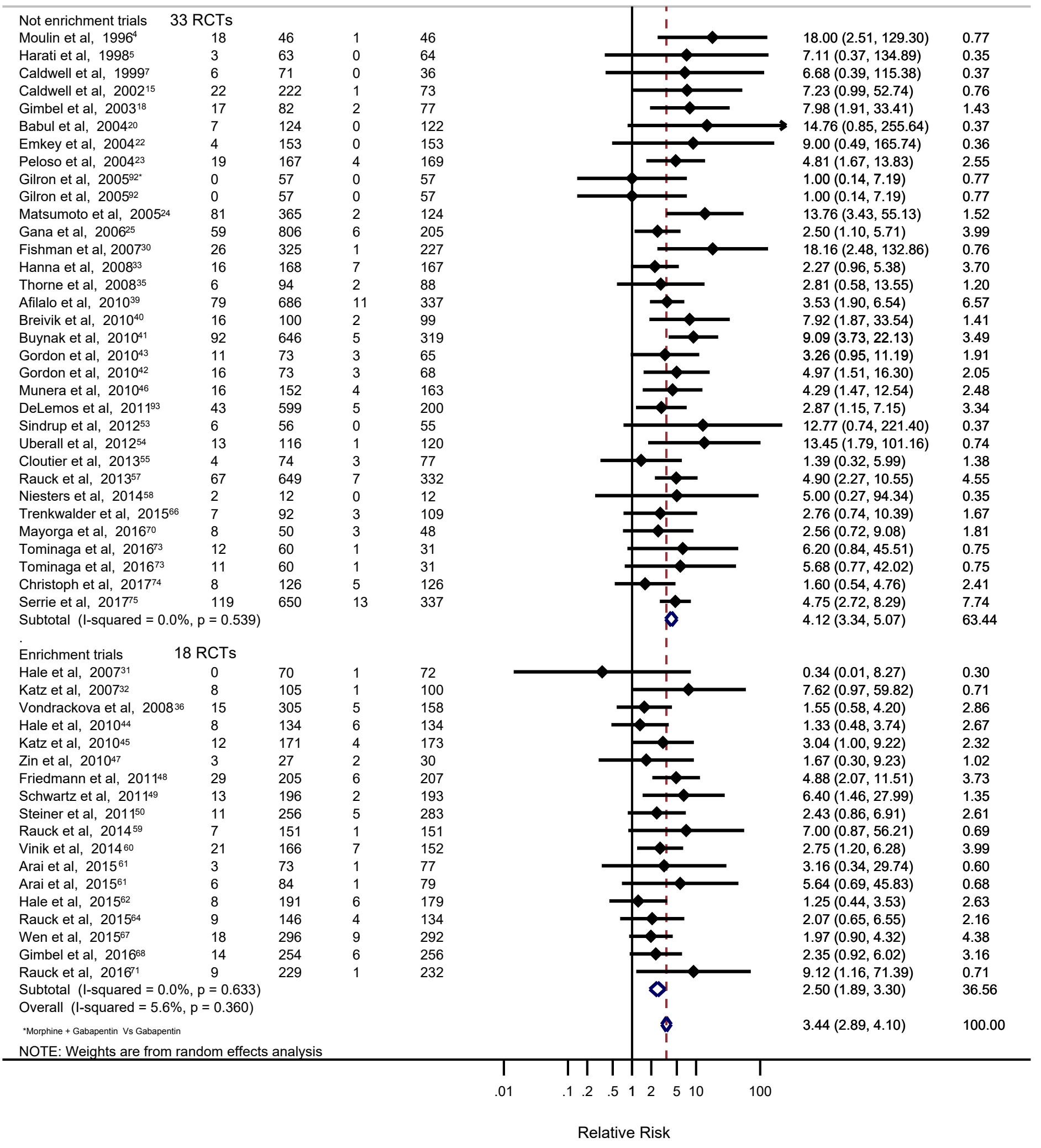


p-value =0.03 for the slope among 31 trials

The size of circle represents the weight of each study in the fitted random-effects meta-regression model (i.e. the inverse of its total variance)

eFigure 13: Vomiting among chronic noncancer pain patients receiving opioids vs. placebo from 51 randomized clinical trials

Study	Opioids group Events	Opioids group Sample size	Placebo group Events	Placebo group Sample size	RR (95% CI)	% Weight
Not enrichment trials	33 RCTs					
Moulin et al, 1996[4]	18	46	1	46	18.00 (2.51, 129.30)	0.77
Harati et al, 1998[5]	3	63	0	64	7.11 (0.37, 134.89)	0.35
Caldwell et al, 1999[7]	6	71	0	36	6.68 (0.39, 115.38)	0.37
Caldwell et al, 2002[15]	22	222	1	73	7.23 (0.99, 52.74)	0.76
Gimbel et al, 2003[18]	17	82	2	77	7.98 (1.91, 33.41)	1.43
Babul et al, 2004[20]	7	124	0	122	14.76 (0.85, 255.64)	0.37
Emkey et al, 2004[22]	4	153	0	153	9.00 (0.49, 165.74)	0.36
Peloso et al, 2004[23]	19	167	4	169	4.81 (1.67, 13.83)	2.55
Gilron et al, 2005[92*]	0	57	0	57	1.00 (0.14, 7.19)	0.77
Gilron et al, 2005[92]	0	57	0	57	1.00 (0.14, 7.19)	0.77
Matsumoto et al, 2005[24]	81	365	2	124	13.76 (3.43, 55.13)	1.52
Gana et al, 2006[25]	59	806	6	205	2.50 (1.10, 5.71)	3.99
Fishman et al, 2007[30]	26	325	1	227	18.16 (2.48, 132.86)	0.76
Hanna et al, 2008[33]	16	168	7	167	2.27 (0.96, 5.38)	3.70
Thorne et al, 2008[35]	6	94	2	88	2.81 (0.58, 13.55)	1.20
Afilalo et al, 2010[39]	79	686	11	337	3.53 (1.90, 6.54)	6.57
Breivik et al, 2010[40]	16	100	2	99	7.92 (1.87, 33.54)	1.41
Buynak et al, 2010[41]	92	646	5	319	9.09 (3.73, 22.13)	3.49
Gordon et al, 2010[43]	11	73	3	65	3.26 (0.95, 11.19)	1.91
Gordon et al, 2010[42]	16	73	3	68	4.97 (1.51, 16.30)	2.05
Munera et al, 2010[46]	16	152	4	163	4.29 (1.47, 12.54)	2.48
DeLemos et al, 2011[93]	43	599	5	200	2.87 (1.15, 7.15)	3.34
Sindrup et al, 2012[53]	6	56	0	55	12.77 (0.74, 221.40)	0.37
Uberall et al, 2012[54]	13	116	1	120	13.45 (1.79, 101.16)	0.74
Cloutier et al, 2013[55]	4	74	3	77	1.39 (0.32, 5.99)	1.38
Rauck et al, 2013[57]	67	649	7	332	4.90 (2.27, 10.55)	4.55
Niesters et al, 2014[58]	2	12	0	12	5.00 (0.27, 94.34)	0.35
Trenkwalder et al, 2015[66]	7	92	3	109	2.76 (0.74, 10.39)	1.67
Mayorga et al, 2016[70]	8	50	3	48	2.56 (0.72, 9.08)	1.81
Tominaga et al, 2016[73]	12	60	1	31	6.20 (0.84, 45.51)	0.75
Tominaga et al, 2016[73]	11	60	1	31	5.68 (0.77, 42.02)	0.75
Christoph et al, 2017[74]	8	126	5	126	1.60 (0.54, 4.76)	2.41
Serrie et al, 2017[75]	119	650	13	337	4.75 (2.72, 8.29)	7.74
Subtotal (I-squared = 0.0%, p = 0.539)					4.12 (3.34, 5.07)	63.44
.						
Enrichment trials	18 RCTs					
Hale et al, 2007[31]	0	70	1	72	0.34 (0.01, 8.27)	0.30
Katz et al, 2007[32]	8	105	1	100	7.62 (0.97, 59.82)	0.71
Vondrackova et al, 2008[36]	15	305	5	158	1.55 (0.58, 4.20)	2.86
Hale et al, 2010[44]	8	134	6	134	1.33 (0.48, 3.74)	2.67
Katz et al, 2010[45]	12	171	4	173	3.04 (1.00, 9.22)	2.32
Zin et al, 2010[47]	3	27	2	30	1.67 (0.30, 9.23)	1.02
Friedmann et al, 2011[48]	29	205	6	207	4.88 (2.07, 11.51)	3.73
Schwartz et al, 2011[49]	13	196	2	193	6.40 (1.46, 27.99)	1.35
Steiner et al, 2011[50]	11	256	5	283	2.43 (0.86, 6.91)	2.61
Rauck et al, 2014[59]	7	151	1	151	7.00 (0.87, 56.21)	0.69
Vinik et al, 2014[60]	21	166	7	152	2.75 (1.20, 6.28)	3.99
Arai et al, 2015[61]	3	73	1	77	3.16 (0.34, 29.74)	0.60
Arai et al, 2015[61]	6	84	1	79	5.64 (0.69, 45.83)	0.68
Hale et al, 2015[62]	8	191	6	179	1.25 (0.44, 3.53)	2.63
Rauck et al, 2015[64]	9	146	4	134	2.07 (0.65, 6.55)	2.16
Wen et al, 2015[67]	18	296	9	292	1.97 (0.90, 4.32)	4.38
Gimbel et al, 2016[68]	14	254	6	256	2.35 (0.92, 6.02)	3.16
Rauck et al, 2016[71]	9	229	1	232	9.12 (1.16, 71.39)	0.71
Subtotal (I-squared = 0.0%, p = 0.633)					2.50 (1.89, 3.30)	36.56
Overall (I-squared = 5.6%, p = 0.360)					3.44 (2.89, 4.10)	100.00

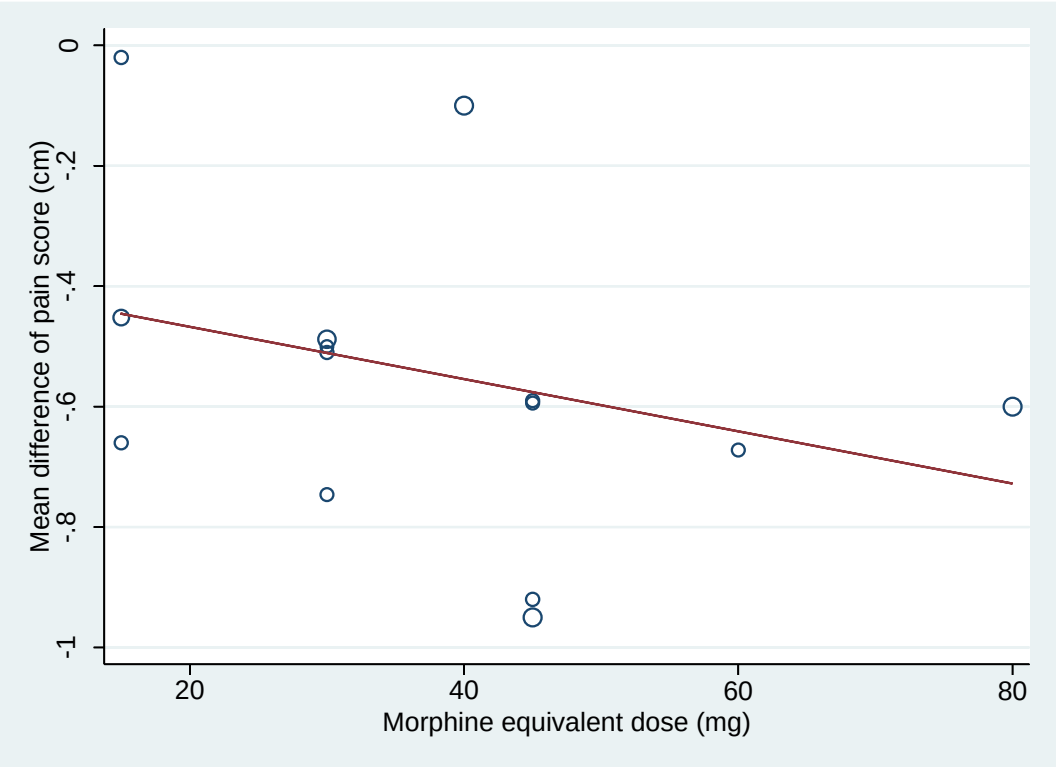


*Morphine + Gabapentin Vs Gabapentin

NOTE: Weights are from random effects analysis

Test of interaction p=0.007 for enrichment trials vs not; RR: relative risk; RCTs: Randomized clinical trials; enrichment trials precede randomization with an open-label treatment phase that is undertaken to exclude patients with problematic adverse events and/or poor response to treatment; events represent the number of patients experiencing vomiting in each group

eFigure 14: Meta-regression for pain relief and opioid dose among 5 trials with 14 within-study comparisons

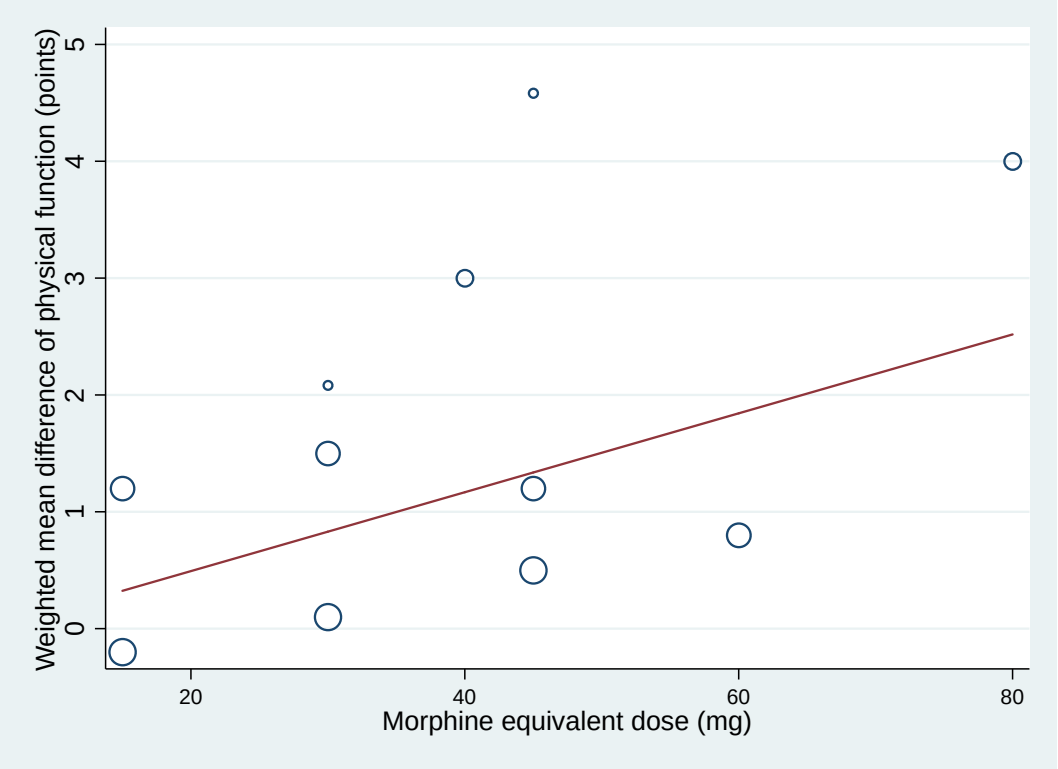


P-value = 0.39 for the slope among 5 trials with 14 within-study comparisons

One of six trials were excluded from meta-regression as they randomized patients to receive the opioid 'Cebranopadol' for which there is no established morphine equivalent dose (MED) conversion factor[74]

The size of circle represents the weight of each study in the fitted random-effects meta-regression model (i.e. the inverse of its total variance)

eFigure 15: Meta-regression for physical function and opioid dose among 4 trials with 11 within-study comparisons

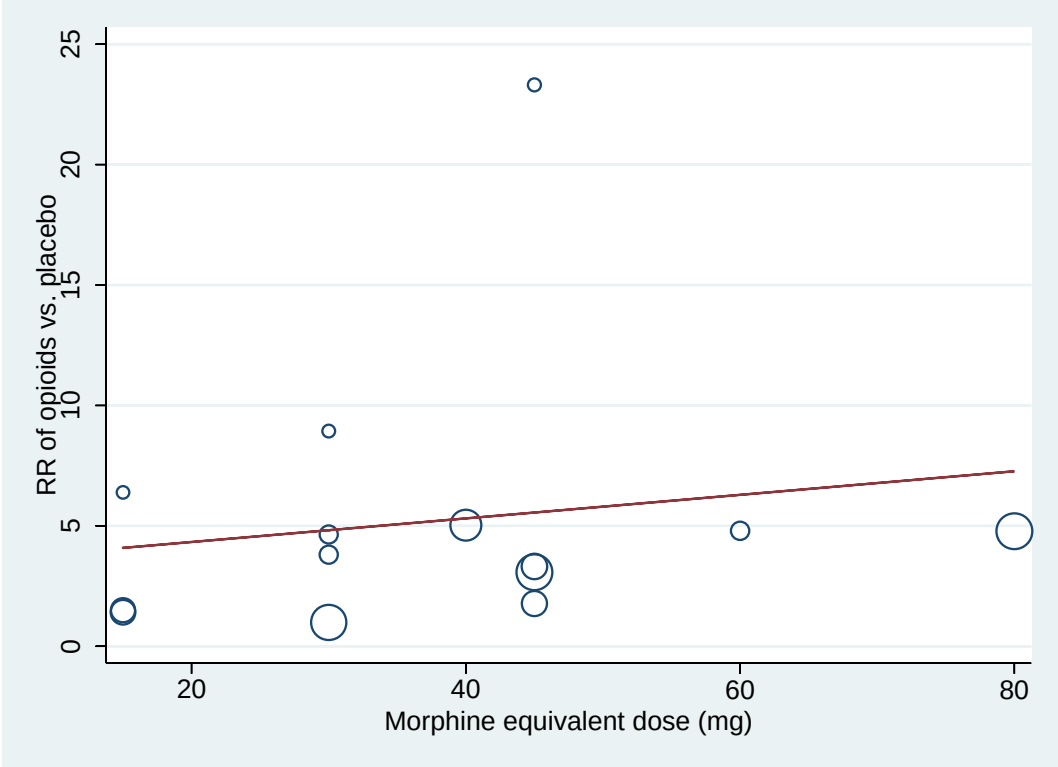


P-value = 0.22 for the slope among 4 trials with 11 within-study comparisons

One of six trials were excluded from meta-regression as they randomized patients to receive the opioid 'Cebranopadol' for which there is no established morphine equivalent dose (MED) conversion factor[74]

The size of circle represents the weight of each study in the fitted random-effects meta-regression model (i.e. the inverse of its total variance)

eFigure 16: Meta-regression for gastrointestinal adverse events and opioid dose among 5 trials with 14 within-study comparisons



P-value = 0.12 for the slope among 5 trials with 14 within-study comparisons; RR: relative risk;

The size of circle represents the weight of each study in the fitted random-effects meta-regression model (i.e. the inverse of its total variance)

One of six trials were excluded from meta-regression as they randomized patients to receive the opioid 'Cebranopadol' for which there is no established morphine equivalent dose (MED) conversion factor[74]