Drug Class Review

Long-Acting Opioid Analgesics

Final Update 5 Report
Evidence Tables

April 2008

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Update 4: April 2006
Update 3: April 2005
Update 2: April 2004
Update 1: September 2003
Original Report: November 2002

The literature for this topic is scanned periodically.

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The medical literature relating to the topic is scanned periodically (see http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for scanning process description). The Drug Effectiveness Review Project governance group elected to proceed with another update of this report based on the information contained in the scan. Please see timeline on the DERP website for details on the date of its release. Prior versions of this report can be accessed at the DERP website.

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Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up (%), Analyzed
Allan, 2005	Randomized, open-label controlled trial Multicenter Clinic type and number not specified	A: Transdermal fentanyl (titrated from 25 mcg/hr) (Mean dose 57 mcg/h) B: Long acting morphine (titrated from 30 mg q 12 hrs) (Mean dose 140 mg) 13 months	Adults with chronic low back pain requiring regular strong opioids	Receipt of more than 4 doses of strong opioids in a week in the 4 weeks before the study, high risk of ventilatory depression or intolerance to study drugs, prior alcohol or substance abuse, presence of other chronic pain disorders, or life-limiting illness	Short acting analgesics permitted	Not reported Not reported 683 enrolled	342 (50%) 608

VAS = visual analogue scale; BID=twice daily; Q AM=every morning; Q PM=every evening

Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Allan, 2005	Avg. 54.0 years 61% female Race: not reported 35% nociceptive 4% neuropathic 46% nociceptive and neuropathic 3% nociceptive with psychologic factors 4% neuropathic with psychologic factors 83% mechanical low back pain 8% inflammatory 39% trauma/surgery 1% metabolic 3% other Prior opioid use not reported Pain duration average 124.7 months	**Pain relief** VAS (0-100) assessed at baseline and every week **Bowel function** PAC-SYM baseline, day 15, day 29, and monthly **Quality of Life** (SF-36) baseline, day 29, then monthly or 3-monthly **Back pain at rest, on movement, during day, and at night** scale not specified **Glocal assessment** investigator assessment on 3-point scale (deteriorated, unchanged, improved) **Rescue medication use** **Work status** number of days lost to work	FAIR: Allocation performed centrally. Groups similar at baseline, but baseline pain scores not reported. Eligibility criteria specified. Outcome assessors, care providers, and patients not blinded. High overall loss to follow-up: 50% completed trial. No intention-to-treat analysis for primary outcome (pain relief) (analyzed 608 of 683 randomized patients). Follow-up 56 weeks.

VAS = visual analogue scale; BID=twice daily; Q AM=every morning; Q PM=every evening

Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Allan, 2005	Fentanyl (A) vs. Long acting morphine (B) **Pain score** (mean, 0-100 VAS) at 56 weeks (N=608): 56.0 (A) vs. 55.8 (B) **Severe pain at rest (per protocol analyses, n=248 and 162)** 22/248 (9%) (A) vs. 20/162 (12%) (B), p=0.030 (no significant differences in ITT analysis, but data not provided) **Severe pain on movement (per protocol)** 70/248 (28%) (A) vs. 43/162 (27%) (B), p=0.61 **Severe pain during the day (per protocol)** 48/248 (19%) (A) vs. 40/162 (25%) (B), p=0.385 **Severe pain at night (per protocol)** 25/248 (10%) (A) vs. 26/162 (16%) (B), p=0.003 (no significant differences in ITT analysis, but data not provided) **Rescue strong opioids use** 154/296 (52%) (A) vs. 154/291 (53%) (B) **Quality of life (SF-36)** No differences between interventions **Loss of working days** No differences between interventions	Number screened not reported. Number eligible not reported. Clinic setting not described. Baseline or previous opioid use not reported.	Janssen Pharmaceutical. One author employed by Janssen.	Not blinded. ITT results not reported for several outcomes.

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Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up (%), Analyzed
Allan, 2001	Randomized open-label controlled trial Crossover International Multicenter (35) Pain clinics	A: Transdermal fentanyl (titrated) (Mean dose 57.3 mcg/h) B: Long acting morphine (titrated) (Mean dose 133.1 mg/day) 4 weeks initial intervention followed by 4 week crossover	Patients with chronic non-cancer pain requiring continuous treatment with potent opioids	Includes pain not responding to opioids, life threatening disease, skin disease precluding use of transdermal system, other significant medical or psychiatric illness, possible pregnancy or lactation	Immediate release morphine	Not reported Not reported 256	60 (23%) 212

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Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Allan, 2001	Avg. 51.4 years 47% female 98% white 26% neuropathic 50% nociceptive 24% combined neuropathic and nociceptive 76% (194/256) on Morphine prior to study Pain duration average 9 years	**Patient Preference** assessed at end of trial or at time of withdrawal **Pain Intensity** VAS (0-100, 100 excruciating) assessed at baseline and end of each treatment period **Pain Control** categorical scale (scale not specified), assessed at each visit (timing of visits not specified) and at end of each treatment period. **Quality of Life** (SF-36) assessed at baseline and end of each treatment period **Rescue Drug Use**: mean mg/day **Global Efficacy** categorical scale (scale not specified), timing of assessment not reported	POOR: Treatment allocation done using central randomization minimization technique. Groups similar at baseline. Eligibility criteria specified. Outcome assessors, care providers, and patients not blinded. 196/256 completed trial. No comparison of groups completing trial provided. High overall and differential withdrawal rates: 38 (16%) (A) vs. 22 (9%) (B). Follow-up 8 weeks total, 4 weeks per intervention. Results reported such that it is not possible to evaluate each half of the crossover trial independently.

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Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Allan, 2001	Fentanyl (A) vs. Long acting morphine (B) **Patient Preference**: "Preferred" or "Very Much Preferred" 138/212 (65%) A vs. 59/212 (28%) B (p<0.001) No difference in results between pain types. Better pain control main reason **Pain Intensity Score** (mean): 57.8 (A) vs. 62.9 (B) (p<0.001) **Pain Control** "Good" or "Very Good": 35% (A) vs. 23% (B) (p=0.002) **Quality of Life** (mean SF-36 scores) Summary score for physical functioning: 28.6 (A) vs. 27.4 (B) (p=0.004) Summary score for mental health: 44.4 (A) vs. 43.1 (B) (p=0.030) **Rescue Drug Use** (mean): 29.4 mg (A) vs. 23.6 mg (B) (p<0.001) **Global Efficacy (patient)** "Good" or "Very Good": 60% (A) vs. 36% (B) (p<0.001)	Number screened not reported. Number eligible not reported. Exclusion criteria not reported. High percent of enrollees on morphine prior to study. Difficult to assess external validity.	Janssen-Cilaj (Fentanyl) provided grant. No authors employed.	Not blinded, its main outcome measure is patient preference, and 76% of enrollees had been on Morphine prior to study. High withdrawal rate. Unable to accurately assess external validity. Post-hoc sub-group analysis excluding 24 patients reporting "bad" or "very bad" score on pre-trial morphine found that 69% expressed a "strong" or "very strong" preference for fentanyl.

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Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up (%), Analyzed
Caldwell, 2002	Randomized double blinded controlled trial USA Multicenter Clinic type and number not specified	A. Long acting morphine Q AM B. Long acting morphine Q PM C. Long acting morphine BID D. Placebo Mean dose 30 mg/day 4 weeks	40 years or older, osteoarthritis of hip or knee, prior suboptimal response to NSAIDS and acetaminophen or previous use of intermittent narcotics; baseline VAS 40 or more	Serious concomitant disease, history of or imminent joint surgery, weight <100 lbs., recent steroids, opioid treatment for >3 months, opioids allergy	Not permitted	Not reported Not reported 295	111 (37%) 295
Hale, 2005	Randomized double-blinded controlled trial USA Multicenter Clinic type and number not specified	A: Long acting oxymorphone (titrated) (Mean dose 79.4 mg/day) B: Long acting oxycodone (titrated) (Mean dose 155 mg/day) C: Placebo 18 days	18 to 75 years, moderate to severe low back pain for at least 15 days per month for past 2 months, stable dose of opioids for at least 3 days prior to enrollment	Fibromyalgia, multiple specified causes for back pain, malignancy, infection, neurologic dysfunction, psychiatric conditions, concomitant illness, history of drug or alcohol dependence, hypersensitivity to opioids, back surgery within 2 months or nerve/plexus block within 4 weeks, active or pending litigation	Immediate release morphine 15 mg q 4-6 hrs for first 4 days, then limited to 30 mg/day (mean 25 mg in active treatment groups for first four days, then mean 14 mg/day)	420 screened 330 underwent randomized titration 235 enrolled in stable dose intervention phase	96 (41%) 213

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Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Caldwell, 2002	Avg. 62.4 years 63% female 85% white 100% osteoarthritis (no further details reported) Pain duration not reported	**Pain intensity index joint** VAS (0-500, 500 extreme pain) assessed at baseline and weekly; difference from baseline reported **Pain intensity overall arthritis pain** VAS(1-100, 100 extreme pain) assessed at baseline and weekly; difference from baseline reported **Physical function** VAS (0-1700, 1700 extreme functional difficulty) assessed at baseline and weekly; difference from baseline reported **Stiffness index** VAS (0-200, 200 extreme stiffness) assessed at baseline and weekly; difference from baseline reported **Sleep duration** 12 point scale (1-12 hours) assessed at baseline and weekly; difference from baseline reported in hours **Sleep measures** including trouble falling asleep due to pain, need for sleep medication, awakening during the night	FAIR: Method of randomization not reported. Method of treatment allocation not reported. Groups similar at baseline. Comparison of prior opioid use not provided. Eligibility criteria specified. Trial double-blind using matched placebo pills. Blinding not evaluated. Intention to treat analysis provided. It is not clear how missing data are handled. 111/295 completed trial. No comparison of groups completing trial provided. Loss to follow up not differential. 4 weeks follow-up.
Hale, 2005	Median age=46 years 47% female Race not reported Median duration of low back pain 8 years "Most common" etiologies: degenerative disc disease, disc herniation, fracture, spondylosis, and spinal stenosis	Pain intensity on VAS (0 to 100) at baseline and at 18 days and by 4 point categorical scale (0=none to 3=severe) Pain relief on VAS (0=no relief to 100=complete relief) Brief pain inventory Global evaluation on 5-point categorical scale (poor to excellent) Interference with normal activities on 100 point scale (0=no interference to 10=complete interference)	FAIR: Adequate randomization and treatment allocation. Groups reported as similar at baseline but data not clearly reported. Prior opioid use not reported. Clear eligilbility criteria. Blinded. No intention-to-treat analysis. 41% did not complete trial. No comparison of groups completing and not completing trial provided. 18 days follow-up.

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Author, Year	Outcomes	External validity	Funding source and role	Other comments
Caldwell, 2002	Long acting morphine qam (A) vs. Long acting morphine qpm (B) vs. Long acting morphine bid (C) vs. placebo (D) **Pain intensity index joint:** -17.2 (A) vs -20.1 (B) vs. -18.4 (C) vs -6.48 (D) (treatment groups significantly different from placebo) **Pain intensity overall arthritis pain:** -25.8 (A) vs -21.9 (B) vs -22.3 (C) vs -13.7 (D) (not significantly different) **Physical function:** -207 (A) vs -204 (B) vs -181 (C) vs -96.7 (D) (not significantly different) **Stiffness index:** -23.6 (A) vs -23.5 (B) vs -20.5 (C) vs -15.7 (D) (not significantly different) **Increased sleep duration (hrs):** 0.6 (A) vs 0.25 (B) vs 0.3 (C) vs 0.2 (D) (not significantly different) **Improved overall quality of sleep:** 12 (A) vs 10 (B) vs 5 (C) vs 2 (D) (significantly different from placebo; A also significantly different from D) **Less trouble falling asleep:** -18 (A) vs -12 (B) vs -16 (C) vs -5 (D) (A and C significantly different from placebo) **Less need for sleep medication:** -13 (A) vs -6 (B) vs -5 (C) vs -1 (D) (A significantly different from placebo)	Number screened not reported. Number eligible not reported. Exclusion criteria provided. Osteoarthritis pain patients.	Funding source not reported.	Out of multiple sleep measures, one found a significant different between long acting morphine A and long acting morphine C
Hale, 2005	Long-acting oxymorphone (n=71) (A) vs. long-acting oxycodone (n=75) (B) vs. placebo (n=67) (C) **Pain Intensity** Mean difference from baseline vs. placebo (VAS): -18.2 vs. -18.6 **Pain Intensity** Categorical scale: Proportion rating pain intensity "none" or "mild" similar for A and B vs. C **Pain Relief** 56.8 vs. 54.1 vs. 39.1 **Pain Intereference** A and B similar and superior to C for general activity, mood, normal work, relations with other people, and enjoyment of life (no difference for sleep and walking ability) **Global Assessment** "Good", "very good", or "excellent':59% vs. 63% vs. 27% **Discontinuation due to treatment failure (treatment phase)** 20% vs. 16% vs. 57% **Discontinuation due to treatment failure (dose titration phase)** 7/166 (4.2%) vs. 4/134 (2.4%) **Rescue medication use** 13.8 vs. 14.7 mg/day after first 4 days	High number of patients screened and enrolled in titration phase not enrolled into randomized phase	Endo Pharmaceuticals Inc and Penwest Pharmaceuticals Co	Results of first randomization to long acting oxymorphone versus long acting oxycodone (titration phase) not reported. Not clear how patients re-randomized to treatment phase.

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Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up (%), Analyzed
Matsumoto, 2005	Parallel-group USA Multicenter Clinic setting not described	A: Sustained-release oxymorphone 20 mg bid x 2 weeks, then 40 mg bid B: Sustained-release oxymorphone 20 mg bid C: Sustained-release oxycodone 10 mg bid x 2 weeks, then 20 mg bid D: Placebo 4 weeks	Typical knee or hip joint symptoms and signs and radiographic evidence of osteoarthritis, taking an analgesic for at least 75 of 90 days prior to screening visit with suboptimal visit, >40 years, adequate birth control or abstinence in women of child-bearing potential, negative serum pregnancy test	Inflammatory arthritis, gout, Paget's disease, chronic pain syndrome, fibromyalgia, requiring arthroplasty within 2 months, weight <100 pounds, difficulty swallowing capsules or tablets, prior history of substance or alcohol abuse, corticosteroid or investigational drug use within 1 month, prior history of intolerance to opioids	Not specified	Number approached and eligible not reported 491 randomized (121 oxymorphone 40 mg bid, 121 oxymorphone 20 mg bid, 125 oxycodone 20 mg bid, 124 placebo)	222/491 (45%) 467 analyzed

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Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Matsumoto, 2005	Median age: 61 vs. 63 vs. 63 vs. 62 years Female gender: 64% vs. 56% vs. 58% vs. 65% Non-white race: 12% vs. 18% vs. 10% vs. 14% Duration of osteoarthritis >5 years: 64% vs. 71% vs. 67% vs. 77% Knee osteoarthritis: 78% vs. 77% vbs. 75% vs. 75% Baseline pain: Not reported Previous opioids: Not reported	Pain intensity VAS (0 to 100) WOMAC pain, stiffness, and physical function subscales SF-36 Global assessments of therapy (method not reported) Sleep assessment (method not reported)	SEE APPENDIX E

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Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Matsumoto, 2005			Endo Pharmaceuticals Inc. and Penwest Pharmaceuticals	

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Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up (%), Analyzed
Nicholson, 2006	Parallel-group USA Multicenter Clinic setting not described	A: Extended-release morphine (Kadian) initially dosed once daily according to previous analgesic dose and titrated (dose and frequency up to twice daily) (mean dose 79 mg/day) B: Sustained-release oxycodone initially dosed twice daily according to previous analgesic dose and titrated (dose and frequency up to three times daily) (mean dose 85 mg/day)	18-85 years, moderate to severe non-cancer pain, continuous treatment with a sustained-release opioid indicated, pain predominantly non-neuropathic, baseline pain >=4 on a 0 to 10 scale	Underlying cancer, hypersensitivity to opioids, conditions contraindicating treatment with morphine, impaired bowel motility or intractable vomiting caused or agitated by opioids, significant respiratory disease (including asthma) or respiratory distress likely to be worsened by opioids, clinically significant lab abnormalities that might affect safety, likely to require drugs not permitted by protocol, other conditions or findings judged to possibly affect results, pregnancy, lactating, not using effective contraception		Number approached and eligible not reported 112 randomized (53 to extended-release morphine and 59 to sustained-release oxycodone)	5/112 (4%) dropped out due to non-compliance 52/112 (46%) 97/112 (87%) analyzed

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Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Nicholson, 2006	"Similar" for age (mean 51 years), non-white race (6%) Female gender: 63% vs. 41% (p<0.05) Back pain: 63% vs. 52% (p=0.31) Duration of symptoms (not reported) Baseline SF-36 Physical Component Summary scores: 26.4 vs. 31.1 (p <0.05) Baseline Pain scores: 7.2 vs. 7.4 Prior opioid use: "No difference"	Pain: 0 (no pain) to 10 (worst pain imaginable) categorical scale SF-36 Physical and Mental Component Summaries (0 to 100 each) Sleep Interference Scale of the Brief Pain Inventory: 0 (pain does not interfere with sleep) to 10 (completely interferes with sleep) Patient global assessment: -4 (completely dissatisfied) to +4 (completely satisfied) Clinician global assessment	SEE APPENDIX E

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Author, Year	Outcomes	External validity	Funding source and role	Other comments
Nicholson, 2006	Extended-release morphine (Kadian) once daily versus sustained-release oxycodone twice daily (mean improvement from baseline) SF-36 Physical Component Scale: +2.5 vs. +2.1 (NS) SF-36 Mental Component Scale: +0.8 vs. +4.2 (p for differences between groups not reported, but p<0.05 vs. baseline only for sustained-release oxycodone) Pain (0 to 10): -1.9 vs. -1.4 (NS) Sleep Interference Scale (0 to 10): -2.6 vs. -1.6 (p<0.05) Patient Global Assessment (-4 to +4): +2.6 vs. +1.7 (NS) Use of concomitant medications: 80% vs. 88% (NS) Withdrawal (lack of efficacy): 2% (1/53) vs. 7% (4/59)		Alpharma Branded Products Division	

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Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up (%), Analyzed
Niemann, 2000	Randomized open-label controlled crossover trial Denmark Multicenter Outpatient clinics	A: Transdermal fentanyl (titrated) (Mean dose 55.6 mcg/hr) B: Long acting morphine (titrated) (Mean dose 128.3 mg/day) 4 weeks initial intervention followed by 4 week crossover	Patients with opioid treated painful chronic pancreatitis	Not specified	Immediate release morphine tablets of 10 mg (mean dose not reported)	Not reported Not reported 18 enrolled	1/18 (5.6%) 18

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Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Niemann, 2000	Median age=47 years 33.3% female Race not reported Median duration of chronic abdominal pain=9 years Etiology of chronic pancreatitis Alcohol abuse=17(94.4%) Sjogren's syndrome=1(5.6%)	Preference recorded at end of study (assessment method not reported, categorical scale used) Global pain control assessment of last two weeks of trial periods compared to last month prior to study entry (assessment method not reported, categorical scale used) Quality of life assessed using SF-36 questionnaire at end of each 4-week period Side effects assessed using unspecified questionnaire at weeks 1, 2, and 4 of each trial period	FAIR: Method of randomization not reported. Method of treatment allocation not reported. Groups similar at baseline. Prior opioid use provided. Minimal eligibility criteria specified. Open trial. Intention to treat analysis provided. It is not clear how missing data are handled. 17/18 completed trial. No comparison of groups completing trial provided. No loss to follow up. 4 weeks follow-up.

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Evidence Table 1.1. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Niemann, 2000	Fentanyl (A) vs. Long acting morphine (B) **Patient Preference** (n=17): "Preference" or "Strong Preference" 8(47%) A vs. 7(41.2%) B (NS) **Pain Control** "Good" or "Very Good"(n=18): 8(44.4%) (A) vs. 6(33.3%) (B) (NS) **Quality of Life**: A vs B (NS) in physical functioning, general health, role physical, pain intensity, social functioning, mental health, and side effects summary median scores	Number screened not reported. Number eligible not reported. Exclusion criteria not provided. Chronic pancreatitis pain patients.	Janssen Research Foundation	Open-label design. Chronic pancreatitis pain patients. A and B equivalent in pain control; but supramaximal doses of A used, as well as higher doses of rescue morphine IR in the A group

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Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled
Caldwell, 1999	Randomized trial US Multicenter (9) Rheumatology clinics	A: Long acting oxycodone (titrated) B: Short acting oxycodone (titrated) + Acetaminophen C: Placebo Mean dose of oxycodone 40 mg/day 30 days	Adult osteoarthritis patients with moderate to severe daily pain despite regular NSAID use at stable doses and if greater than 1 month of frequent or persistent pain. Osteoarthritis determined using predefined clinical and radiographic criteria.	Involvement in litigation related to pain Intraarticular steroid injection within 6 weeks if injection involved joint being evaluated Contraindication to narcotic use Active cancer, severe organ dysfunction History of substance abuse Also excluded if withdrew during titration phase	Not permitted	Not reported Not reported 167
Gostick, 1989	Randomized trial Crossover Canada Multicenter Number and types of clinics not specified	A: Long acting dihydrocodeine (titrated, 60-120 mg BID) B: Short acting dihydrocodeine (titrated, 30-60 mg QID) Average dose not reported 2 weeks initial intervention with 2 weeks crossover	Chronic back pain due to osteoarthritis of weight bearing joints or chronic back pain	Pregnancy, lactation, contraindication to study medication	Paracetamol 500 mg, up to 8/day	Not reported Not reported 61

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Withdrawals or lost to follow-up, Analyzed	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Caldwell, 1999	36 (34%) 107 60 patients withdrew during titration phase, prior to randomization	Avg. 58 years 68% female 88% white 32%>65 years old 100% osteoarthritis back/neck 49% knee 37% 60% (101/167) on unidentified narcotics prior to study and discontinued at time of enrollment Pain duration average not reported.	**Pain intensity** in target joint (0-4, categorical, none-severe) collected globally at baseline, at end of 4 week titration phase, and at 2 and 4 weeks in RCT. Also collected in diary for 3 days preceding the end of the titration and RCT phases. **Quality of sleep** (1-5, categorical, poor-excellent) collected in a similar fashion as pain intensity.	FAIR: Randomization method not described. Treatment allocation by central randomization technique. At beginning groups similar in gender, age, global pain intensity scores & diary scores. Comparison of prior narcotic use not provided. Global quality of sleep score better at baseline for those randomized to long acting Oxycodone than short acting Oxy (p = 0.0068). Compared with those who did not complete titration phase, only significant difference was more women not randomized. Blinding performed, not evaluated. Intention to treat analysis provided. Differential loss to follow up due to withdrawal. Control group received usual care.
Gostick, 1989	16 (26%) 42	Avg. 52 years 56% female Race not reported Ostheoarthritis 45% Chronic back pain 55% Pain duration not reported	**Pain intensity:** Scale not described. Mean and Maximum scores collected daily **Rescue drug use:** average number of doses used per day **Global efficacy:** Scale not described. **Preference:** Percent preferring each treatment arm at end of study.	Fair: Randomization method not reported. Treatment allocation method not reported. Groups similar at baseline. No differential loss to follow up, therefore likely to be similar at end of trial, though data not supplied. Intention to treat not provided (analyses of 42/61 randomized patients). Blinding of patients and assessors done using identical placebo tablets. Blinding not assessed. Crossover design. Groups received similar care. 2 week follow up per arm.

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Caldwell, 1999	Long acting Oxycodone (A) vs. short acting Oxycodone + acetaminophen (B) vs. Placebo (C) **Pain intensity**: 1.3 (A), 1.3 (B), 2.0 (C) (p < 0.05, A vs. C) (p < 0.05, B vs. C), (NS, A vs. B). (Estimated from graph) **Mean Pain Intensity Increase:** 0.44 (A), 0.49 (B), 1.0 (C) (p < 0.004, A vs. C) (p < 0.004, B vs C) (NS, A vs. B) **Sleep quality**: 3.9 (A), 3.2 (B), 2.6 (C), (p = 0.0382 (A vs B) however, were significantly different from each other at baseline, p < 0.05 (A vs C), p < 0.05 (B vs. C)).	Number screened not reported. Number eligible not reported. Exclusion criteria provided. Osteoarthritis pain patients. High percent of enrollees on narcotics prior to study. Difficult to assess external validity.	Purdue Pharma (Long acting Oxycodone) sponsored this study. 1 author employed by Purdue.	Patients enrolled but not randomized were equal to those randomized except for % female in which greater women were not randomized.
Gostick, 1989	Long acting Dihydrocodeine (A) vs.short acting Dihydrocodeine (B) **Pain intensity (daily average):** 1.75 (A) vs. 1.80 (B); (p NS) **Pain intensity (maximum):** 2.48 (A) vs. 2.33 (B); (p NS) **Rescue drug use:** 1.54 (A) vs. 1.61 (B); (p NS) **Global efficacy:** no difference **Preference**: no difference	Number screened not reported. Number eligible not reported. Exclusion criteria provided. Difficult to assess external validity.	Not specified. One author employed by Napp Pharmecutical, maker of long acting dihydrocodeine.	

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled
Hale, 1997	Randomized trial US 1 or 2 Centers	A: Long acting codeine (fixed) + acetaminophen B: Short acting codeine (titrated) + acetaminophen Mean dose opioid 200 mg/day (A) 71 mg/day (B) 5 days	Patients with chronic low back pain deemed by investigators to be in need of opioid or fixed combination codeine analgesics for control of stable mild to moderately severe pain	18 years and older; no medical contraindication to the use of codeine or acetaminophen	Acetaminophen 325 mg every four hours as needed (group A) or Acetaminophen 325 + codeine 30 mg every four hours as needed (group B)	Not reported Not reported 104
Hale, 1999	Randomized trial Crossover US Multicenter (5) Rheumatology clinics and others	A: Long acting oxycodone B: Short acting oxycodone Mean dose 40 mg/day 4-7 days followed by crossover	Patients at least 18 years old with stable, chronic moderate-to-severe low back pain caused by nonmalignant conditions, on maximum doses of nonopioid analgesics, with or without opioids.	History of substance abuse Involved in litigation regarding back pain condition. Able to achieved stable analgesia within 10 days during titration phase.	Short acting oxycodone 5-10mg/dose as needed	Not reported Not reported 57

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Withdrawals or lost to follow-up, Analyzed	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Hale, 1997	23 (22%) 82	Avg. 52 years 54% female Race not reported Back pain due to Arthritis (33%) mechanical injury (45%) Prior opioid use mentioned but not reported in detail. Pain duration not reported.	**Pain intensity** recorded at baseline and four times a day (0-3 categorical, no pain-severe) **Rescue medication use:** number of doses used.	FAIR: Randomization method not reported. Treatment allocation method not reported. Groups similar at baseline except baseline pain scores higher in group A. RCT blinded. Large overall withdrawal rate (23/104, 22%). Intention to treat not provided (82/104 analyzed). Attrition reported. Crossover and contamination not permitted. Groups received same care, except for type of rescue medication given: group A receieved acetaminophen only while group B received acetaminophen plus codeine. Follow up for 5 days.
Hale, 1999	3 (6%) 47 10 patients withdrew during titration phase. All randomized patients were included in analysis.	Avg. 55 years 51% female Race not reported Back pain due to: 1) intervertebral disc disease 2) osteoarthritis. 88% (50/57) were on unspecified narcotics prior to study Pain duration not reported	**Pain intensity** recorded in daily diary (0-3, categorical, none-severe) in morning, afternoon, evening, bedtime **Rescue drug use**: doses used per day	FAIR: Randomization method not reported. Treatment allocation method not reported. Groups reported to be similar at baseline though data not provided. RCT blinded but success not evaluated. Intention to treat not provided but is calculable. Unclear if maintained similar groups. Attrition reported. Crossovers and contamination not permitted. No differential loss to follow-up. Groups received same care. Follow up for 6 days.

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Hale, 1997	Long acting Codeine + Acetaminophen (A) vs. short acting Codeine + Acetaminophen (B) **Pain intensity:** Daily Pain Intensity Differences Scores: 4.25 (A) vs. 2.0 (B) (p = 0.008) Pain Score Variation: increases 2.0 vs 4.0 (p = 0.032) decreases 2.2 vs. 4.6 (p = 0.006) **Rescue medication use:** Night: 3.0 vs. 4.0 (p=0.032) Day: 1.01 vs. 1.53 (p = 0.018)	Number screened not reported. Number eligible not reported. Exclusion critera provided. Low back pain patients. External validity difficult to assess.	Purdue Frederick sponsored study. 1 author (corresponding) employed by Purdue.	Groups received different rescue medications. Not clear if rescue medication was blinded as well.
Hale, 1999	Long acting Oxycodone (A) vs. short acting Oxycodone (B) **Overall Pain intensity**: 1.2 (A) vs 1.1 (B) (not significantly different). **Mean Pain Intensity**: Slight (A) vs. Slight (B) (not significantly different). **Rescue drug use**: 0.6 doses per day on average (no difference between treatment groups).	Number screened not reported. Number eligible not reported. Exclusion criteria provided. Low back pain pain patients. External validity difficult to assess.	Purdue Pharma sponsored study. 4 authors employed by Purdue.	Titration study results reported in Saltzman. Titration phase randomized but not blinded to short acting or long acting Oxycodone. No information provided about the numbers in each group.

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled
Jamison, 1998	Randomized trial US Single center Pain clinic	A: Long acting morphine + short-acting oxycodone + NSAID B: Short-acting oxycodone + NSAID C: Naproxen Mean dose A: 41.1 mg morphine equivalent/day Mean dose B: Not reported, max 20 mg oxycodone/day Mean dose C: Not reported, max 1000 mg/day 16 weeks	Chronic back pain >6 months duration, age 25 to 65 years, average pain intensiy >40 on scale of 0 to 100, unsuccessful response to traditional pain treatment	Cancer, acute osteomyelitis or acute bone disease, spinal stenosis and neurogenci claudication, nonambulatory, significant psychiatric history, pregnancy, treatment for drug or alcohol abuse, clinically unstable systemic illness, acute herniated disc within 3 months	Permitted, not specified	48 screened Not reported 36 enrolled
Lloyd, 1992	Randomized trial UK multicenter general practice clinics	A: Long acting dihydrocodeine B: Short acting dextropropoxyphene + paracetamol Average dose not reported 2 weeks	Severe hip osteoarthritis diagnosed by xray, hip replacement a future possibility 18 years or older, on dihydrocodeine and/or NSAIDs or expected to benefit from this therapy	COPD, known allergy to study medicine, use of MAOIs within 2 weeks of study, history of alcohol or drug abuse, severe cardiac, hepatic, or renal insufficiency, hypothyroidism, pregnancy, lactation, irregular bowel habits, or current pain medication regimen >240 mg of dihydrocodiene or 8 dextropropoxy-phene/paracetamol per day.	Not permitted	Not reported Not reported 86

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Withdrawals or lost to follow-up, Analyzed	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Jamison, 1998	1 (3%) 36	Avg. 43 years 57% female Race not reported 39% failed back syndrome 25% myofascial pain syndrome 19% degenerative spine disease 14% radiculopathy 3% discogenic back pain Prior opioid use not reported Average pain duration 79 months	**Pain Intensity:** timing not specified, Comprehensive Pain Evaluation Questionnaire **Functional status:** baseline and at end of treatment (SF-36) **Symptom checklist:** baseline and at end of treatment (Symptom Checklist-90) **Weekly activity record** at baseline and once a month **Medication diary** weekly **Overall helpfulness** during titration and at end of study (categorical scale, 0= no help, 10=extremely helpful)	FAIR: Randomization method not described, nor was method of treatment allocation. Open-label. Baseline characteristics for different intervention groups not reported. Appears to be intention-to-treat analysis.
Lloyd, 1992	29 (34%) 60	Avg. 66 years 71% female Race not reported Severe osteoarthritis of the hips Prior opioid use not reported Pain duration average 17 months	**Pain intensity**: 4 times per day (Visual Analogue Scale, 0-100, 0 = no pain) **Night time awakening** due to pain every morning **Pain with passive movement** assessed by investigators at baseline, and each week (categorical scale, 0-4, no pain - severe).	FAIR: Randomization method not described, nor was method of treatment allocation. Groups appear similar at baseline, but differential loss to follow-up occurred and no information provided about the remaining participants. Study reported to be double blind, but no description of method is provided. It is not clear how missing data are handled, though the report says that all measures were fully analyzed to maximize the available data.

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Jamison, 1998	Long acting Morphine + short acting Oxycodone (A) vs. short acting Oxycodone (B) **Average pain (means, 0-100 VAS):** 54.9 vs. 59.8 **Current pain (means, 0-100 VAS):** 51.3 vs. 55.3 **Highest pain (means, 0-100 VAS):** 71.4 vs. 75.5 **Anxiety (means):** 11.2 vs. 15.0 **Depression (means):** 10.8 vs. 16.4 **Irritability (means):** 17.7 vs. 20.5 **Level of activity (means, 0-100 scale):** 49.3 vs. 49.3 **Hours of sleep (means):** 5.9 vs. 5.9	Number eligible not reported. Number on previous narcotics not reported. Difficult to assess external validity.	Roxane Laboratories sponsored study (maker of long-acting morphine and short-acting oxycodone). Not clear if authors employed by Roxane.	Nonequivalent dose of opioids given. Most statistical comparisons involved comparisons across all three groups (including naproxen only arm).
Lloyd, 1992	Long acting Dihydrocodeine (A) vs. short acting Dextropropoxyphene + Paracetamol (B) **Maximum daily pain score (means)**: Week 1: 58.3 (A) vs. 48.6 (B) (NS), Week 2: 49.8 (A) vs. 49.2 (B) (NS); (A) scores significantly different week 1 vs. week 2 (p = 0.05) **Mean daily pain score**: Week 1: 50.1 (A) vs. 38.2 (B) (NS), Week 2: 39.2 (A) vs. 39.8 (B) (NS); (A) week 1 vs. week 2 score significantly different (p = 0.02) **Average nights wakened by pain per week**: NS, although (B) group improved wakening from week 1 to week 2 (p = 0.05). **Pain on passive movement**: (A) group improved pain from wk 1 to wk 3. (p = 0.02). For both treatments more patients improved than worsened.	Number screened not reported. Number eligible not reported. Number on previous narcotics not reported. Osteoarthritis pain. Difficult to assess external validity.	Not reported. However 5th author appears to be an employee of Napp Laboratories (maker of long acting dihydrocodone) and is the correspondence author.	Authors conclude that A improves pain control better than B because A pain control significantly improved at week 3 vs week 1 for treatment group A but not for treatment group B. However, direct week-to-week comparison of these two treatments shows not significant difference in level of pain intensity.

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled
Salzman, 1999	Randomized trial US Multicenter (5) Rheumatology clinics and others	A: Long acting Oxycodone (titrated) B: Short acting Oxycodone (titrated) Titration comparison Mean dose A: 104 mg/day Mean dose B: 113 mg/day 10 days	18 years or older, chronic stable moderate to severe back pain despite analgesic therapy with or without opioids.	Contraindication to opioid history of substance abuse Unable to discontinue non-study narcotic Current oxycodone dose >80 mg/day Titration to 80 mg without achieving pain control.	Short acting oxycodone 5-10 mg/day every 4 hrs. as needed	Not reported Not reported 57

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Withdrawals or lost to follow-up, Analyzed	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Salzman, 1999	10 (18%) 57	Avg. 56 years 54% Female 87% White 13% Hispanic Intervertebral disc disease, nerve root entrapment, spondylolisthesis, osteoarthritis, and other non-malignant conditions 84% (48/57) Pain duration not reported	**Pain Intensity**: daily diary, categorical scale (0-3, none-severe) **Study Medication Use**: daily diary, amount used **Rescue Drug Use**: daily diary, amount used **Achievement of Stable Pain Control**: Stable pain control considered achieved if pain intensity rated as 1.5 or less for 48 hours with no more than 2 doses of rescue medication **Time to Stable Pain Control**: Days	FAIR: Method of randomization not discussed, nor was method of treatment allocation. Intention to treat calculation analysis not performed for primary pain outcome. Groups comparable at baseline, including prior use of opioids. Differential loss to follow up present. No analysis provided of groups that completed study vs. those who dropped out.

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.2. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Salzman, 1999	Long acting Oxycodone (A) vs. short acting Oxycodone (B) **Pain Intensity**: Not significantly different at baseline. **Mean decrease in pain intensity**: 1.1 units (A) vs. 1.3 units (B) (NS) **Acheivment of stable analgesia**: 87% (26) (A) vs. 96% (26) (B) (p = 0.36) 5/47 patients did not achieve stable analgesia: 1 titrated to maximum dose of short acting without control (80 mg); 4 experienced adverse side effects (3 long acting, 1 short acting) **Time to stable pain control**: 2.7 days (A) vs. 3.0 days (B) (p = 0.90). **Mean number of dose adjustments**: 1.1 adjustments (A) vs. 1.7 adjustments (B) (p = 0.58)	Number screened not reported. Number eligible not reported. High percent of enrollees on narcotics prior to study. Back pain. Difficult to assess external validity.	Purdue Pharma sponsored study. 2 authors employees of Purdue. Role not otherwise reported.	This paper reported results of two RCTs, one looking at patients with cancer, the other looking at patients with back pain of non-malignant origin. The presented results are from the non-cancer RCT. This study is the 10 day titration phase that preceded the study reported by Hale.

RCT=randomized controlled trial; NSAID=non-steroidal anti-inflammatory drug; NS=non significant; BID=twice a day; QID=four times a day; COPD=chronic obstructive pulmonary disease; MAOI=Monoamine oxidase inhibitor

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up, Analyzed
Arkinstall. 1995	Randomized trial Crossover Canada Multicenter (4) Clinic types not identified	A: Long acting codeine B: Placebo Mean dose 273 mg/day 7 days initial intervention, followed by crossover	History of chronic non-malignant pain of at least moderate intensity	Hypersensitivity to study medications, intolerance of rescue meds, concomitant use of other opioids, headache, intractable nausea, vomiting, history of substance abuse	Acetaminophen + short acting codeine, 1-2 tabs every 4 hrs. as needed	Not reported Not reported 46	13 (28%) 30
Gilron, 2005	Randomized trial Multiple crossovers Canada Single center Pain clinic	A: Long acting morphine titrated up to 120 mg/day B: Gabapentin C: Long-acting morphine plus gabapentin D: Lorazepam (active placebo) Average dose of morphine 45.3 mg (A) and 34.4 mg (B) 5 weeks initial intervention, followed by crossovers to each of the other three interventions	Diabetic neuropathy or postherpetic neuralgia for three months of more, moderate pain, age 18 to 89	Hypersensitivity to study medications, another severe pain condition, serious mood disorder, history of serious drug or alcohol abuse, pregnancy, lactation, no primary care physician, significant comorbdities	Nonopioid drugs other than gabapentin permitted	86 screened Number eligible not clear 57	16 (28%) 54

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Arkinstall. 1995	Avg. 55.1 years 57% female Race not reported Rheumatologic pain 43% (13) (9 osteo, 2 rheum, 2 other) Back pain 30% (9) Fibromyalgia 13% (4) Other 13% (4) 10% on morphine, 100% on Tylenol with codeine Pain duration average 72 months	**Pain Intensity:** twice daily, visual analogue scale (0-100, none-excruciating) and categorical (0-4, none-excruciating) **Disability Index:** visual analogue scale (0-10, none-complete disability) for 7 measures totaled together **Rescue drug use:** average doses per day **Patient preference:** which arm preferred **Investigator preference:** which arm seemed to provide better control	FAIR: Randomization done by computer. Treatment allocation done by central pharmacist. No report of groups at baseline, thus unable to compare comparability or report if maintained similar groups. Attrition reported. Crossover trial, results of initial intervention not reported. Contamination was not allowed. Groups received similar care except for study drug. Follow up for 7 days per arm.
Gilron, 2005	Avg 60 (diabetic neuropathy) and 68 (PHN) years Female gender: 49% and 36% Non-white race: 3% and 0% Diabetic neuropathy 61% Postherpetic neuralgia: 39% Prior morphine or oxycodone: 9% and 5% Duration of pain: 4.5 and 4.6 years	**Pain intensity:** 0 (none) to 10 (worst pain imaginable) scale **Adverse events** Pain: McGill Pain Questionnaire (0 to 45) Pain-related interference: Brief Pain Inventory (0 to 10) Mood: Beck Depression Inventory (0 to 63) Health status: SF-36 (0 to 100) Mental status: Mini-mental status examination (0 to 30) Global pain relief: 6 point scale (pain worse to complete relief Administered at baseline and during each treatment period when on maximal dose	GOOD. Results adjusted for treatment carryover effects

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Arkinstall. 1995	Long acting codeine (A) vs. placebo (B) **Pain intensity**: 35 vs 49 (p = 0.0001) **Disability index**: 25.0 vs. 35.1 (p = 0.0001) **Rescue drug use**: 3.6 vs. 6.1 (p = 0.0001) **Patient preference**: 73% vs. 10% (p = 0.016) **Investigator preference**: 80% vs. 7% (p = 0.0014)	Number screened not reported. Number eligible not reported. 10% of enrollees on morphine prior to study. Heterogenous pain patients. Difficult to assess external validity.	Purdue Frederick provided a research grant. 3 authors employed by Purdue including the corresponding author.	Patients who wished to continue treatment with long acting codeine after the study were offered this option (28 of 30 accepted).
Gilron, 2005	Long-acting morphine (A) vs. gabapentin (B) vs. long-acting morphine + gabapentin (C) vs. placebo (D) Mean pain intensity (baseline 5.72 +/- 0.23): 3.70 +/- 0.34 vs. 4.15 +/- 0.33 vs. 3.06 +/- 0.33 vs. 4.49 +/- 0.34 (C superior to A, B, and D) Brief Pain Inventory, general activity (baseline 4.7): 3.1 vs. 3.0 vs. 2.9 vs. 4.5 SF-36 Physical functioning (baseline 51.7): 57.8 vs. 61.1 vs. 62.4 vs. 56.0 Beck Depression Inventory (baseline 10.3): 6.7 vs. 6.4 vs. 6.0 vs. 8.5	Neuropathic pain patients. Pain clinic based.	Canadian Institutes for Health Research provided funding; gabapentin provided by Pfizer and morphine by Aventis-Pharma	Results of initial intervention not reported. 44% of patients and 33% of research nurses correctly guessed morphine treatment.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up, Analyzed
Gimbel, 2003	Randomized trial US Multicenter Pain clinic	A: Long-acting oxycodone titrated up to 60 mg bid B: Placebo Average dose 29 mg/day 6 weeks intervention	Chronic (>3 months), at least moderately painful symmetric distal diabetic polyneuropathy documented by Einstein Focused Neurologic Assessment	Unstable or poorly controlled diabetes, chronic pain unrelated to diabetic neuropathy, substance or alcohol abuse within the last 10 years, creatinine >2.5, hepatic dysfunction >3 times the upper limit of normal, active cancer, hypersensitivity to opioids, rapidly escalating pain or recent neurologic deficit, more than 3 doses a day of short-acting opioids within 3 weeks of study, treatment with any long-acting opioid, autonomic neuropathy, need for elective surgery, pregnant or breast-feeding	Opioid rescue not allowed, nonopioid analgesics could only be taken at pre-study doses	Not reported Not reported 160	44 (28%) 159

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Gimbel, 2003	Avg 58.9 years 48% female 16% non-white All diabetic neuropathy Baseline pain intensity mean 7 (out of 10) 12% short-acting opioids (not specified) Pain duration not reported	Primary end points Pain Intensity: numeric analogue scale (0-10, none-high), daily diary Worst pain (0-10) Satisfaction: 1 (not) to 6 (totally satisfied) Sleep: 0 (poor) to 10 (excellent) Recorded daily Secondary end points Brief Pain Inventory, Rand Mental Health Inventory, Sickness Impact Profile, SF-36 Health Survey Administered on days 0 and 42, and on days 14 and 28 (Brief Pain Inventory only)	GOOD

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Gimbel, 2003	Long-acting oxycodone (A) vs. placebo (B) Average pain intensity (change from baseline): -2.0 vs. -1.0, p<0.001 Pain right now (change from baseline): -2.1 vs. -1.1, p=0.002 Worst pain (change from baseline): -2.4 vs. -1.3, p=0.001 Satisfaction with study drug (postbaseline value): 3.4 vs. 2.4, p<0.001 Sleep quality (change from baseline): 1.2 vs. 0.5, p=0.024 Brief Pain Inventory (change from baseline): 9 out of 14 scores significantly improved for A vs. B SF-36, Rand Mental Health Inventory: No significant differences Sickness Impact Profile: 1 of 16 subscales significantly improved for A vs. B	Number screened and eligible not reported. Specific to stable diabetic patients with moderately painful peripheral neuropathy. Pain clinic based.	Purdue Pharma provided funding and one of the authors employed by them.	

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up, Analyzed
Hale, 2007	Parallel-group RCT USA Multicenter Multidisciplinary pain centers	A: Sustained-release oxymorphone q 12 hours , dose based on stable doses achieved during open-label titration (average 81 mg) B: Placebo	>=18 years, moderate to severe chronic low back pain present for at least several hours each day for a minimum of 3 months, taking at least 60 mg/day of morphine (or equivalent) for the two weeks before screening	Not taking adequate contraception, pregnant, lactating, radiculopathy, fibromyalgia, reflex sympathetic dystrophy or causalgia, acute spinal cord compression, severe lower extremity weakness or numbness, bowel or bladder dysfunction secondary to cauda equina compression, diabetic amyotrophy, meningitis, diskitis, back pain caused by secondary infection or tumor, surgical procedure for back pain within 6 months, pain due to cancer, dysphagia or difficulty swallowing tablets, previous exposure to oxymorphone, hypersensitivity to opioid analgesics, history of seizure, ileostomy or colostomy	Sustained-release oxymorphone 5 mg q 4 to 6 hours as needed for first four days, then no more than 2 tabs daily	Number screened not reported 251 eligible and 244 enrolled in open-label titration 143 randomized (70 to sustained-release oxymorphone and 73 to placebo)	3/143 (2%) withdrawal due to protocol violation 76/143 (53%) did not complete trial Number analyzed: 142/143

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Hale, 2007	Mean age: 48 vs. 46 years Female gender: 57% vs. 33% Non-white race: 16% vs. 11% Degenerative disc disease: 43% vs. 32% Osteoarthritis: 23% vs. 14% Baseline pain (0 to 100); 68 vs. 72	Pain: VAS (0 to 100) Patient and physician rating of satisfaction: 5 point scale (1 = poor to 5 = excellent)	SEE APPENDIX E

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Hale, 2007	Sustained-release oxymorphone vs. placebo Pain intensity, change from baseline: +8.7 vs. +31.6 (p<0.001) Patient global rating "very good" or "excellent": 58% vs. 22% (p<0.001) Discontinuation due to lack of efficacy: 11% (8/70) vs. 53% (39/73)		Endo Pharmaceuticals Inc	

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up, Analyzed
Harke, 2001	Randomized trial Two phase study (morphine vs. placebo second phase) Germany Single center Pain clinic	A: Long acting morphine 60-90 mg/day B: Placebo 8 days	Neuropathic pain patients treated successfully with spinal cord stimulation (SCS) with reproducible pain off SCS who agreed to forgo SCS and who completed an RCT looking at carbamazapine vs. placebo.	Heart disease Allergies Current analgesic use Patients were not allowed to receive SCS treatment if MMPI positive for signs of strong psychological and affective components	Not permitted	43 38 38	3 (8%) 35

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Harke, 2001	Avg. 55 years 51% female Race not reported (Please note these statistics are for the 43 pts. who entered the initial RCT.) Radiculitis 39% (17) Peripheral nerve damage 16%(7) Reflex sympathetic dystrophy 15% (7) Postherpetic neuralgia 14% (6) Phantom limb pain 7% (3) Diabetic neuropathy 7% (3) 61% weak opioids 28% strong opioids Pain duration average 13 months	**Pain intensity:** numeric analogue scale (0-10, none-high) recorded every 2 hours **Time to SCS reactivation:** days to reactivation of spinal cord stimulator (SCS)	FAIR: Randomization method not discussed. Treatment allocation concealment not reported. Treatment groups appear similar prior to the RCT conducted before the RCT of interest to this report, however, demographics are not reported for the specific RCT of interest. Unclear if outcome assessor blind. Point estimate and measure of variance provided for "partial responders" but not for total study groups. Results provided in unusual manner creating three groups of very small numbers.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Harke, 2001	Long acting morphine (A) vs. placebo (B) Responders (1 (A) vs. 0 (B)): **Maximum Pain Intensity**: 1 (A) vs. N/A (B) **Time to reactivation**: 13 days (A) vs. N/A (B) Partial Responders: (13 (A) vs. 11 (B)) **Maximum Pain Intensity**: 6.7 (A) vs. 6.1 (B) (p = 0.41) **Time to reactivation**: 53 hrs (A) vs. 43 hrs (B) (p = 0.32) Nonresponders: (6 (A) vs. 4 (B)) **Maximum Pain Intensity**: 8.3 (A) vs. 8.3 (B) **Time to reactivation**: 4.3 hrs (A) vs. 3.3 hrs (B)	Number screened reported. Number eligible reported. A fair number of enrollees on narcotics prior to this study. Neuropathic pain patients.	Not reported	The method used to report the results is unusual and makes interpretation difficult.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up, Analyzed
Huse, 2001	Randomized trial Crossover Germany 1 center Pain clinic	A: Long acting morphine (individually titrated) (70-300 mg/day) B: Placebo Average dose not reported 4 weeks initial intervention followed by crossover	Unilateral amputees with phantom limb pain with an intensity of at least 3 out of 10 between ages 18-75	Neurological and psychiatric disorders, the presence of severe illness, pregnancy or breast-feeding, women with insufficient contraceptive protection, and presence of morphine-specific risk factors (allergy, heightened brain pressure, hypotension with hypovolemia, hyperplasia of the prostate, biliary disease, obstructive or inflammatory bowel disease, pheochromocytoma, and hypothyreosis)	Aspirin and paracetamol up to 6 times per day as needed.	12 12 12	0 (0%) 12

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Huse, 2001	Avg. 50.6 years 16% female Race not reported Phantom Limb Pain 2 upper limb 9 lower limb 1 both Prior opioid use not reported 16 years since amputation	**Pain intensity**: visual analogue scale (0-10, none at all-extreme) collected hourly. In addition, sensory and affective pain were also collected on a similar scale at the end of each treatment period. **Treatment responders**: defined as those who showed a greater than 50% reduction in pain; partial responders showed some reduction, nonresponders had no reduction	FAIR: Randomization method not reported. Treatment allocation concealment adequate. Baseline statistics of treatment groups not reported. Not clear how many people were initially recruited for study nor how many people were included in the calculations. Blinding technique used included identical medications. However, both patients and physicians were reliably able to predict when they were on MST.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Huse, 2001	Long acting morphine (A) vs. placebo (B) **Pain intensity**: less during A than baseline 3.26 (A) vs. 4.65 baseline, general, p < 0.01 0.80 (A) vs. 1.49 baseline, affective, p < 0.01 0.71 (A) vs. 2.00 baseline, sensory, p < 0.001 less during A than B 3.26 (A) vs. 3.99 (B), general, p=0.036 0.80 (A) vs. 1.57 (B), affective p < 0.001 0.71 (A) vs. 1.73 (B), sensory p < 0.01 B not different than baseline 3.99 (B) vs. 4.65 baseline, general, p = 0.026 1.57 (B) vs. 1.49 baseline, affective, p NS 1.73 (B) vs. 2.00 baseline, sensory p NS **Treatment responders:** 42% (A) vs 8% (B) treatment responders (p< 0.05) 8% (A) vs. 8% (B) partial treatment responders (p NS) 50% (A) vs. 84% (B) nonresponders (p=0.08) No effect on psychological variables.	Number screened reported. Number eligible reported. No report of prior narcotic use. Highly specific pain population. Pain clinic based.	Mundipharma (maker of MST Morphine) and Deutsche Forschungs-gemeinschaft provided funding.	Authors tested whether enrollees and physicians knew which drug the patient was on and found that both were able to reliably predict active treatment, but did not find an association between treatment outcome expectancy and positive treatment effect.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up, Analyzed
Katz, 2007	Parallel-group RCT USA Multicenter Clinical setting not reported	A: Sustained-release oxymorphone 5 mg q 12 hours for 2 days followed by dose titration if necessary B: Placebo Mean dose 39 mg/day	>=18 years, opioid-naïve (<5 mg oxycodone or equivalent for 14 days prior to screening), initial pain intensity >=50 on 100 point VAS, moderate to severe chronic low back pain daily for at least several hours per day for >=3 months	Reflex sympathetic dystrophy or causalgia, acute spinal cord compression, cauda equina compression, acute nerve root compression, other exclusion criteria as listed for Hale 2005	NSAIDs and other stabilized analgesics (other than opioids or acetaminophen) allowed	Number screened not reported 326 eligible and 325 enrolled in open-label titration 205 randomized (105 to sustained-release oxymorphone and 100 to placebo)	87/205 (42%) did not complete trial 205/205 (100%) analyzed for main outcome; 68% analyzed for other outcomes 6/205 (3%) withdrawal due to protocol violation

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Katz, 2007	Mean age: 51 vs. 48 years Female gender: 56% vs. 50% Non-white race: 11% vs. 9% Average pain intensity: 12.2. vs. 11.3 Degenerative disc disease: 32% vs. 28% Osteoarthritis: 25% vs. 29% Baseline pain (0 to 100): 71 vs. 68	Pain: VAS (0 to 100) Time to discontinuation due to lack of efficacy Patient and physician global rating Adjective Rating Scale for Withdrawal Clinical Opiate Withdrawal Scale	SEE APPENDIX E

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Katz, 2007	Sustained-release oxymorphone vs. placebo Pain intensity, change from baseline: 26.9 vs. 10.0 (p<0.0001) Proportion with >=30% decrease in pain intensity: 93% (66/71) vs. 72% (34/47) (p=0.002) Proportion with >=50% decrease in pain intensity: 86% (61/71) vs. 55% (26/47) Patient global rating good, very good, or excellent: 82% vs. 42% vs2% (p<0.0001) Discontinuation due to lack of efficacy: 11% (12/105) VS. 35% (35/100)		Endo Pharmaceuticals Inc	

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up, Analyzed
Kivitz, 2006	Parallel-group RCT USA Multicenter Clinic setting not reported	A: Sustained-release oxymorphone 10 mg q 12 hours B: Sustained-release oxymorphone 20 mg q 12 hours x 1 week, then 40 mg q 12 hrs x 1 week C: Sustained-release oxymorphone 20 mg q 12 hours x 1 week, then 50 mg q 12 hrs x 1 week D: Placebo	>=18 years, osteoarthritis (based on specific diagnostic criteria including radiographic evidence), regularly took acetaminophen, NSAIDs, or opioid analgesics for 90 days before screening with suboptimal response, on birth control or sexually abstinent if a premenopausal woman	Concomitant bone/musculoskeletal disease, history of seizure, knee or hip arthroplasty within 2 months, difficulty swallowing medication, history of substance of alcohol abuse, investigational drug use within 1 month, corticosteroid therapy within 2 months, intra-articular visco-supplementation within past 3 to 6 months, intolerance to opioids	Not allowed	516 screened 408 eligible 370 randomized (95 to controlled release oxymorphone 10 mg bid, 93 to controlled release oxymorphone 40 mg bid, 91 to controlled release oxymorphone 50 mg bid, 91 to placebo)	172/370 (46%) did not complete trial Number analyzed: 357/370 (96%) 1 withdrawal due to protocol violation

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Kivitz, 2006	Mean age: 63 vs. 62 vs. 62 vs. 60 years Female gender: 68% vs. 62% vs. 54% vs. 57% Non-white race: 14% vs. 6% vs. 9% vs. 11% Duration or severity of baseline pain: Not reported 25-40% on weak opioids prior to trial entry	Pain: VAS (0 to 100) WOMAC (pain, stiffness, physical function subscales and composite index) SF-36 Chronic Pain Sleep Inventory (0 to 100)	SEE APPENDIX E

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Kivitz, 2006	Sustained-release oxycodone 10 mg vs. 40 mg vs. 50 mg vs. placebo Pain (VAS, 0 to 100), change from baseline, least squares mean: -21 vs. -28 vs. -29 vs. -17 (p 0.012 and p=0.006 for 40 mg and 50 mg vs. placebo; no significant difference between 40 mg and 50 mg arms) WOMAC Composite Index (0 to 2400), change from baseline: -350 vs. -370 vs. -450 vs. -160 (estimated from graph; all oxycodone groups p<0.025 vs. placebo) WOMAC Physical Function score (0 yo 1700): -230 vs. -260 vs. -320 vs. -110 (estimated from graph, p<0.025 for all oxycodone groups vs. placebo) SF-36 Physical Component Summary, change from baseline: +3.9 vs. +4.6 vs. +3.6 vs. -0.1 (p<0.001) Chronic Pain Sleep Inventory, change from baseline: -17 vs. -22 vs. -24 vs. -12 (p<=0.05 for 40 mg and 50 mg vs. placebo) Withdrawal due to lack of efficacy: 7% (7/95) vs. 5% (5/93) vs. 4% (4/91) vs. 16% (15/91)		Endo Pharmaceuticals Inc and Penwest Pharmaceuticals Co	Duration and severity of baseline pain unclear

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up, Analyzed
Langford, 2006	Parallel-group RCT Europe and Canada Multicenter Clinical setting not reported	A: Transdermal fentanyl 25 mcg/hr, titrated to maximum 100 mcg/hr B: Placebo 1 week run-in period (no change in therapy), 6 week intervention Median dose of transdermal fentanyl: 1.7 patches/day	>=40 years, meet ACR criteria for hip or knee osteoarthritis, requiring joint replacement surgery, radiographic evidence of disease in affected joints, pain >3 months, >20 days each month, average pain >50 on 100 point scale	Receipt of strong opioid in last 4 weeks, recently started new therapy, deemed unsuitable for opioid	Acetaminophen up to 4 gm/day	553 screened Number eligible not reported 416 randomized (allocation only reported for 399, 202 to transdermal fentanyl and 197 to placebo)	217/416 (52%) did not complete trial Number analyzed: 399/416

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Langford, 2006	Mean age: 66 vs. 66 years Female gender: 65% vs. 68% Non-white race: Not reported Baseline pain score (0 to 100 mm): 73 vs. 73 Duration of pain: Not reported Knee osteoarthritis: 52% vs. 54% 88% on weak opioids prior to trial entry	Pain: VAS (0 to 100) WOMAC (normalized to 0 to 10) SF-36 Investigator assessed pain control, side effects, convenience of use, overall impression of treatment Patient-assessed questionnaire (10 items, each on a 5 point Likert scale) Short Opiate Withdrawal Scale: 10 items, each scored 0 to 3	SEE APPENDIX E

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Langford, 2006	Transdermal fentanyl vs. placebo (changes from baseline) VAS pain score (0 to 100): -23.6 vs. -17.9 (p=0.025) WOMAC Overall score (normalized to 0 to 10): -3.9 vs. -2.5 (p=0.009) WOMAC Pain score (0 to 10): -1.5 vs. -0.8 (p=0.001) WOMAC Physical Functioning score (0 to 10): -1.1 vs. -0.7 (p=0.064) SF-36, Physical component: +3.4 vs. +2.4, p=0.171 SF-36, Mental component: -0.9 vs. +1.1 , p=0.041 SF-36, Pain index: +11.4 vs. +7.1 (p=0.047) Discontinuation due to lack of efficacy: 7% (15/202) vs. 32% (64/197)		Janseen-Cilag	Population restricted to those needing surgery and failing weak opioids.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up, Analyzed
Maier, 2002	Randomized trial Crossover Germany Multicenter (8) Pain clinic	A: Long acting morphine (20 mg/day titrated up to 180 mg/day) B: Placebo Median daily dose 100 and 103 mg/day 1 week intervention followed by crossover	Neuropathic pain, nociceptive pain from chronic pancreatitis or from vertebral lesions and pain >5 on Numerical Rating Scale despite pretreatment (not including potent opioids)	Significant pulmonary or other comorbidities and pregancy	Non-opioids and co-analgesics allowed; step II opioids also allowed	997 Not reported 49	12 (24%) 48 included in ITT analyses

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Maier, 2002	Avg. 52.3 years 54% female Race not reported 4 postherpetic neuralgia 11 neuralgia 12 radiculopathy or neuropathy 6 other neuropathic pain 12 low back pain 3 other nociceptive pain Prior opioid use not reported Average 9.5 (group I) and 7 years (group II) pain duration	**Pain intensity:** Numeric rating scale (0=none to 10=worst pain imaginable) **Tolerability of pain:** 7 point scale (no pain to not bearable) **Sleep quality:** Visual rating scale (1 to 5) **Physical fitness:** Numeric rating scale (0 to 10) **Pain disability index:** Numeric rating scale (0 to 10) **Mental state and mood:** Numeric rating scale (0 to 10) **Depression scale:** Scale not specified **Symptoms intensity:** 20 symptoms, scored 0 (no) to 3 (severe) and summed (0 to 60) **Side effects:** Visual rating scale 0 (none) to 3 (severe)	FAIR: Not clear if randomization adequate ("random generator") and allocational concealment not described. Baseline characteristics not reported to test randomization. High loss to follow-up in patients randomized to morphine first after crossover to placebo compared to patients on placebo first. Blinding technique not adequately described and >87% of patients and investigators able to recognize morphine.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Maier, 2002	Morphine (A) vs. Placebo (B) **Responder (pain relief at least 50% or pain intensity <5 on 10 point scale, tolerability of pain 3 or lower 0 to 6 scale, and adverse effects tolerable or controlled by medication):** 11/25 (44%) vs. 0/23 (0%) after 1 week Other outcomes not reported prior to crossover	Small proportion of patients eligible for trial entered. Had to fail other treatments before enrollment.	Munidipharma GmbH provided funding.	Most patients and investigators knew when they were receiving morphine.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up, Analyzed
Markenson, 2005	Parallel-group RCT USA Multicenter Clinic setting not reported	A: Sustained-release oxycodone 10 mg q 12 hours, titrated to maximum 60 mg q 12 hours B: Placebo Up to 90 days intervention	Meet ACR criteria for osteoarthritis, moderate to severe pain for at least 1 month, pain rated 5 or greater on 10 point scale, on NSAIDs or acetaminophen for at least 2 weeks (or NSAID-intolerant or high risk for adverse events) or on <=60 mg oxycodone/day	Allergy to opioids, scheduled to have surgery, unstable coexisting disease or active dysfunction, active cancer, pregnant or nursing, past or present history of substance abuse, involved in litigation related to their pain, received intra-articular or intramuscular steroid injections involving the joint or site under evaluation within 6 weeks prior to baseline	Could continue usual NSAID or acetaminophen	Number approached and eligible not reported 109 randomized (56 oxycodone, 53 placebo)	1 withdrawal due to protocol violation 73/109 (67%) did not complete trial Number analyzed: 107/109 (98%)

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Markenson, 2005	Mean age: 62 vs. 64 years Female gender: 68% vs. 78% Non-white race: 7% vs. 6% Prior opioid use: 54% vs. 65% Baseline average pain intensity (Brief Pain Inventory): 6.9 vs. 6.3 Baseline composite score from WOMAC Osteoarthritis Index: 64.7 vs. 63.8 Knee osteoarthritis: 32% vs. 26% Prior opioid use: 54% vs. 65%	Brief Pain Inventory (0 to 10) WOMAC (pain, stiffness, physical function) (0 to 100) Patient Generated Index (PGI): 6 areas of function, each rated 0 to 100 Patient-reported satisfaction with medication (0 to 10) Patient-reported acceptability of medication (1 to 6)	SEE APPENDIX E

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Markenson, 2005	Sustained-release oxycodone vs. placebo (changes from baseline) Brief Pain Inventory (0 to 10), average pain intensity at day 90: -1.7 vs. -0.6 (p=0.024) WOMAC Pain (0 to 100) , at 60 days: -17.8 vs. -2.4 (p<0.05) WOMAC Physical Function (0 to 100), at 60 days: -17.1 vs. -3.8 (p<0.05) WOMAC Stiffness (0 to 100), at 60 days: -21.7 vs. +0.1 (p<0.001) WOMAC Composite Index (0 to 100), at 60 days: -18.9 vs. -2.1 (p<0.05) Proportion experienced >=30% pain relief at 90 days: 38% vs. 17.6% (p=0.031) Proportion experiencing >=50% pain relief at 90 days: 20% vs. 5.9% (p=0.045) Brief Pain Inventory, Function composite: -1.9 vs. -0.4 (p=0.001) Patient Generated Index, primary activity, at day 45: 51.2 vs. 39.7 Withdrawal due to inadequate pain control: 16% vs. 67% (p<0.001)		Purdue Pharma	

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up, Analyzed
Morley, 2003	Randomized trial U.K. 1 center Pain clinic	A: Methadone 5 mg bid or 10 mg bid B: Placebo Phase I: methadone 5 mg bid or placebo every other day, with no treatment in between, for 20 days Phase II: methadone 10 mg bid or placebo every other day, with no treatment in between, for 20 days	Age 18-80 years with neuropathic pain, who were able to understand the trial assessments	Pregnant or lactating, known hypersensitivity to opioids or a history of alcohol or drug abuse.	Not specified	Not reported 33 19	8 (42%) 11 completed both phases

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Morley, 2003	Avg. 57.0 years 32% female Race not reported 3 post-herpetic neuralgia 4 diabetic polyneuropathy 2 post-stroke pain 3 sciatica or radiculopathy 7 other neuropathic pain 8/19 (42%) previously on opioid analgesic	**Pain Intensity**: Neuropathic Pain Scale (NPS) of Galer and Jensen completed after each phase and visual analogue scale (0-100, 100=worst) completed daily	FAIR: Not clear if randomization adequate (eight replications of a Latin Square Design) and allocation concealment not described. Baseline characteristics not reported to test randomization. Unusual study design where patients received methadone or placebo during each phase of the study, randomly, only every other day. High loss to follow-up prior to Phase II.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Morley, 2003	Methadone (A) vs. Placebo (B) **Mean intensity of relief (difference between methadone and placebo)**: 5.07 (p=0.064) for Phase I and 9.07 (p=0.015) for Phase II	Number screened not reported. High proportion of eligible patients declined to participate. Majority of patients on prior narcotics. Heterogeneous patients with neuropathy. Pain center based. Trial design different from clinical practice.	Stanley Thomas Johnson Foundation provided funding.	Patients reported improved pain relief with methadone on days methadone taken. Trial design not similar to clinical practice (methadone or placebo given on alternate days randomly, with no intervention on in-between days).

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up, Analyzed
Moulin, 1996	Randomized trial Crossover Canada 1 center Pain clinic	A: Long acting morphine (titrated) B: Benztropine (titrated) Mean daily dose 83 mg/day 6 weeks initial intervention followed by crossover	Age 18-70 referrals to pain clinic, stable non-malignant pain for at least 6 months, moderate or greater in intensity for last week, regional pain of a myofascial, musculoloskeletal or rheumatic nature, failure to respond to NSAIDs and at least one tricyclic anti-depressant	Women of childbearing age had to be on effective birth control. History of drug or alcohol abuse, history of psychosis or major depression, neuropathic pain syndromes including reflex sympathetic dystrophy, isolated headache syndromes, congestive heart failure, history of MI in past year, allergy to morphine or codeine, history of asthma, epilepsy, hepatic or renal disease, history of use of major opioid (oxycodone, morphine, hydromorphone), history of codeine use OK.	Paracetamol 500 mg every 4 hrs as needed	Not reported 103 61	18 (30%) 46

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Moulin, 1996	Avg. 40.4 years 59% female Race not reported 12.9 years average education 25% employed 23 head, neck, shoulder pain, 21 low back pain 9 hip, or knee pain 5 neck and back pain 1 TMJ and coccygial 85% injury related 60/61 on codeine prior to study Pain duration average 4.1 years	**Mean Pain Intensity**: visual analogue scale (0-10, 10=worst) completed weekly **Mean Pain Rating Index**: visual analogue scale (0-100, 100 worst) completed weekly **Mean Pain Relief**: visual analogue scale (0-10, 10=worst) completed weekly **Functional Status**: Pain Disability Index completed weekly (no other details provided) **Rescue drug use**: average daily number of rescue drug used per day completed daily	FAIR: Randomization method not described. Treatment allocation method not mentioned. Study groups compared in terms of demographics and previous narcotic usage. Blinding done using identical tablets. Study evaluated the success of blinding. It was not successful.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Moulin, 1996	Long acting morphine (A) vs. Benztropine (B) **Mean Pain Intensity:** 6.5 (A) vs. 7.5 (B) (p < 0.01) (values estimated from graph) **Mean Pain Rating Index**: 45 (A) vs. 45 (B) (p NS) (values estimated from graph) **Mean Pain Relief**: 2.75 (A) vs. 2.25 (B) (p NS) (values estimated from graph) **Functional Status**: no significant difference (values not provided) **Mean Daily Rescue Drug Use**: 3.5 (A) vs 3.9 (B) (p=0.40) The study found evidence of a carry-over effect between arms therefore only the results from first arm were reported.	Number screened not reported. Number eligible reported. Majority of patients on prior narcotics. Heterogenous pain patients. Pain center based.	Purdue Frederick provided funding. Medical Research Council of Canada provided funding.	According to the authors, benztropine has no analgesic properties but mimics many of the possible side-effects of morphine (sedation, lightheadedness, nausea, dry mouth, constipation, urinary hesitancy).

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up, Analyzed
Peloso, 2000	Randomized trial Canada Multicenter (4) Hospital based	A: Long acting codeine B: Placebo Average final dose 318 mg/day 4 weeks	Primary osteoarthritis pain, >35 years old, requiring use of acetaminophen, or other medication use for at least 3 months. Patients were required to DC previous medication and had to experience a flair in pain to be eligible.	Pregnancy; Known allergy to codeine, other opioid or acetaminophen; History of drug seeking behavior; Secondary OA; Steroid use in past 2 months; Intraarticular viscosupplementation in past 5 months; Grade 4 OA awaiting replacement.	Acetaminophen 650 three times a day as needed	Not reported Not reported 103	37 (36%) 66

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Peloso, 2000	Avg. 61.6 years 62% female Race not reported 88% (58) knee pain 48% (32) hip pain (some enrollees have both) 13% on Codeine prior to study Pain duration average 10 years	**Daily Pain Intensity**: visual analogue scale (0-500, 500=extreme pain) collected daily **Weekly Pain Intensity**: visual analogue scale (0-100, 100=extreme pain) collected weekly **Pain over last 24 hours**: visual analogue scale (0-100, none-extreme) **Stiffness**: visual analogue scale (0-100, none-extreme) **Physical Function**: visual analogue scale(1-1700, no limitations-extreme limitations) **Trouble falling asleep**: visual analogue scale (0-100, no problems-extreme difficulty) **Need Medication to sleep**: visual analogue scale (0-100, never-always) **Pain on awakening**: visual analogue scale (0-100, none-extreme) **Rescue drug use**: average daily drug use	FAIR: Randomization method not described. Treatment allocation method not mentioned. Groups similar at baseline, nicely presented and described. No differential loss to follow-up occurred. Blinding achieved through use of identical placebo tablets. No assessment of success of blinding.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Peloso, 2000	Long acting codeine (A) vs. placebo (B) **Average Daily Pain Intensity**: 145.4 (A) vs. 221.3 (B) (p = 0.0004) **Weekly Pain Intensity**: 29.4 (A) vs. 47.8 (B) (p = 0.0001) **Pain over last 24 h**: 32.5 (A) vs. 47.7 (B) (p = 0.0001) **Stiffness**: 66.2 (A) vs. 87.1 (B) (p=0.003) **Physical function**: 456.2 (A) vs. 687.5 (B) (p=0.0007) **Trouble Falling Asleep**: 11.2 (A) vs. 23.8 (B) (p = 0.022) **Need Medication to Sleep**: 9.3 (A) vs. 22.3 (B) (p = 0.0039) **Pain on Awakening**: 21.5 (A) vs. 30.9 (B) (p=0.02321) **Rescue drug use**: 4.2 (A) vs. 9.2 (B) (p=0.005) **Global assessment score**: 2.1 (A) vs. 0.9 (B) (p=0.0001)	Number screened not reported. Number eligible not reported. A minority of patients on prior narcotics. Osteoarthritis pain patients. Difficult to assess external validity	No mention of funding is made. Purdue Frederick (maker of long acting codeine) employs 2 of the authors.	

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up, Analyzed
Roth, 2000	Randomized trial US Multicenter (7) Rheumatology clinics	A1: Long acting oxycodone 20 mg every 12 hours A2: Long acting oxycodone 10 mg every 12 hours B: Placebo 14 days	Patients with >1 month history of osteoarthritis clinically and radiographically	Severe organ dysfunction History of drug or alcohol abuse	Not permitted	Not reported Not reported 133	70 (53%) 133

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Roth, 2000	Avg. 62 years 74% female Race not reported 46% back 31% knee 61% (81/133) on unspecified opioids prior to study Pain duration average 9 years	**Pain intensity**: categorical scale (0-3, none-severe) daily; a 20% reduction in pain considered successful. **Achievement of successful pain reduction**: % achieving 20% reduction in pain from baseline **Quality of sleep**: categorical (1-5, very poor-excellent) daily, reported as "improvement from baseline" **Brief Pain Inventory**: visual analogue scale (0-10, 10=extreme) at baseline and Q week to assess pain intensity and function, reported as "improvement from baseline"	FAIR: Randomization technique not reported. Treatment allocation concealment by pharmacist. Groups similar at baseline, but do not report % of persons in each group who took and discontinued narcotics. Time delay between discontinuation of previous narcotics and beginning of trial not specified. Eligibility criteria specified. Outcome assessors, care providers, and patients all blinded, though effectiveness of blinding not evaluated. Attrition reported. High overall loss to follow-up: 70/133 (53%) did not complete trial. No report on whether those completing trial were similar to those who did not. Groups received similar care. No differential loss to follow up, though reasons for loss from each treatment group are different.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Roth, 2000	Long acting oxycodone 20 mg(A1) vs. Long acting oxycodone 10 mg (A2) vs. placebo (B) **Achievement of successful reduction in pain**: A1: Achieved at day 1 A2: Achieved at day 2 B: Never achieved **Mean Pain Intensity**: (estimated from graph) 1.6 (A1) vs. 1.9 (A2) vs. 2.2 (B) ($p < 0.05$, A1 vs. B) **Quality of Sleep**: A1 better than B ($p < 0.05$, A1 vs. B) **Brief Pain Inventory**: (values estimated from graph) Pain right now: A1 better than B ($p < 0.05$) Worst Pain: A1 better than B ($p < 0.05$) Average Pain: A1 better than B ($p < 0.05$) Mood: 3.1 (A1) vs. 1.7 (A2) vs. 0.7 (B) ($p < 0.05$, A1 vs. B) Sleep: 3.2 (A1) vs. 1.7 (A2) vs. 1.2 (B) ($p < 0.05$, A1 vs. B) Life Enjoyment: 2.6 (A1) vs. 1.7 (A2) vs. 0.6 (B) ($p < 0.05$, A1 vs. B)	Number screened not reported. Number eligible not reported. Majority on prior narcotics. Osteoarthritis pain patients. Rheumatology clinic based. Difficult to assess external validity.	Purdue Pharma (LA Codeine) provided funding. 1 author employed by Purdue (corresponding author). Role not otherwise specified.	Trial had open-label extension for up to 18 months for patients who wished to participate

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up, Analyzed
Rowbotham, 2003	Randomized trial U.S.A. 1 center (1) Pain clinic	A: Levorphanol 0.75 mg up to 7 tabs tid B: Levorphanol 0.15 mg up to 7 tabs tid Mean doses 8.9 mg/day versus 2.7 mg/day 4 weeks intervention, with 4 weeks titration and 4 weeks taper	Adults with confirmed neuropathic pain due to defined conditions (peripheral neuropathy, focal nerve injury, postherpetic neuralgia, spinal cord injury, stroke or focal brain lesion, or multiple sclerosis)	Previous opioid therapy exceeding equivalent of 360 mg of codedin/day, allergy to levorphanol, another server pain problem, cognitive impairment, significant psychiatric illness, significant other medical condition, immunosuppression, current drug or alcohol abuse, history of opioid abuse	Not specified	Not reported 100 81	22 (27%) 81 (100%) analyzed
Watson, 1998	Randomized trial Crossover Canada 1 center (1) Pain clinic	A: Long acting oxycodone (titrated) B: Placebo Mean final dose 45 mg/day 4 weeks initial intervention followed by 4 week crossover	Patients referred to pain specialist with postherpetic neuralgia of at least 3 months duration and pain intensity of at least moderate for half or more of the day	Hypersensitivity to opioids; Intolerance to oxycodone; History of drug or alcohol abuse; Pain of significant alternate etiology	Not permitted	Not reported Not reported 50	11 (22%) 38

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Rowbotham, 2003	Avg. 65 vs. 64 years 51% female 12% non-white race 8 multiple sclerosis 5 spinal cord injury 10 post-stroke or focal brain lesion 26 post-herpetic neuralgia 32 peripheral neuropathy or focal peripheral nerve injury Mean duration of pain 86 vs. 75 months Previous opioid treatment 15% vs. 22%	**Pain Intensity**: visual analogue scale (0-100, 100=worst) daily **Pain Relief**: cateogical scale (0-5, 5 'complete' pain relief) **Mood Disturbance**: Profile of Mood States (65 items) **Effects of Pain on Quality of Life**: Multidimensional Pain Inventory (61 items) **Attention or Concentration**: Symbol-Digit Modalities Test **Agonist and Antagonist Activity**: Opiate-Agonist Effects Scale (16 items) and Opiate Withdrawal Scale (21 items)	FAIR: Methods of randomization and allocation concealment not described, blinding methods not described. High loss to follow-up, but all enrolled patients analyzed.
Watson, 1998	Avg. 70 years 58% female Race not reported Postherpetic neuralgia 63% thoracic 26% trigeminal 5% cervical 3% other 45% on narcotis prior to study Pain duration average 31 months	**Pain Intensity**: visual analogue scale (0-100, 100=unbearable) and categorical scale (0-4, no pain-unbearable) recorded daily in a diary **Pain relief:** categorical scale (0-6, 0=pain worse-5=complete relief) collected daily in a diary **Steady Pain, Paroxysmal Pain, Allodynia:** each assessed weekly using pain intensity and pain relief scales. **Disability:** categorical scale (0-3, no disability-severe disability) assessed weekly **Treatment Effectiveness:** categorical scale (0-3, not effective-highly effective) assessed weekly **Affective state**: assessed weekly using POMS and BDI. **Preference:** Patients asked after trial which treatment arm preferred.	FAIR:Method of randomization not described. Treatment allocation appears to have been blind (blocked in sets of 4). Comparison of groups at baseline not provided, however, is crossover design in which enrollee serves as their own control. Blinding performed with identical placebo tablets. Adequacy of blinding not assessed. No differential loss to follow-up.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Rowbotham, 2003	High-dose levorphanol (A) vs. low-dose levorphanol (B) Pain intensity reduction (percent improvement in VAS): 36% vs. 21% (p=0.02) Pain relief: No difference at week 8, categorical scale Mood disturbance and cognitive impairment: No differences in Profile of Mood States or Symbol-Digt Modalities Test Quality of Life: No differences in Multidimensional Pain Inventory	Number screened not reported. Some enrollees on prior opioids. Pain clinicbased.	National Institue on Drug Abuse and the National Institue of Neurological Disorders and Stroke	
Watson, 1998	Long acting Oxycodone (A) vs. placebo (B) **Mean daily pain intensity**: 35 (A) vs. 54 (B) (p=0.0001) VAS 1.7 (A) vs. 2.3 (B) (p=0.0001) categorical **Pain relief**: 2.9 (A) vs. 1.9 (B) (p=0.0001) **Steady pain**: 34 (A) vs. 55 (B) (p=0.0001) VAS 1.6 (A) vs. 2.3 (p=0.0001) categorical **Allodynia:** 32 (A) vs. 50 (B) (p=0.0001) VAS 1.6 (A) vs. 2.0 (B) (p=0.0155) **Paroxysmal pain:** 22 (A) vs. 42 (B) (p=0.0001) VAS 1.2 (A) vs. 1.9 (B) (p=0.0002) categorical **Disability**: 0.3 (A) vs. 0.7 (B) (p=0.041) **Treatment effectiveness:** 1.8 (A) vs. 0.7 (B) (p=0.0001) **Affective state:** No differences. **Patient preference:** 67% (A) vs. 11% (B) (p=0.001)	Number screened reported. Number eligible not reported. A substantial number of enrollees were on narcotics prior to study. Postherpetic neuraliga. Pain clinic based.	Purdue Frederick provided a research grant. 1 authors is employed by of Purdue Frederick.	No report given of differences between study groups because patients served as their own controls. Analyzed for carry-over effect: none found.

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Type of study, Setting	Interventions Dose Duration	Eligibility criteria	Exclusion criteria	Rescue drug	Screened Eligible Enrolled	Withdrawals or lost to follow-up, Analyzed
Watson, 2003	Randomized trial Crossover Canada 2 centers (2) Pain clinics	A: Long acting oxycodone (titrated from 10 mg q 12 hrs) B: Benztropine (active placebo) Mean final dose 40 mg/day 4 weeks initial intervention followed by 4 week crossover	Diabetes mellitus with stable control and with painful symmetrical distal sensory neuropathy	Intolerance to oxycodone, history of drug or alcohol abuse, significant pain of alternate etiology	Acetaminophen 325-650 mg q 6 hrs	204 55 45	9 (20%) 36
Zautra, 2005	Parallel-group RCT USA Multicenter Clinic setting not described	A: Sustained-release oxycodone 10 mg q 12 hours, titrated up to 120 mg/day B: Placebo	Osteoarthritis as defined by American College of Rheumatology guidelines, pain for at least 1 month with score >5 (>3 if on opioid)	>60 mg/day of oxycodone equivalent, allergic to opioids, scheduled for surgery, unstable coexisting disease or active severe organ dysfunction, active cancer, pregnant or breast-feeding, prior or present history of substance abuse, intra-articular or intramuscular steroid injections involving the joint under evaluation within 6 weeks	Not permitted (stable regimens of non-opioids allowed)	Number approached and eligible not reported 107 randomized (56 to sustained-release oxycodone, 51 to placebo)	71/107 (66%) 104/107 (97%) analyzed

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Overall rating and comments
Watson, 2003	Avg. 70 years 47% female Race not reported Prior opioid use not reported 53% on non-opioid analgesics	**Pain intensity**: visual analogue scale (0-100, 100=worst pain) and categorical (0-4, 4=worst) scale **Pain relief**: 0-5 (5=worse) categorical scale **Pain-related disability**: Pain Disability Index **Health-related status**: Short-Form 36 **Impact of pain on sleep**: Pain and Sleep Questionnaire **Effectiveness and Preference**: Patients and investigators rated each at end	FAIR:Method of randomization and allocation concealment (blocked in sets of 4) appear blind. Comparison of groups at baseline not provided, however, is crossover design in which enrollee serves as their own control. Not clear how blinding performed with benztropine (active control) and testing of blinding showed 88% of investigators and 88% of patients identified oxycodone. High loss to follow-up, but not differential.
Zautra, 2005	Mean age: 63 vs. 64 years Female gender: 67% vs. 80% Non-white race: 6% vs. 7% Baseline pain score: 6.61 vs. 6.81 Duration of symptoms: Not reported	Pain intensity 0 to 10 categorical scale) Positive and negative affect scales Coping effort: Vanderbilt Multidimensional Pain Coping Inventory Coping efficacy: 5 point scale Arthritis Helplessness Index: 5 items, each on a 6-point scale	SEE APPENDIX E

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 1.3. Efficacy of opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid to placebo or non-opioid

Author, Year	Outcomes	External validity	Funding source and role	Other comments
Watson, 2003	Long-acting Oxycodone (A) vs. benztropine (B) **Pain intensity**: 21.8 (p=0.0001 vs. baseline) vs. 48.6 VAS 1.2 (p=0.0001 vs. baseline) vs. 2.0 categorical **Pain relief**: 1.7 vs. 2.8 (p<0.0005) categorical **Pain and disability**: 16.8 (p<0.05 vs. baseline) vs. 25.2 total Pain Disability Index **Patient Preference**: 88% preferred oxycodone (p=0.0001) **Patient rated at least moderately effective**: 95% for oxycodone	Number screened and eligible reported. Number previously on opioids not reported. Diabetic retinopathy. Pain clinic based.	Purdue Pharma provided funding. One author employed by Purdue Pharma.	No report given of differences between study groups because patients served as their own controls. Analyzed for carry-over effect: none found. Most investigators and patients could identify active intervention.
Zautra, 2005	Sustained-release oxycodone (A) vs. placebo (B) (all results at 2 weeks) 2 point or greater improvement in pain score (10-point scale): 40% (22/55) vs. 10% (5/49) (p<0.001) 24-hour pain (0 to 10): 4.96 vs. 6.34 (p<0.001) Positive affect: 2.95 vs. 2.79 (NS) Negative affect: 2.02 vs. 1.94 (NS) Active coping: 3.27 vs. 3.15 (NS) Coping efficacy: 3.39 vs. 3.11 (p=0.006) Arthritis Helplessness: 3.56 vs. 3.77 (p=0.05) Withdrawal due to lack of efficacy: 16% (9/56) vs. 67% (34/51)		Supported in part by Purdue Pharma LP	

NSAID=non-steroidal anti-inflammatory drugs; DC=discontinue; OA=osteoarthritis; NS=non-significant; POMS=profile of mood states questionnaire; BID=twice a day

Evidence Table 2.1. Adverse events from opioids for non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Type of study	Interventions (dose, duration)	Number enrolled	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven met)
Allan, 2005	Randomized	A: Transdermal fentanyl (titrated from 25 mcg/hr) (Mean dose 57 mcg/h) B: Long acting morphine (titrated from 30 mg q 12 hrs) (Mean dose 58 mg) 13 months	683	Constipation (normal, diarrheal, constipated) based on entries in patient diaries, bowel function questionnaire (PAC-SYM), use of laxatives and other supplemental medications; other adverse events recorded but methods not stated	FAIR. Selection did not appear biased. High overall and differential loss to follow-up; not clear how losses to follow-up handled in calculation of adverse event rates. Constipation pre-specified but not clearly defined. Adverse events measured by bowel function assessment but validity of instrument not clear. Patients and assessors not blinded to intervention. No statistical analysis of potential confounders. Adequate duration of follow-up (up to 13 months). (4)
Allan, 2001	Randomized Crossover	A: Transdermal fentanyl (titrated to mean dose 57.3 mcg/hr) B: Long-acting morphine (titrated to mean dose 133.1 mg/day) 4 weeks initial intervention followed by 4 weeks crossover	256	Any treatment-related adverse event, assessment methods not clear other than a bowel function questionnaire was performed	POOR. Selection did not appear biased. High overall and differential loss to follow-up. Adverse events not specified or defined. Ascertainment techniques inadequately described. Patients and assessors not blinded to intervention. No statistical analysis of potential confounders. Adequate duration of follow-up, 4 weeks of initial intervention followed by 4 weeks cross-over. (2)

Evidence Table 2.1. Adverse events from opioids for non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Rate and number of adverse events	Comments
Allan, 2005	Transdermal fentanyl (n=338) vs. long-acting oral morphine (n=342) Any adverse event: 87% vs. 91% Constipation (ITT): 176/338 (52%) vs. 220/338 (65%) (p<0.05) Nausea: 54% vs. 50% Vomiting: 29% vs. 26% Somnolence: 17% vs. 30% Dizziness: 25% vs. 24% Fatigue: 17% vs. 14% Pruritus: 15% vs. 20% Application site reactions: 9% in transdermal fentanyl group Deaths: None Addiction: None reported Use of laxatives: 177/336 (53%) vs. 221/336 (66%) (p<0.001) Use of antiemetics/anticholingergics: 38% vs. 36% Use of antihistamines: 21% vs. 12% (p=0.002) Withdrawal due to adverse events: 125/335 (37%) vs. 104/337 (31%) (p=0.098)	Most common reasons for discontinuations due to adverse events: nausea (37% in both groups), vomiting (24% for transdermal fentanyl and 20% for long-acting oral morphine), and constipation (11% vs. 23%).
Allan, 2001	Transdermal fentanyl (n=250) vs. long-acting oral morphine (n=238) Rates of adverse events reported for entire trial: Overall: 74% vs. 70% Nausea: 26% vs. 18% Constipation: 16% vs. 22% Constipation by bowel function questionnaire: 29% vs. 48%, p<0.001 "Serious" (not defined): 2.8% vs. 3.8% Deaths: None Withdrawals due to adverse event (all patients): 11% vs. 4% Withdrawals due to adverse event (patients not previously on fentanyl or morphine): 11% (7/66) vs. 9.8% (6/66)	Adverse events not reported for initial 4 week intervention period. Differential withdrawal rates during initial intervention period may have led to biases during crossover period. 76% of patients on long-term morphine prior to trial. Not clear how analgesic requirements determined at beginning of trial; mean doses of opioid analgesics during trial not reported.

Evidence Table 2.1. Adverse events from opioids for non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Type of study	Interventions (dose, duration)	Number enrolled	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven met)
Caldwell, 2002	Randomized	A: Once-daily morphine (30 mg) in a.m. B: Once-daily morphine (30 mg) in p.m. C: Twice daily morphine (15 mg bid) D: Placebo 4 weeks	295	Any treatment-related adverse event, assessment methods not clear	POOR. Selection did not appear biased. High overall loss to follow-up. Adverse events not specified or defined. Ascertainment techniques inadequately described. Patients and assessors blinded to intervention. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 4 weeks. (3)
Hale, 2005	Randomized	A: Long acting oxymorphone (titrated) (Mean dose 79.4 mg/day) B: Long acting oxycodone (titrated) (Mean dose 155 mg/day) C: Placebo 18 days	235 enrolled in treatment phase	Patients queried on nausea, vomiting, constipation, pruritus, sedation, lightheadedness, and sweating (methods not described in any more detail)	POOR. Selection did not appear biased. High overall loss to follow-up. Basis of sample sizes for adverse events not clear (N=110, 111, and 108) Adverse events not specified or defined. Ascertainment techniques inadequately described. Patients and assessors blinded to intervention. No statistical analysis of potential confounders. Duration of follow-up 18 days. (3)

Evidence Table 2.1. Adverse events from opioids for non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Rate and number of adverse events	Comments
Caldwell, 2002	Once-daily morphine in a.m. (n=73) vs. once-daily morphine in p.m. (n=73) vs. twice-daily morphine (n=76) vs. placebo (n=73), adverse events reported in >5% of any treatment group (significant differences reported between active treatment groups): Constipation: 49% vs. 40% vs. 29% vs. 4% (p<0.05 twice-daily morphine vs. once-daily morphine in a.m.) Nausea: 21% vs. 32% vs. 26% vs. 10% Somnolence: 16% vs. 12% vs. 12% vs. 0% Dizziness: 10% vs. 10% vs. 12% vs. 1% Vomiting: 6% vs. 16% vs. 8% vs. 1% (p<0.05 once-daily morphine in a.m. vs. once-daily morphine in p.m.) Headache: 6% vs. 4% vs. 7% vs. 6% Pruritus: 6% vs. 10% vs. 3% vs. 0% Asthenia: 1% vs. 6% vs. 9% vs. 0% (p<0.05 twice-daily morphine vs. once-daily morphine in a.m.) Dry mouth: 6% vs. 4% vs. 3% vs. 1% Pain: 3% vs. 4% vs. 5% vs. 1% Diarrhea: 0% vs. 4% vs. 1% vs. 6% Withdrawal (overall): 37% vs. 45% vs. 37% vs. 32% Withdrawal (adverse events): 23% vs. 25% vs. 24% vs. 7% Withdrawal (lack of efficacy): 12% vs. 16% vs. 11% vs. 19% "Serious" (not defined): 6 overall	42% of patients were on opioids prior to trial; specific opioids or doses not reported. High withdrawal rates; not clear how withdrawn patients accounted for in adverse event rates. "Serious" adverse events not defined and rate in different treatment groups not reported.
Hale, 2005	Long-acting oxymorphone (A) vs. long-acting oxycodone (B) vs. placebo (C) Constipation: 39/110 (35%) vs. 32/111 (29%) vs. 12/108 (11%) Sedation: 19/110 (17%) vs. 22/111 (20%) vs. 2/108 (2%) Any adverse events: 85% vs. 86% vs. NR "Serious" adverse events possibly or probably related to study medication: 2 vs. 1 vs. NR (sample sizes not clear) Withdrawal (overall, titration phase): 53/166 (32%) vs. 42/164 (26%) Withdrawal (overall, treatment phase): 22/80 (28%) vs. 21/80 (26%) vs. 53/75 (71%) Withdrawal (adverse events, titration phase): 25/166 (15%) vs. 26/164 (16%) Withdrawal (adverse events, treatment phase): 2/80 (2.5%) vs. 4/80 (5.0%) vs. 5/75 (6.7%)	Not clear what sample sizes were used to calculate adverse events. Rates for most adverse events not reported.

Evidence Table 2.1. Adverse events from opioids for non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Type of study	Interventions (dose, duration)	Number enrolled	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven met)
Matsumoto, 2005	Parallel-group USA Multicenter Clinic setting not described	A: Sustained-release oxymorphone 20 mg bid x 2 weeks, then 40 mg bid B: Sustained-release oxymorphone 20 mg bid C: Sustained-release oxycodone 10 mg bid x 2 weeks, then 20 mg bid D: Placebo 4 weeks	491	Electrocardiogram, physical examination, vital signs, and clinical laboratory assessments; methods not described	

Evidence Table 2.1. Adverse events from opioids for non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Rate and number of adverse events	Comments
Matsumoto, 2005	Sustained-release oxymorphone 40 mg bid (n=114) vs. sustained-release oxymorphpone 20 mg bid (n=114) vs. sustained-release oxycodone 20 mg bid (n=120) vs. placebo (n=119) Constipation: 32% vs. 40% vs. 36% vs. 11% Dry mouth: 12% vs. 12% Vs. 15% vs. 0.8% Dizziness: 31% vs. 29% vs. 26% vs. 4% Headache: 11% vs. 29% vs. 26% vs. 4% Nausea: 60% vs. 61% vs. 43% vs. 10% Pruritus: 20% vs. 19% vs. 8% vs. 2% Somnolence: 31% vs. 30% vs. 27% vs. 5% Vomiting: 34% vs. 23% vs. 10% vs. 2% Withdrawal (overall): 56% (68/121) vs. 48% (58/121) vs. 40% (50/125) vs. 37% (46/124) Withdrawal (adverse events): 47% (57/121) vs. 38% (46/121) vs. 25% (31/125) vs. 27% (34/124) Any adverse events: 91% vs. 95% vs. 88% vs. 57%	

Evidence Table 2.1. Adverse events from opioids for non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Type of study	Interventions (dose, duration)	Number enrolled	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven met)
Nicholson, 2006	Parallel-group USA Multicenter Clinic setting not described	A: Extended-release morphine (Kadian) initially dosed once daily according to previous analgesic dose and titrated (dose and frequency up to twice daily) (mean dose 79 mg/day) B: Sustained-release oxycodone initially dosed twice daily according to previous analgesic dose and titrated (dose and frequency up to three times daily) (mean dose 85 mg/day)	112	Clinical observations and assessments of Aes entered on a case report form. Incidence, severity and drug relationship of Aes awere assessed and summarized. Categorized as mild, moderate, or severe. Investigator assessed.	
Rauck, 2006 and 2007	Parallel-group USA Multicenter Clinic setting not described	A: Extended-release morphine (Avinza) once daily (mean dose 64 mg) B: Sustained-release oxycodone (Oxycontin) twice daily (mean dose 53 mg)	392	Patients daily answered the Elicited Opioid Side Effect Questionnaire (captures occurrence and severity of constipation, nausea, vomiting, dizziness, drowsiness, dry mouth, and itchiness). Serious Aes, including opioid misuse or abuse, were recorded by investigators and reported to the clinical research organization that managed the trial.	

Evidence Table 2.1. Adverse events from opioids for non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Rate and number of adverse events	Comments
Nicholson, 2006	Extended-release morphine (Kadian) once daily versus sustained-release oxycodone twice daily Any adverse event: Not reported Serious adverse events: 12 overall Constipation: 26% vs. 10% (p=0.04) Nausea: 14% vs. 14% Somnolence: 10% vs. 7% Cognitive disorder: 4% vs. 2% Fatigue: 4% vs. 2% Headache: 4% vs. 0% Dizziness: 2% vs. 5% Edema: 0% vs. 3% Sedation: 0% vs. 5% Withdrawal (overall): 57% (30/53) vs. 51% (30/59) Withdrawal (adverse events): 28% (15/53) vs. 22% (13/59)	
Rauck, 2006 and 2007	Extended-release morphine (Avinza) once daily versus sustained-release oxycodone (Oxycontin) twice daily Serious adverse events: 3% (7/203) vs. 5% (9/189) Drug abuse or diversion: 0% (0/203) vs. 2% (4/189) Constipation: 92% vs. 90% Dizziness: 67% vs. 71% Drowsiness: 85% vs. 88% Dry mouth: 85% vs. 81% Itchiness: 67% vs. 62% Nausea: 60% vs. 56% Vomiting: 28% vs. 23% Withdrawal (overall): 46% (93/203) vs. 42% (79/189(Withdrawal (adverse events): 19% (38/203) vs. 14% (27/189)	

Evidence Table 2.2. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Type of study	Interventions (dose, duration)	Number enrolled	Method of adverse event assessment and adverse events assessed
Caldwell, 1999	Randomized	A: Long-acting oxycodone + acetaminophen (titrated) B: Short-acting oxycodone (titrated) C: Placebo Mean dose of oxycodone 40 mg/day 30 days of intervention	167 (107) 60 patients withdrew during titration phase, prior to randomization	Any adverse event at least possibly related to study medication, spontaneously reported by patients
Gostick, 1989	Randomized Crossover	A: Long acting dihydrocodeine (titrated, 60-120 mg BID) B: Short acting dihydrocodeine (titrated, 30-60 mg QID) Average dose not reported 2 weeks initial intervention with 2 weeks crossover	61	Methods not reported
Hale, 1997	Randomized	A: Long-acting codeine (fixed) plus acetaminophen B: Short-acting codeine (titrated) plus acetaminophen Mean doses 200 mg in group A, 71 mg group B 5 days	104	Any adverse event reported by >5% of either treatment group

Evidence Table 2.2. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Quality rating (number of criteria out of seven met)	Rate and number of adverse events	Comments
Caldwell, 1999	POOR. Low overall and differential loss to follow-up. Adverse events not specified or defined. Ascertainment techniques inadequately described and based only on patient self-report. Inadequate statistical analysis (elderly patients only). Adequate duration of follow-up, 30 days. (3)	Long-acting oxycodone vs. short-acting oxycodone vs. placebo (Significance reported for differences between active treatments groups) Somnolence: 18/34 (53%) vs. 26/37 (70%) vs. 13/36 (36%), NS Constipation: 24/34 (71%) vs. 20/37 (54%) vs. 16/36 (44%), NS Nausea: 5/34 (15%) vs. 14/37 (38%) vs. 13/36 (36%), p=0.03 Pruritus: 11/34 (32%) vs. 14/37 (38%) vs. 10/36 (28%), NS Dizziness: 4/34 (12%) vs. 9/37 (24%) 10/36 (28%), NS Dry mouth: 11/34 (32%) vs. 20/37 (54%) vs. 12/36 (36%), NS Vomiting: 2/34 (6%) vs. 4/37 (11%) vs. 0/36 (0%), NS Withdrawal due to adverse events: 3/34 (6%) vs. 5/37 (14%) vs. 3/36 (8%), NS	More males randomized to controlled-release oxycodone group, otherwise demographic characteristics comparable. Approximately 1/3 did not get randomized because of issues during titration phase on immediate-release codeine. Limited statistical analysis of adverse events in elderly vs. younger patients during titration phase. Elderly patients (>65) during titration phase less frequent headache (2% vs. 8%) and pruritus (21% vs. 35%); more frequent vomiting (19% vs. 11%); other adverse event rates reported "similar". P values not provided.
Gostick, 1989	POOR. High overall (19/61) withdrawal/loss to follow-up. Adverse events not specified or defined. Ascertainment technique not described. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 2 weeks each intervention. (2)	Long-acting dihydrocodeine vs. short-acting dihydrocodeine Bowel movement less frequently than once every two days: 23/42 (55%) vs. 21/44 (48%) Daily use of laxaztive: 1/41 (2.4%) vs. 3/42 (7.1%) Withdrawals due to adverse events: 16/61 (26%) overall, "no treatment differences" Other adverse events: Not reported ("no significant differences")	
Hale, 1997	POOR. High overall (22/104) and differential (15/53 vs. 5/51) loss to follow-up. Adverse events not specified or defined. Ascertainment technique not described. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 5 days. (2)	Long-acting codeine (fixed) plus acetaminophen vs. short-acting codeine (titrated) plus acetaminophen (rate of "serious" adverse events in brackets) Nausea: 16/52 (31%) [15%] vs. 9/51 (18%) [4%] Vomiting: 5/52 (10%) [8%] vs. 1/51 (2%) [2%] Constipation: 10/52 (19%) [2%] vs. 8/51 (16%) [0%] Dizziness: 9/52 (17%) [4%] vs. 2/51 (4%) [0%] Headache: 8/52 (15%) [0%] vs. 4/51 (8%) [4%] Somnolence: 5/52 (10%) [0%] vs. 2/51 (4%) [0%] Dyspepsia: 4/52 (8%) [4%] vs. 2/51 (4%) [2%] Dry mouth: 8/52 (15%) [0%] vs. 0/51 (0%) [0%] Pruritus: 3/52 (6%) [4%] vs. 2/51 (4%) [2%] Withdrawal due to adverse events: 13/53 (25%) vs. 4/51 (8%)	Two arms did not receive equivalent doses of codeine. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates. "Serious" adverse events not defined.

Evidence Table 2.2. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Type of study	Interventions (dose, duration)	Number enrolled	Method of adverse event assessment and adverse events assessed
Hale, 1999	Randomized Crossover	A: Long-acting oxycodone B: Short-acting oxycodone Mean dose 40 mg/day 4-7 days followed by crossover	57 (47) 10 patients withdrew during titration phase	Any adverse event at least possibly related to study medication, assessed at each contact, assessment methods not clear
Jamison, 1998	Randomized	A: Long acting morphine + short-acting oxycodone (titrated doses) + NSAID B: Short-acting oxycodone (fixed dose) + NSAID C: Naproxen Mean dose A: 41.1 mg morphine equivalent/day Mean dose B: Not reported, max 20 mg oxycodone/day Mean dose C: Not reported, max 1000 mg/day 16 weeks	36	Pre-specified set of adverse events assessed on 0 to 10 scale by weekly phone interview

Evidence Table 2.2. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Quality rating (number of criteria out of seven met)	Rate and number of adverse events	Comments
Hale, 1999	POOR. High overall loss to follow-up (11/47). Adverse events not specified or defined. Ascertainment technique inadequately described. Adverse events ascertained only by patient self-report. No statistical analysis of potential confounders. Duration of follow-up may be inadequate, ranged from 4-7 days for each intervention phase.(3)	Long-acting oxycodone vs. short-acting oxycodone (initial intervention) Nausea: 4/25 (16%) vs. 9/22 (41%), NS Constipation: 8/25 (32%) vs. 10/22 (45%), NS Dizziness: 4/25 (16%) vs. 2/22 (9%), NS Pruritus: 7/25 (28%) vs. 6/22 (27%), NS Somnolence: 3/25 (12%) vs. 4/22 (18%), NS Vomiting: 0/25 (0%) vs. 0/22 (0%), NS Headache: 2/25 (8%) vs. 2/22 (9%), NS Withdrawal due to adverse events (initial intervention + crossover phase): 2/47 (4%) vs. 1/47 (2%)	88% of patients (as reported by Salzman 1999) were on opioids prior to entry into trial, specific opioids used not reported. Rates of adverse events reported during second intervention (crossover) period were not significantly different between treatment groups. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates.
Jamison, 1998	FAIR. All patients completed 16 week intervention phase. Adverse events pre-specified but not defined. Ascertainment technique adequately described. Patients and assessors not blinded to intervention. (5)	Long-acting morphine + short-acting oxycodone vs. short-acting oxycodone (proportion reported weekly, sample sizes not clear) Dry mouth: 35% vs. 26% Drowsiness: 37% vs. 22% Headache: 32% vs. 20% Constipation: 30% vs. 18% Nausea: 31% vs. 14% Itching: 15% vs. 15% Dizziness: 6% vs. 19% Muddled thinking: 0% vs. 1.4% Withdrawal due to adverse events: 1/11 (9.1%) vs. 2/13 (15%)	Higher adverse events in long-acting morphine + short-acting oxycodone arm, but they also received higher average doses of opioids.

Evidence Table 2.2. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Type of study	Interventions (dose, duration)	Number enrolled	Method of adverse event assessment and adverse events assessed
Lloyd, 1992	Randomized	A: Long-acting dihydrocodeine (titrated) B: Dextropropxyphene + paracetamol (titrated) Average dose not reported 2 weeks	86	Any adverse event, assessed by patient diary
Salzman, 1999	Randomized	A: Long-acting oxycodone (titrated) B: Short-acting oxycodone (titrated) Mean dose A: 104 mg/day Mean dose B: 113 mg/day Duration up to 10 days	57	Any adverse event reported by >10% of one treatment group and at least possibly related to study medication, assessed by daily patient diary

Evidence Table 2.2. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Quality rating (number of criteria out of seven met)	Rate and number of adverse events	Comments
Lloyd, 1992	POOR. High overall and differential loss to follow-up (19/43 vs. 7/43). Adverse events not specified or defined. Ascertainment technique inadequately described. Patients and assessors blinded to intervention. Inadequate statistical analysis (rates of adverse events vs. time since intervention). Duration of follow-up appears adequate, 2 weeks. (3)	Long-acting dihydrocodeine vs. dextropropoxyphene plus paracetamol (figures only reflect side effect rated moderate or severe, results only reported from end of week 1 because of high rate of withdrawal): Nausea: 12/39 (31%) vs. 4/41 (10%) Vomiting: 8/39 (21%) vs. 3/41 (7%) Constipation: 3/39 (8%) vs. 4/41 (10%) Drowsiness: 10/39 (26%) vs. 6/41 (15%) Difficulty concentrating: 4/39 (10%) vs. 2/41 (5%) Withdrawal due to adverse events: 17/43 (40%) vs. 4/43 (9%)	Higher dosage regimen not associated with increased rate of adverse events. High overall and differential withdrawal rate. Not clear how patients and assessors blinded to treatment regimen (not reported in study), medications given at different frequency. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates.
Salzman, 1999	POOR. High overall loss to follow-up (16/57). Adverse events not specified or defined. Ascertainment techniques adequately described. Patients and assessors not blinded, adverse events ascertained only by patient self-report. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 10 days. (3)	Long-acting oxycodone vs. short-acting oxycodone Somnolence: 8/30 (27%) vs. 10/27 (37%) Nausea: 15/30 (50%) vs. 9/27 (33%) Vomiting: 6/30 (20%) vs. 1/27 (4%) Postural hypotension: 0% vs 0% Constipation: 9/30 (30%) vs. 10/27 (37%) Pruritus: 9/30 (30%) vs. 7/27 (26%) Confusion: 1/30 (3%) vs. 0% Dry mouth: 0/30 (0%) vs. 3/27 (11%) Dizziness: 9/30 (30%) vs. 6/27 (22%) Nervousness: 0/30 (0%) vs. 2/27 (7%) Asthenia: 2/30 (7%) vs. 3/27 (11%) Headache: 4/30 (13%) vs. 7/27 (26%) Withdrawal due to adverse events: 6/30 (20%) vs. 2/27 (7%)	Open-label dose-titration study. Study results from 48 cancer patients not abstracted (n=48). 88% of patients previously on opioid analgesics, specific opioids not reported. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates.

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Type of study	Interventions (dose, duration)	Number enrolled	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven adequately met)
Arkinstall, 1995	Randomized Crossover	A: Controlled-release codeine (titrated) B: Placebo Mean dose 273 mg 7 days initial intervention, followed by crossover	46	Any adverse event reported in >5% of any treatment group, patients recorded adverse events in diary, also spontaneously reported and investigator-observed adverse events at end of each 7 day phase	FAIR. High differential and overall loss to follow-up. Adverse events not specified or defined. Techniques to ascertain adverse events adequately described. Adverse events ascertained by patient self-report or investigator-observed. No statistical analysis of potential confounders. Adequate duration of follow-up, 7 days initial intervention followed by 7 days cross-over. (4)
Gilron, 2005	Randomized Multiple crossovers	A: Long-acting morphine (titrated) B: Gabapentin C: Long-acting morphine + gabapentin D: Placebo 5 weeks initial interventinon, followed by crossovers to each of the other 3 interventions	57	Any reported adverse event	FAIR. Adverse events not pre-specified or defined. Inadequate description of adverse event assessment technique. No analysis of confounders. (4)

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Rate and number of adverse events	Comments
Arkinstall, 1995	Long-acting codeine vs. placebo (Sample size for reported rates not clear, only rates reported) Rates of adverse events reported for entire trial (initial intervention and crossover period): Constipation: 20.9% vs. 9.5%, NS Nausea: 33% vs. 12%, p=0.013 Dizziness: 21% vs. 14%, NS Dry mouth: 14% vs. 14%, NS Headache: 23% vs. 14%, NS Somnolence: 16% vs. 4.8%, NS Vomiting: 14% vs. 4.8%, NS Asthenia: 9.3% vs. 9.5%, NS Abdominal pain: 9.3% vs. 9.5%, NS Pruritus: 7.0% vs. 0%, NS Sweating: 0% vs. 4.8%, NS Withdrawal due to adverse events: 7/46 (15%) vs. 1/46 (2%)	Adverse events not reported for initial 1 week intervention period. Patients were on chronic long-term opioids prior to entry (though proportion of patients on prior opioids and specific opioids used not reported); withdrawal symptoms may have occurred in placebo group that could not be distinguished from adverse events. Not reported if differential loss to follow-up occurred in initial intervention period. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates.
Gilron, 2005	Long-acting morphine vs. gabapentin vs. long-acting morphine + gabapentin vs. placebo Withdrawals (overall) during first intervention: 4/16 (25%) vs. 3/13 (23%) vs. 4/14 (29%) vs. 0/14 (0%) Constipation: 39% vs. 2% vs. 21% vs. 5% Sedation: 16% vs. 8% vs. 21% vs. 6% Dry mouth: 5% vs. 6% vs. 21% vs. 0% Cognituve dysfunction: 2% vs. 2% vs. 7% vs. 2% Nausea: 5% vs. 0% vs. 0% vs. 7%	Adverse events not reported for initial 5 week intervention period. Withdrawals due to adverse events not clear.

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Type of study	Interventions (dose, duration)	Number enrolled	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven adequately met)
Gimbel, 2003	Randomized	A: Long-acting oxycodone titrated up to 60 mg bid B: Placebo Average dose 29 mg/day 6 weeks intervention	160	Investigator assessed for adverse events at each visit, and reported events graded for severity and probability of relationship to study drug	FAIR. Adverse events not pre-specified or defined. Inadequate description of adverse event assessment technique. No analysis of confounders. (4)
Hale, 2007	Parallel-group RCT USA Multicenter Multidisciplinary pain centers	A: Sustained-release oxymorphone q 12 hours, dose based on stable doses achieved during open-label titration (average 81 mg) B: Placebo	143	Physical exam, vital signs (blood pressure, heart rate, respiratory rate, temperature). Investigators observed patients for Aes and patients were asked to report any AE since the last visit. Coded by investigator as mild, moderate, or severe. Investigators recorded withdrawal symptoms based on DSM-IV criteria. 2 validated scales of opioid withdrawal were used during the first 4 weks of treatment.	

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Rate and number of adverse events	Comments
Gimbel, 2003	Long-acting oxycodone vs. placebo Constipation: 35/82 (42%) vs. 11/77 (14%), p<0.001 Somnolence: 33/82 (40%) vs. 1/77 (1%), p<0.001 Nausea: 30/82 (36%) vs. 6/77 (8%), p<0.001 Dizziness: 26/82 (32%) vs. 8/77 (10%), p<0.001 Pruritus: 20/82 (24%) vs. 6/ 77 (8%), p=0.005 Vomiting: 17/82 (21%) vs. 2/77 (3%), p<0.001 Dry mouth: 13/82 (16%) vs. 2/77 (3%), p=0.005 Asthenia: 12/82 (15%) vs. 5/77 (7%), p=0.125 Headache: 9/82 (11%) vs. 18/77 (23%), p=0.055 Withdrawals (overall): 19/82 (23%) vs. 25/77 (32%) Withdrawals (adverse event): 7/82 (9%) vs. 4/77 (5%)	
Hale, 2007	Sustained-release oxymorphone vs. placebo Withdrawal due to adverse event: 10% (7/70) vs. 11% (8/72) Withdrawal due to opioid withdrawal symptoms: 0% (0/70) vs. 7% (5/72) At least one adverse event: 44% (31/70) vs. 38% (27/72) Nausea: 3% vs. 1% Constipation: 6% vs. 1% Headache: 3% vs. 0% Somnolence: 3% vs. 0% Vomiting: 0% vs. 1% Pruritus: 1% vs. 0%	

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Type of study	Interventions (dose, duration)	Number enrolled	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven adequately met)
Huse, 2001	Randomized Crossover	A: Long-acting morphine (titrated) B: Placebo Final dose between 70 to 300 mg/day morphine 4 weeks initial intervention, followed by crossover	12	Any reported adverse event, recorded in daily patient diary	FAIR. No loss to follow-up. Adverse events not specified or defined. Ascertainment technique adequately described. Patients and assessors blinded to intervention. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 4 weeks initial intervention followed by 2 week washout then crossover. (4)
Katz, 2007	Parallel-group RCT USA Multicenter Clinical setting not reported	A: Sustained-release oxymorphone 5 mg q 12 hours for 2 days followed by dose titration if necessary B: Placebo Mean dose 39 mg/day	205	Vital signs at each study visit. Opioid withdrawal monitored for the first 4 weeks, with assessments at baseline, day 4, day 7, and then weekly. Investigators were required to assess the reason for study discontinuation, including opioid withdrawal.	

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Rate and number of adverse events	Comments
Huse, 2001	Long-acting morphine vs. placebo (results for initial intervention not reported), 10 cm visual analogue scale (cm) Tiredness: 2.21 vs. 1.33, NS Dizziness: 1.27 vs. 0.71, NS Sweating: 1.32 vs. 0.93, NS Constipation: 0.03 vs. 0.02, p<0.05 Micturition difficulties: 0.01 vs. 0, NS Nausea: 0.74 vs. 0.4, NS Vertigo: 0.98 vs. 0.42, NS Itching: 0.92 vs. 0.55, NS Slowing of respiration: 0.73 vs. 0.55, NS Withdrawal due to adverse events not reported	Not clear how dose of morphine titrated during intervention.
Katz, 2007	Sustained-release oxymorphone vs. placebo Withdrawal due to adverse event: 9% (9/105) vs. 8% (8/100) Withdrawal due to opioid withdrawal symptoms: 1% (1/105) vs. 2% (2/100) At least one adverse event: 58% (61/105) vs., 44% (44/100) At least one serious adverse event: 2% (2/105) vs. 3% (3/100) Constipation: 7% vs. 1% Somnolence: 2% vs. 0% Nausea: 11% vs. 9% Dizziness: 5% vs. 3% Headache: 4% vs. 2% Pruritus: 3% vs. 1% Vomiting: 8% vs. 1% Diarrhea: 6% vs. 6%	

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Type of study	Interventions (dose, duration)	Number enrolled	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven adequately met)
Kivitz, 2006	Parallel-group RCT USA Multicenter Clinic setting not reported	A: Sustained-release oxymorphone 10 mg q 12 hours B: Sustained-release oxymorphone 20 mg q 12 hours x 1 week, then 40 mg q 12 hrs x 1 week C: Sustained-release oxymorphone 20 mg q 12 hours x 1 week, then 50 mg q 12 hrs x 1 week D: Placebo	370	Assessment included Aes, ECG, physical examinations, vital signs, and clinical laboratory parameters. Elicited at each clinic visit by questioning patients. Severity coded as mild, moderate, severe, or life-threatening. Physical exams at screening and during 2-week clinical visit or upon withdrawal from the study; full chemistry panel.	
Langford, 2006	Parallel-group RCT Europe and Canada Multicenter Clinical setting not reported	A: Transdermal fentanyl 25 mcg/hr, titrated to maximum 100 mcg/hr B: Placebo 1 week run-in period (no change in therapy), 6 week intervention Median dose of transdermal fentanyl: 1.7 patches/day	416	Short Opiate Withdrawal Scale used to assess possible withdrawal symptoms. Vital signs recorded at start and end of study. Adverse events were recorded (methods not described)	

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Rate and number of adverse events	Comments
Kivitz, 2006	Sustained-release oxycodone 10 mg vs. 40 mg vs. 50 mg vs. placebo Withdrawal due to adverse events: 25% (24/95) vs. 55% (51/93) vs. 52% (47/91) vs. 10% (9/91) Nausea: 23% vs. 41% vs. 55% vs. 9% Vomiting: 10% vs. 27% vs. 35% vs. 2% Dizziness: 16% vs. 22% vs. 31% vs. 6% Pruritus: 5% vs. 20% vs. 24% vs. 1% Constipation: 18% vs. 27% vs. 22% vs. 4% Somnolence: 10% vs. 23% vs. 21% vs. 3% Headache: 10% Vs. 15% vs. 19% vs. 10% Increasing sweating: 5% vs. 8% vs. 10% vs. 1% Decreased appetite: 1% vs. 4% vs. 9% vs. 1% Dry mouth: 6% vs. 11% vs. 9% vs. 0% Diarrhea: 0% vs. 3% Vs. 7% vs. 7% Fatigue: 5% vs. 12% vs. 3% vs. 1% Euphoric mood: 5% vs. 3% vs. 1% vs. 1%	
Langford, 2006	Transdermal fentanyl vs. placebo Withdrawal due to adverse events: 26% (55/216) vs. 8% (15/200) At least one adverse event: 78% (169/216) vs. 51% (101/200) Nausea: 44% (94/216) vs. 19% (37/200) Vomiting: 28% (61/216) vs. 3% (5/200) Somnolence: 22% (48/216) vs. 4% (7/200) Dizziness: 12% (26/216) vs. 5% (10/200) Headache: 11% (23/216) vs. 12% (23/200) Application site reaction: 4% (9/216) vs. 11% (221/200) Constipation: 10% (22/216) vs. 2% (3/200)	

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Type of study	Interventions (dose, duration)	Number enrolled	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven adequately met)
Maier, 2002	Randomized Crossover	A: Long-acting morphine (titrated) Placebo Median dose 100 and 103 mg/day 1 week initial intervention, followed by crossover	49	20 symptoms or complaints rated on 0 (none) to 3 (severe) scale; some central nervous system and gastrointestinal symptoms pre-specified	FAIR. Low proportion of eligible patients entered into trial. High and differential loss to follow-up according to randomization sequence. Some adverse events pre-specified. Ascertainment technique inadequately described. Blinding not successful. No statistical analysis of potential confounders. (3)
Markenson, 2005	Parallel-group RCT USA Multicenter Clinic setting not reported	A: Sustained-release oxycodone 10 mg q 12 hours, titrated to maximum 60 mg q 12 hours B: Placebo Up to 90 days intervention	109		

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Rate and number of adverse events	Comments
Maier, 2002	Morphine vs. placebo Withdrawal due to adverse events (initial intervention): 3/25 (12%) vs. 0/23 (0%) Severe side effects: 28/48 (58%) vs. 10/45 (22%), any side effects 36% vs. 27% Severe gastrointestinal: 21/48 (44%) vs. 5/45 (11%) Severe constipation: 10/48 (20%) vs. 2/45 (4.5%), any constipation 19% vs. 4.5% Severe nausea: 8/48 (16%) vs. 2/45 (4.5%), any nausea 23% vs. 13.5% Severe sedation: 6/48 (12%) vs. 6/45 (13%), any sedation 23% vs. 2% Severe micturition problems: 5/48 (10%) vs. 1/45 (2%) Severe dizziness: 2/48 (4%) vs. 1/45 (2%), any dizziness 20.5% vs. 4.5%	Not clear how lost to follow-up handled in safety analysis. Only withdrawal due to adverse events reported prior to crossover.
Markenson, 2005	Sustained-release oxycodone vs. placebo Withdrawal due to adverse events: 36% (20/56) vs. 4% (2/51) (p<0.001) Any adverse event: 93% (52/56) vs. 55% (28/51) "Serious" adverse event: 5% (3/56) vs. 0% (0/51) Deaths: None Constipation: 48% (27/56) vs. 9.8% (5/51) Nausea: 41% (23/56) vs. 14% (7/51) Somnolence: 32% (18/56) vs. 10% (5/51) Dizziness: 32% (18/56) vs. 6% (3/51) Pruritus: 21% (12/56) vs. 0% (0/51) Headache: 20% (11/56) vs. 20% (10/51) Diarrhea: 12% (7/56) vs. 8% (4/51) Vomiting: 12% (7/56) vs. 2% (1/51) Sweating: 11% (6/56) vs. 4% (2/51)	

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Type of study	Interventions (dose, duration)	Number enrolled	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven adequately met)
Morley, 2003	Randomized	A: Methadone 5 mg bid (Phase I) or 10 mg bid (Phase II) B: Placebo	19	Not specified	POOR. High loss to follow-up. Adverse events not specified or defined. Ascertainment technique not described. Blinding methods unclear. No statistical analysis of potential confounders. Not clear if duration of follow-up adequate because of unusual study design (methadone or placebo randomly given only every other day). (1)
Moulin, 1996	Randomized Crossover	A: Long-acting morphine (titrated) B: Benztropine (titrated) Mean daily dose 83 mg/day morphine 6 week initial intervention, followed by crossover	61	Any reported adverse event, assessed by weekly or biweekly adverse effects questionnaire	FAIR. Selection of patients does not appear biased. High overall and differential loss to follow-up (11/61 vs. 4/61). Adverse events not specified or defined. Ascertainment technique adequately described. Patients and assessors blinded to intervention, adverse events questionnaire was used. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 6 weeks followed by 6 weeks crossover. (4)

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Rate and number of adverse events	Comments
Morley, 2003	Methadone vs. placebo Withdrawal due to adverse event: 1/19 vs. 0/19 (phase I); 3/17 vs. 3/17 (phase II) Nausea: 7/19 vs. 4/19 (phase I); 8/17 vs. 4/17 (phase II) Vomiting: 4/19 vs. 1/19 (phase I); 1/17 vs. 1/17 (phase II) Somnolence: 2/19 vs. 2/19 (phase I); 3/17 vs. 2/17 (phase II) Dizziness: 6/19 vs. 0/19 (phase I); 3/17 vs. 1/17 (phase II) Constipation: 2/19 vs. 1/19 (phase I); 3/17 vs. 1/17 (phase II) Dry mouth: 0/19 vs. 1/19 (phase I); 0/17 vs. 0/17 (phase II) Adverse effects reported on day of or day after taking methadone vs. placebo	Not clear how lost to follow-up handled in safety analysis. Adverse events reported on day of or day after taking methadone or placebo.
Moulin, 1996	Long-acting morphine vs. benztropine (active placebo) (Adverse events reported for entire trial): Vomiting: 18/46 (39%) vs. 1/46 (2%), p=0.0002 Dizziness: 17/46 (37%) vs. 1/46 (2%), p=0.0004 Constipation: 19/46 (41%) vs. 2/46 (4%), p=0.0005 Poor appetite/nausea: 18/46 (39%) vs. 3/46 (7%), p=0.002 Abdominal pain: 10/46 (22%) vs. 2/46 (4%), p=0.04 Fatigue: 10/46 (22%) vs. 3/46 (7%), p=0.10 Dry skin/itching: 7/46 (15%) vs. 2/46 (4%), p=0.18 Dry mouth: 8/46 (17%) vs. 5/46 (11%), NS Diarrhea: 6/46 (13%) vs. 6/46 (13%), NS Blurred vision: 6/46 (13%) vs. 9/46 (20%), NS Sleeplessness: 6/46 (13%) vs. 8/46 (17%), NS Confusion: 4/46 (9%) vs. 7/46 (15%), NS Dose-limiting side effects: 13/46 (28%) vs. 1/46 (2%), p=0.003 Withdrawal due to adverse events not reported	Data not reported in such a way that adverse events in initial intervention period could be calculated. 60/61 study participants on codeine (average dose 126 mg) at time of study entry. Multidisciplinary pain management program offered to study participants. Differential loss to follow-up during titration phase may have biased results of crossover phase. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates.

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Type of study	Interventions (dose, duration)	Number enrolled	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven adequately met)
Peloso, 2000	Randomized	A: Long-acting codeine (titrated) B: Placebo Average final codeine dose 318 mg/day 4 weeks active treatment	103	Any reported adverse event, assessed by weekly nondirected adverse events questionnaire	FAIR. Not clear if selection of patients biased, number eligible not reported. High overall loss to follow-up (37/103). Adverse events not specified or defined. Ascertainment technique adequately described. Patients and assessors blinded to intervention, adverse events questionnaire was used. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 4 weeks. (3)
Roth, 2000	Randomized	A1: Long-acting oxycodone 10 mg bid A2: Long-acting oxycodone 20 mg bid B: Placebo 14 days	133	Any adverse event reported in >10% of patients, assessed by spontaneous patient reported or observed by investigators at each weekly visit	FAIR. High overall loss to follow-up (70/133). Adverse events not specified or defined. Ascertainment techniques adequately described. Patients and assessors blinded. Adequate statistical analysis of potential confounders (dose relationship, age, gender). Duration of follow-up appears adequate, 14 days. (5)

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Rate and number of adverse events	Comments
Peloso, 2000	Long-acting codeine vs. placebo (study reports adverse events for "all patients randomized to treatment", assume intention-to-treat analysis as only rates reported) Constipation: 25/51 (49%) vs. 6/52 (11%), p<0.01 Somnolence: 20/51 (39%) vs. 5/52 (10%), p<0.01 Dizziness: 17/51 (33%) vs. 4/52 (8%), p<0.01 Overall (any): 42/51 (82%) vs. 30/52 (58%), p<0.01 Nausea: not significantly different (rates not reported) Long-acting codeine only: Severe constipation 13/51 (26%), severe somnolence 8/51 (16%), severe dizziness 6/51 (12%), severe nausea 2/51 (4%) Withdrawal due to adverse events: 15/51 (29%) vs. 4/52 (8%), p not reported	Patients required to discontinue baseline medications upon study entry, including opioids. 7/52 in placebo and 7/51 in codeine group previously on codeine; other baseline opioid and analgesic use not reported. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates.
Roth, 2000	Long-acting oxycodone 20 mg bid vs. long-acting oxycodone 10 mg bid vs. placebo: Nausea: 18/44 (41%) vs. 12/44 (27%) vs. 5/45 (11%) Constipation: 14/44 (32%) vs. 10/44 (23%) vs. 3/45 (7%) Somnolence: 12/44 (27%) vs. 11/44 (25%) vs. 2/45 (4%) Vomiting: 10/44 (23%) vs. 5/44 (11%) vs. 3/45 (7%) Dizziness: 9/44 (20%) vs. 13/44 (30%) vs. 4/45 (9%) Pruritus: 7/44 (16%) vs. 8/44 (18%) vs. 1/45 (2%) Headache: 5/44 (11%) vs. 4/44 (9%) vs. 3/45 (7%) Withdrawal due to adverse events: 14/44 (32%) vs. 12/44 (27%) vs. 2/45 (4%)	Trial had open-label extension for up to 18 months for patients who wished to participate. Older (>65 years) patients more likely to have somnolence, other adverse event rates not significantly different. No difference in adverse event rates between genders. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates.

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Type of study	Interventions (dose, duration)	Number enrolled	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven adequately met)
Rowbotham, 2003	Randomized	A: Levorphanol 0.75 mg up to 7 tabs tid B: Levorphanol 0.15 mg up to 7 tabs tid Mean doses 8.9 mg/day versus 2.7 mg/day 4 weeks intervention, with 4 weeks titration and 4 weeks taper	81	Not specified. Reported withdrawal due to adverse events, and serious adverse events	FAIR. High overall loss to follow-up (25). Adverse events not specified or defined. Ascertainment techniques not described. Patients and investigators blinded. Analyzed underlying condition's effect on withdrawal due to adverse events. Duration of follow-up appears adequate, 4 weeks intervention in addition to titration and taper. (4)
Watson, 1998	Randomized Crossover	A: Long-acting oxycodone (titrated) B: Placebo Mean final dose 45 mg/day 4 week intervention followed by 4 week crossover	50	Most frequently reported adverse event, assessed by weekly questionnaire	FAIR. Not clear if selection of patients biased, number eligible not clear. High overall loss to follow-up (11/50), with an additional patient unaccounted for. Adverse events not specified or defined. Ascertainment techniques adequately described. Patients and investigators blinded. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 4 weeks for each intervention period. (3)

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Rate and number of adverse events	Comments
Rowbotham, 2003	High-dose levorphanol vs. low-dose levorphanol (sample sizes for adverse event assessment not clear): Withdrawal due to adverse event: 25/81 overall, not reported by intervention Death: 0/43 vs. 1/38 Serious events: None Increased in high-dose group: itchy skin, sweating, and skin clammy Anger, irritability or mood or personality change: 6/43 vs. 0/38 Weakness or confusion: 5/43 vs. 0/38 Dizziness: 2/43 vs. 0/38	
Watson, 1998	Long-acting oxycodone vs. placebo (sample sizes not clear): Any adverse event: 76% vs. 49%, p=0.0074 Constipation (5 patients), nausea (4 patients), sedation (3 patients) most commonly reported adverse events Withdrawal due to adverse events not reported	Trial reports 11 withdrawals, 1 enrolled patient not accounted for. 45% of patients on opioids prior to trial, all withdrawn at least 1 week before intervention began. Opioids previously used not specified. Sample size for adverse events not clear. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates.

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Type of study	Interventions (dose, duration)	Number enrolled	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven adequately met)
Watson, 2003	Randomized Crossover	A: Long acting oxycodone (titrated from 10 mg q 12 hrs) B: Benztropine (active placebo) Mean final dose 40 mg/day 4 weeks initial intervention followed by 4 week crossover	45	Events spontaneously reported by patients and observed by investigators recorded at each visit.	POOR. 9/20 lost to follow-up. Adverse events not specified or defined. Ascertainment techniques not described. Doesn't appear blinded. No statistical analysis of confounders. Duration of follow-up appears adequate (4 weeks per intervention). (3)
Zautra, 2005	Parallel-group RCT USA Multicenter Clinic setting not described	A: Sustained-release oxycodone 10 mg q 12 hours, titrated up to 120 mg/day B: Placebo	107		

Evidence Table 2.3. Adverse events from opioids for chronic non-cancer pain: Randomized controlled trials comparing a long-acting opioid with placebo or non-opioid

Author, Year	Rate and number of adverse events	Comments
Watson, 2003	Long-acting oxycodone (A) vs. placebo (B) Withdrawal due to adverse events: 7/45 vs. 1/45 Serious adverse events: 0/45 vs. 3/45 Nausea: 16/45 vs. 8/45 (p=0.09) Vomiting: 5/45 vs. 2/45 (p=0.26) Somnolence: 9/45 vs. 11/45 (p=0.56) Constipation: 13/45 vs. 4/45 (p=0.02) Dizziness: 7/45 vs. 3/45 (p=0.16) Asthenia: 2/45 vs. 5/45 (p=0.26) Insomnia: 3/45 vs. 4/45 (p=0.71) Pruritus: 4/45 vs. 1/45 (p=0.18) Sweating: 4/45 vs. 1/45 (p=0.18)	Not clear how withdrawals handled in safety analysis.
Zautra, 2005	Sustained-release oxycodone vs. placebo Withdrawal (adverse events): 36% (20/55) vs. 4% (2/49)	

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: Cohort studies of long-acting opioids

Author, Year	Type of study, Setting	Medications evaluated (dose, duration)	Eligibility criteria	Exclusion criteria	Other pain medications used or allowed
Ackerman, 2004	Retrospective cohort U.S. Population-based (California Medicaid)	A: Transdermal fentanyl B: Long-acting oxycodone	California Medicaid patients prescribed transdermal fentanyl or long-acting oxycodone during 3 consecutive months	California Medicaid ineligible, <18 years old, prescribed other long-acting opioid, prescribed codeine, prescribed transdermal fentanyl or long-acting oxycodone after start date, or prescribed both medications	Short-acting opioids and tricyclics controlled in analyses
Arkinstall, 1995	Prospective cohort (open-label extension of randomized trial) Canada Multicenter Pain clinics	Long-acting codeine, titrated to adequate pain control Mean dose at end of trial 264 mg Average duration 132 days	Patients completing trial by Arkinstall 1996 requesting continued long-term treatment with controlled-release codeine	Same as trial by Arkinstall 1996	Acetaminophen + codeine (short-acting)

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: Cohort studies of long-acting opioids

Author, Year	Number screened Number eligible Number enrolled	Number withdrawn or lost to follow-up Number analyzed	Population characteristics	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven met)
Ackerman, 2004	Not reported Not reported 2106	Not applicable	Transdermal fentanyl vs. long-acting oxycodone Age: 67 vs. 54 years Female: 74% vs. 65% Non-white race: 31% vs. 26% Cancer: 10% vs. 3.16% Low daily dose: 41% vs. 28%	First episode of constipation event (ICD-9 code) using inpatient and outpatient claims data	FAIR. Inception cohort and number unable to be assessed not reported. Not clear if assessors blinded. Adequate duration of follow-up, 90 days. (5)
Arkinstall, 1995	30 screened 30 eligible 28 enrolled	13/28 (46%) withdrawn or lost to follow-up Not clear how many patients included in analysis	Age, gender, race not reported; Diagnosis, duration of pain not reported recruited from trial by Arkinstall 1996	Any adverse event spontaneously reported or investigator-observed, timing not clear	POOR. Not clear if selection of patients biased; number eligible in randomized trial not clear. High overall loss to follow-up (13/28). Adverse events not specified or defined. Ascertainment techniques inadequately described (timing not clear). Assessors do not appear to have been blinded. No statistical analysis of potential confounders. Adequate duration of follow-up, 132 days. (1)

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: Cohort studies of long-acting opioids

Author, Year	External validity	Funding sources and role of funder	Rate and number of adverse events	Comments
Ackerman, 2004	Population adequately described. California Medicaid population. Approximately 25% on short-acting opioids.	Janssen (transdermal fentanyl) One author employed by funder, not reported if data held by funder	Long-acting oxycodone versus transdermal fentanyl: adjusted odds ratio 2.55 (95% CI 1.33-4.89) for constipation; 7.33 (1.98-27.13) in persons >65 years old	Many significant baseline differences between groups; analysis adjusted for dose, concomitant medications, comorbidities including cancer. Data appears to overlap with Staats 2004.
Arkinstall, 1995	Population adequately described. Highly selected population that completed previous randomized trial. Exclusion criteria specified in original trial, numbers excluded for specific criteria not reported. Patients were on opioids during prior trial.	Purdue (controlled release codeine) One author (corresponding author) employed by funder, not clear if data held by funder	Long-acting codeine: Adverse events "similar to rates reported in trial". Long-term use: 15/28 (54%), not clear how many discontinued medication due to adverse events.	Did not report rates of specific adverse events in long-term follow-up. Reasons for discontinuation of medication in long-term follow-up not reported.

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: Cohort studies of long-acting opioids

Author, Year	Type of study, Setting	Medications evaluated (dose, duration)	Eligibility criteria	Exclusion criteria	Other pain medications used or allowed
Bach, 1991	Retrospective cohort Denmark Single center Pain clinic	A: Long-acting morphine B: Buprenorphine (short-acting) Mean dose at end of intervention 1.2 mg buprenorphine and 80 mg morphine Average duration 58 days	Patients with chronic pain being treated with either sublingual buprenorphine or oral sustained release morphine	Not specified	Anti-inflammatory agents, tricyclic antidepressants, or anticonvulsants
Caldwell, 2002	Prospective cohort US Multicenter Pain clinics	Once-daily morphine titrated to adequate pain relief Mean daily dose at end of intervention 49 mg morphine (max 120 mg/day) 26 weeks of treatment	Adults with clinical and radiographic evidence of osteoarthritis who had failed course of non-opioids for pain and completed a randomized double-blind trial of once-daily morphine, twice-daily morphine, or placebo.	Patients with serious comorbid conditions or conditions that might affect assessment of pain, weight <100 lbs, steroids within 1 month, intra-articular injections within six months, opioids therapy for >3 weeks prior to baseline, substance abuse, unable to tolerate opioid during randomized trial	Acetaminophen, topical analgesics, and non-steroidal anti-inflammatory agents

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: Cohort studies of long-acting opioids

Author, Year	Number screened Number eligible Number enrolled	Number withdrawn or lost to follow-up Number analyzed	Population characteristics	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven met)
Bach, 1991	Unable to assess, no inception cohort	Unable to assess number withdrawn or lost to follow-up, no inception cohort 264 analyzed	avg. 70 years Gender and race not reported 56% of non-cancer pain patients had ischemic leg pain 44% other non-cancer pain Pain duration not reported	Any adverse event as assessed weekly at follow-up visits or telephone calls by pain clinic nurses	POOR. Not clear if selection of patients biased, not clear if consecutive series. Unable to assess loss to follow-up, no inception cohort. Adverse events not specified or defined. Ascertainment techniques inadequately described. Assessors do not appear to have been blinded. No statistical analysis of confounders. Duration of follow-up not reported. (0)
Caldwell, 2002	184 screened 184 eligible 181 enrolled	52% (86/181) discontinued or withdrew prematurely 181 analyzed for adverse events	Age, gender, race not reported Characteristics and duration of osteroarthris pain not reported for patients enrolling in open-label extension	Any adverse event, assessment methods not clear	POOR. Not clear if selection of patients biased, number eligible not reported. High overall loss to follow-up. Adverse events not specified or defined. Ascertainment techniques inadequately described. Patients and assessors blinded to intervention. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 4 weeks. (2)

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: Cohort studies of long-acting opioids

Author, Year	External validity	Funding sources and role of funder	Rate and number of adverse events	Comments
Bach, 1991	Population not adequately described, unable to assess whether population similar to populations in whom the intervention would be applied. Unable to assess how many patients screened. Exclusion criteria not specified.	Not reported	Oral long-acting morphine vs. sublingual buprenorphine: Any adverse event: 33/114 (28.9%) vs. 19.3% (29/150) Individual adverse events not reported according to indication for treatment	Tabulated results exclude 189 patients with cancer pain. Individual side effects not reported for non-cancer pain patients. Not clear if mean doses of medications equipotent between long-acting morphine and buprenorphine.
Caldwell, 2002	Population not adequately described, unable to assess whether population similar to patients in whom the intervention would be applied, Exclusion criteria reported for prior randomized trial, numbers excluded for specific criteria not reported. 28 patients had been on placebo during prior randomized trial.	Funding source not clear; one author employed by drug manufacturer of once-daily morphine (Elan Pharmaceutical)	Adverse events reported in >5% of patients taking once-daily morphine either in a.m. or p.m., n =181 Constipation: 35% Nausea: 16% Diarrhea: 13% Somnolence: 13% Dizziness: 9% Abdominal pain: 8% Pain: 8% Headache: 8% Infection: 7% Insomnia: 6% Peripheral edema: 6% Vomiting: 6% Dry mouth: 4% Accidental injury: 4%	High withdrawal and loss to follow-up rate, not clear how withdrawn patients accounted for in adverse event rates.

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: Cohort studies of long-acting opioids

Author, Year	Type of study, Setting	Medications evaluated (dose, duration)	Eligibility criteria	Exclusion criteria	Other pain medications used or allowed
Dellemijn, 1998	Prospective cohort Netherlands Single center Pain clinic	Transdermal fentanyl titrated to adequate pain relief (max 100 micrograms/hr) Maximum tolerated dose at end of treatment 75 micrograms/hour (7 patients) 12 weeks of treatment, followed by tapering off transdermal fentanyl and substitution with fixed dose long-acting morphine (60 mg bid)	Adults with noncancer neuropathic pain who had completed a randomized double-blind trial with intravenous fentanyl plus diazepam or saline	Use of opioids or modified pain regimens during the 2 weeks before starting the study, contraindications to opioids, presence of multiple sites or other types of pain, intermittent neuropathic pain, and uncertainty about origin of pain	Continued other entry medications at baseline level.
Dunbar, 1996	Retrospective cohort US Single Center Pain clinic	6/20 (30%) oxycodone alone 6/20 (30%) methadone alone 5/20 (25%) methadone and oxycodone 1/20 (5%) morphine SR + oxycodone 1/20 (5%) hydromorphone + oxycodong 1/20 (5%) morphine SR alone Doses not reported Pain duration not reported	Patients with chronic non-cancer pain and a prior history of substance abuse who were managed on opioids for any period of time	None	Not reported

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: Cohort studies of long-acting opioids

Author, Year	Number screened Number eligible Number enrolled	Number withdrawn or lost to follow-up Number analyzed	Population characteristics	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven met)
Dellemijn, 1998	50 screened 50 eligible 48 enrolled	33% (16/48) discontinued or withdrew prematurely 4% (2/48) lost to follow-up 44 analyzed for adverse events	avg. 49 years 77% female Race not reported Neuropathic pain: 58% radiculopathy 19% post-traumatic neuralgia 6% post-herpetic neuralgia 4% phantom pain 6% central pain 6% postrhizotomy pain Pain duration not reported	Any adverse event, assessment methods not clear, severity graded on 0-100 VAS	POOR. Not clear if selection biased; number eligible in prior trial not reported. High overall loss to follow-up (18/48). Adverse events not specified or defined. Ascertainment techniques not described. Patients and assessors not blinded to treatment. Adequate duration of follow-up appears adequate, 12 weeks. (1)
Dunbar, 1996	Unable to assess, no inception cohort	Unable to assess number withdrawn or lost to follow-up, no inception cohort 20 analyzed	35% peripheral neuropathy 20% chronic pancreatitis 10% failed back surgery 20% arachnoiditis 15% other Duration not reported	Prescription drug abuse assigned by physician reviewing data	POOR. Not clear if selection of patients biased, not clear if consecutive series. Unable to assess loss to follow-up, no inception cohort. Adverse events not specified or defined. Ascertainment technique not described. Assessors do not appear to have been blinded. No statistical analysis of confounders. Duration of follow-up not reported. (0)

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: Cohort studies of long-acting opioids

Author, Year	External validity	Funding sources and role of funder	Rate and number of adverse events	Comments
Dellemijn, 1998	Population adequately described. Number eligible and screened in prior trial not reported, unable to assess whether population similar to populations in whom the intervention would be applied. Exclusion criteria reported in prior trial, numbers excluded for specific criteria not reported.	Janssen (transdermal fentanyl) Author not employed by funder, not reported if data held by funder	Side effects on transdermal fentanyl occurring at any time (estimated from graph), n=44: Nausea: 92% Sweating: 68% Headache: 68% Fatigue: 58% Vomiting: 54% Dizziness: 53% Constipation: 36% Dyspnea: 36% Pruritus: 33% Dry mouth: 31% Insomnia: 28% Anorexia: 25% Anxiety: 18% Skin irritation: 18% Other adverse events reported in <20% Long-term use: 9/48 (19%) continued >2 years	High withdrawal and loss to follow-up rate, not clear how withdrawn patients accounted for in adverse event rates.
Dunbar, 1996	Population adequately described. Number eligible and screened not reported, unable to determine whether population similar to populations in whom the intervention would be applied. Exclusion criteria not specified.	Not reported	Abuse: Oxycodone alone 1/6 (16.7%); methadone alone 3/6 (50%); methadone + oxycodone 3/5(60%); long-acting morphine + oxycodone 0/1 (0%); hydromorphone + oxycodone 1/1 (100%); long-acting morphine 1/1 (100%)	Only study addressing risk of abuse in higher-risk population. Diagnosis of abuse not specified or defined and assigned by physician not blinded to patient's prior condition or current treatment. Inadequate detail regarding length of opioid treatment, dose, and severity of underlying pain. No inception cohort.

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: Cohort studies of long-acting opioids

Author, Year	Type of study, Setting	Medications evaluated (dose, duration)	Eligibility criteria	Exclusion criteria	Other pain medications used or allowed
Franco, 2002	Prospective cohort	Transdermal fentanyl Mean dose 42 mg/day 6 months	Patients of either gender aged 18 years or over presenting with chronic non-cancer pain susceptible to be treated with opioids and a mental status sufficient to be able to complete effectiveness tests; unsuccessful pain relief under current treatment with weak opioids at maximal doses (WHO) analgesic ladder to step 3 or previous treatment with morphine (in particular, when > 120 mg/day was required)	Previous treatment with fentanyl; history of alcohol abuse, drug dependence, or severe personality disorders according DSM-III-R criteria	Analgesics
Green, 1996	Retrospective cohort	Methadone Mean dose not reported (range 30 to 120 mg/day) Duration not reported	Patients with chronic non-cancer pain on methadone	Not reported	Not reported

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Author, Year	Number screened Number eligible Number enrolled	Number withdrawn or lost to follow-up Number analyzed	Population characteristics	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven met)
Franco, 2002	Not reported Not reported 236 enrolled	110(46.6%) withdrawn 236 analyzed	avg. 66.2 years 31% female Race not reported 50.8% neuropathic pain Pain duration not reported	Incidence, nature, time of onset, duration and intensity were recorded using non-specific and specific questions related to expected adverse events. Intensity determined by patient subjective evaluation. Investigator determined relationship between the treatment and adverse events.	POOR. Not clear if selection of patients biased, number eligible not reported. High overall loss to follow-up. Adverse events not specified or defined. Ascertainment techniques inadequately described. Patients and assessors not blinded to intervention. No statistical analysis of potential confounders. Duration of follow-up appears adequate, 6 months. (1)
Green, 1996	Unable to assess, no inception cohort	Unable to assess number withdrawn or lost to follow-up, no inception cohort 11 analyzed	avg. 56 years 27% female Race not reported 73% chronic back pain 18% neuropathy 9% chronic headaches Pain duration not reported	Any adverse event, assessment methods not clear	POOR. Not clear if selection of patients biased, not clear if consecutive series. No inception cohort, unable to assess loss to follow-up. Adverse events not specified or defined. Ascertainment technique not described. Assessors do not appear to have been blinded. No statistical analysis of potential confounders. Duration of follow-up not reported. (0)

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Author, Year	External validity	Funding sources and role of funder	Rate and number of adverse events	Comments
Franco, 2002	Population adequately described, unable to assess whether population similar to populations in whom the intervention would be applied. Unable to assess how many patients screened. Exclusion criteria specified.	Not reported	Transdermal fentanyl (n=236) Any adverse effect: 177(75%) Somnolence=53(22.5%) Nausea=51(21.6%) Vomiting=36(15.3%) Constipation=36(15.3%) Dizziness=59(25%) Irritability=12(5.1%) Urinary retention=10(4.2%) Sweating=22(9.3%) Local pruritus=9(3.8%)	High withdrawal rate
Green, 1996	Population adequately described. No inception cohort, unable to determine whether population similar to populations in whom the intervention would be applied. Exclusion criteria not specified.	Not reported	Methadone: Any adverse effect: 6/11 (55%) Abuse: 1/11 (9%) Overdose on patient's methadone by family member or friend: 1/11 (9%) Sudden death: 1/11 (9%) Severe anorexia, sedation, and nausea: 1/11 (9%)	Small study, not clear how patients selected for methadone treatment or how selected for inclusion. No inception cohort.

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Author, Year	Type of study, Setting	Medications evaluated (dose, duration)	Eligibility criteria	Exclusion criteria	Other pain medications used or allowed
Milligan, 2001	Prospective cohort International Multicenter Pain clinics	Transdermal fentanyl (titrated) Mean final dose 90 micrograms/hr 12 months	Patients >18 years old with chronic nonmalignant pain >6 weeks requiring continuous treatment with a potent opioid	Allergy or hypersensitivity to opioids, life-threatening disease, skin condition precluding use of transdermal system, history of substance abuse, other significant disease	Immediate-release morphine for breakthrough pain
Ringe, 2002	Prospective cohort Germany Multicenter	Transdermal fentanyl (titrated) Mean dose not reported 42/64(65.6%) 25 mg/h 3/64(4.6%) 50 mg/h 17/64(25.6%) required unspecified up-titration Median observation duration=30 days	Patients with at least one osteoporotic vertebral fracture causing pain that required continuous administration of strong opioids	Osteoporotic fracture of the femoral neck or with osteoporosis caused by malignant diseases	Nonopioid analgesics Baseline=38/64(59%) Day 15=8/64(12.5%) Weak opioids Baseline=17/64(26.6%) Day 15=4/64(6.3%) Strong opioids Temporary=2/64(3.1%)

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Author, Year	Number screened Number eligible Number enrolled	Number withdrawn or lost to follow-up Number analyzed	Population characteristics	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven met)
Milligan, 2001	Screened unclear Eligible unclear 532 enrolled (Study reports number eligible = number enrolled)	62% (231/532); 226 withdrew, 5 lost to follow-up 530 analyzed for adverse events	avg. 51 years 52% female 99% white 51% neuropathic 69% nociceptive 70% somatic 7.5% visceral Pain duration average 8.8 years	Any adverse event possibly or definitely treatment-related, recorded monthly and at study discontinuation, assessment method not described	POOR. Not clear if selection of patients biased, number eligible not reported. High overall loss to follow-up. Adverse events not specified or defined. Ascertainment technique inadequately described. Patients and assessors not blinded. Inadequate statistical analysis (age only). Duration of follow-up appears adequate, 12 months. (1)
Ringe, 2002	Screened unclear Eligible unclear 64 enrolled	15(23%) withdrew 64 analyzed	Mean age=71 years 86% female Race nr Primary osteoporosis=70% Secondary osteoporosis=30% Median duration of pain=14 days	All adverse events assessed by severity (mild, moderate, severe) and relationship to treatment (none, unlikely, possible or probable)	POOR. Not clear if selection of patients is biased. High overall loss to follow-up. Adverse events not specified or defined. Ascertainment technique inadequately described. Patients and assessors not blinded. No statistical analysis of confounders. Inadequate duration of treatment (30 days). (0)

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Author, Year	External validity	Funding sources and role of funder	Rate and number of adverse events	Comments
Milligan, 2001	Population adequately described. Number of patients eligible and screened not reported, unable to determine whether population similar to populations in whom the intervention would be applied. Exclusion criteria specified, numbers excluded for specific criteria not reported.	Janssen (transdermal fentanyl) One author employed by Janssen, not reported if data held by funder.	Transdermal fentanyl: Severe nausea: 48/530 (9%) Severe vomiting: 42/530 (8%) Severe diaphoresis: 37/530 (7%) All serious adverse events: 146/530 (28%) Serious adverse events probably or possibly treatment related: 38/530 (7%) One or more adverse events considered possibly or definitely related to study medication: 387/530 (73%) and 170/530 (32%) Withdrawals due to adverse events: 130/530 (25%) Respiratory depression: 4/530 (1%) Drug abuse: 3/530 (0.6%) Addiction: None reported Deaths thought related to trial medication: 1/530 (0.2%)	103 patients had participated in trial by Allan. High overall withdrawal rate; not clear how withdrawn patients accounted for in adverse event rates. No significant difference in adverse event rates between older (>65) and younger patients, raw numbers not presented.
Ringe, 2002	Population adequately described. Number eligible and screened not reported, unable to determine whether population similar to populations in whom the intervention would be applied. Limited exclusion criteria not specified.	Janssen-Cilag GmbH	Transdermal fentanyl: Patients with at least one adverse event: 25(39%) Withdrawal due to adverse events: 13(20.3%)	

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Author, Year	Type of study, Setting	Medications evaluated (dose, duration)	Eligibility criteria	Exclusion criteria	Other pain medications used or allowed
Roth, 2000	Prospective cohort (open-label extension of randomized trial) US Multicenter Rheumatology clinics	Long-acting oxycodone (titrated) Average dose 40 mg/day 6 month initial period with two optional 6 month extension periods	Patients completing clinical trial (Roth 2000) who wished to continue controlled-release oxycodone therapy	Severe organ dysfunction or history of drug or alcohol abuse	No rescue medications allowed
Staats, 2004	Retrospective cohort U.S. Population-based (California Medicaid)	A: Transdermal fentanyl B: Long-acting oxycodone C: Long-acting morphine	Random sample of California Medicaid patients, no prior constipation diagnosis, no long-acting opioid during previous 3 months, prescribed one of the included long-acting opioids during 3 consecutive months	Claims for two or more opioids of interest, use of other opioids other than codeine	Not specified

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Author, Year	Number screened Number eligible Number enrolled	Number withdrawn or lost to follow-up Number analyzed	Population characteristics	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven met)
Roth, 2000	133 screened 133 eligible 106 enrolled	60 withdrew 106 analyzed for adverse events	Not reported, population participated in study by Roth 2000	Any adverse event Spontaneously reported or observed by investigator at each visit (weekly to once every 8 weeks)	FAIR. Selection of patients does not appear biased. High overall loss to follow-up. Adverse events not specified or defined. Ascertainment technique adequately described. Patients and assessors not blinded. Inadequate statistical analysis (duration of treatment only). Duration of follow-up appears adequate, 6-18 months. (3)
Staats, 2004	Not reported Not reported 1836	Not applicable	Transdermal fentanyl vs. long-acting oxycodone vs. long-acting morphine Age: 66 vs. 54 vs. 56 years Female: 71% vs. 60% vs. 56% Non-white race: 34% vs. 30% vs. 40% Cancer: 38% vs. 15% vs. 38% Dose (morphine equivalent); 116 vs. 232 vs. 208	First episode of constipation event (ICD-9 code) using inpatient and outpatient claims data	FAIR. Inception cohort and number unable to be assessed not reported. Not clear if assessors blinded. Adequate duration of follow-up, 90 days. (5)

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: Cohort studies of long-acting opioids

Author, Year	External validity	Funding sources and role of funder	Rate and number of adverse events	Comments
Roth, 2000	Population adequately described. Highly selected population, patients completing randomized trial who wanted to continue open-label extension. Exclusion criteria specified, numbers excluded for specific criteria not reported. Patients on prior opioids during previous 14 day trial.	Purdue (sustained release oxycodone) One author employed by funding source, not reported if data held by funder	Long-acting oxycodone: Long-term use: 46/106 (43%) Withdrew due to adverse event: 32/106 (30%) Constipation: 55/106 (52%) Somnolence: 32/106 (30%) Nausea: 25/106 (24%) Pruritus: 21/106 (20%) Nervousness: 16/106 (15%) Headache: 14/106 (13%) Insomnia: 14/106 (13%) Hospitalization during observation period: 13/106 (12%), 5/106 (5%) possibly related to intervention	Varying periods of follow-up. Number enrolled (106) does not match numbers reported in duration of follow-up (114). Not clear how withdrawn patients accounted for in adverse event rates.
Staats, 2004	Population adequately described. California Medicaid population. High proportion with cancer, varied between intervention arms.	Janssen (transdermal fentanyl) One author employed by funder, not reported if data held by funder	Long-acting oxycodone and long-acting morphine versus transdermal fentanyl (comparator): adjusted odds ratio 1.78 (95% CI 1.05-3.03) and 1.44 (0.80-2.60) for constipation	Many significant baseline differences between groups; analysis adjusted for dose, concomitant medications, comorbidities including cancer. Data appears to overlap with Ackerman 2004.

Evidence Table 2.4. Adverse events from opioids for chronic non-cancer pain: Cohort studies of long-acting opioids

Author, Year	Type of study, Setting	Medications evaluated (dose, duration)	Eligibility criteria	Exclusion criteria	Other pain medications used or allowed
Hartung, 2007	Prospective cohort	A: Transdermal fentanyl B: Methadone C: Sustained-release oxycodone D: Sustained-release morphine	Oregon fee-for-service Medicaid enrollees with an initial prescription of a long-acting opioid (at least 28 days worth of medication) from January 1, 2000 and December 31, 2004 with continuous prescriptions for opioids	Not specified	Not reported

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Author, Year	Number screened Number eligible Number enrolled	Number withdrawn or lost to follow-up Number analyzed	Population characteristics	Method of adverse event assessment and adverse events assessed	Quality rating (number of criteria out of seven met)
Hartung, 2007	Not reported	5684 included in analyses, 2027 with non-cancer pain (338 transdermal fentanyl, 508 methadone, 447 sustained-release oxycodone, 734 sustained-release morphine)	Mean age: 62 vs. 49 vs. 54 vs. 52 years (p<0.001) Female sex: 75% vs. 64% vs. 67% vs. 64% (p=0.002) Non-white race: 6% vs. 10% vs. 12% vs. 8% (p=0.028) Morphine equivalent dose/day: 98 vs. 237 vs. 67 vs. 77 mg (p<0.001) Back pain: 57% vs. 65% vs. 59% vs. 65% (p=0.016) Fibromyalgia: 15% vs. 27% vs 20% vs. 19% (p<0.001)	Mortality Emergency department encounter related to constipation, alteration of consciousness, malaise, fatigue, lethargy, respiratory failure, opioid poisoning Hospitalization related to one or more of the above symptoms Opioid poisoning Overdose symptoms (alteration of consciousness, malaise, fatigue, lethargy, respiratory failure) Constipation	

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Author, Year	External validity	Funding sources and role of funder	Rate and number of adverse events	Comments
Hartung, 2007	Population adequately described. Unclear how many patients excluded due to missing data etc. Oregon Medicaid population; 39% with cancer diagnosis.	Not reported	Transdermal fentanyl, methadone, and sustained-release oxycodone versus sustained-release morphine (referent), hazard ratios Emergency department encounter or hospitalization: 1.42 (0.63 to 3.21) vs. 0.70 (0.29 to 1.69) vs. 0.52 (0.22 to 1.23) Mortality: 0.89 (0.43 to 1.84) vs. 0.78 (0.29 to 2.13) vs. 0.98 (0.45 to 2.14) Emergency department encounter: 1.27 (1.02 to 1.59) vs. 1.13 (0.91 to 1.41) vs. 0.91 (0.76 to 1.10) Hospitalizations: 1.16 (0.85 to 1.59) vs. 1.09 (0.78 to 1.52) vs. 0.87 (0.67 to 1.14) Opioid poisoning: NR vs. 2.41 (0.26 to 22.59) vs. 1.16 (0.11 to 12.83) Overdose symptoms: 1.10 (0.72 to 1.68) vs. 1.57 (1.03 to 2.40) vs. 1.07 (0.74 to 1.53) Constipation: 0.95 (0.40 to 2.25) vs. 0.66 (0.29 to 1.53) vs. 0.72 (0.34 to 1.55)	Controlled for age, race, sex, long-term care residence, number of unique prescribers, Charlson Comorbiditiy Index, concomitant drugs (benzodiazepines, sedative hyponotics, muscle relaxants, short-acting opioids), history of opioid dependence, abuse, or enrollment in a substance abuse treatment program