Drug Class Review

Long-Acting Opioid Analgesics

Final Update 6 Evidence Tables

July 2011

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

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Abbreviations used in evidence tables

Abbreviation	Term
ACR	American College of Rheumatology
ACT	Active-control trial
AE	Adverse event
ALO-01	morphine sulfate and naltrexone hydrochloride ER
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ASA	Aspirin
bid	Twice daily
BMI	Body mass index
BTDS	Buphrenorphine transdermal system
CCT	Controlled clinical trial
CI	Confidence interval
CNS	Central nervous system
CR	Controlled release
CR	Controlled release
CV	Cardiovascular
CVS	Cardiovascular system
d	Day
DB	Double-blind
dL	Deciliter
ECG	Electrocardiogram
EEG	Electroencephalogram
EF	Ejection fraction
ER	Extended release
ER	Extended release
ERMS	Extended release morphine sulfate
FDA	US Food and Drug Administration
FU	Follow-up
g	Gram
GI	Gastrointestinal
GP	General practitioner
h	Hour
HDL-C	High density lipoprotein cholesterol
HMO	Health maintenance organization
HR	Hazard ratio
HRQOL	Health-related quality of life
ICD-10	International Classification of Diseases, Tenth Revision

Abbreviation	Term
ICD-9	International Classification of Diseases, Ninth Revision
IR	Immediate release
ITT	Intent-to-treat
L	Liter
LA	Long acting
LBP	Low back pain
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last Observation Carried Forward
LS means	Least squares means
MANCOVA	Multivariate analysis of covariance
mcg	Microgram
mg	Milligram
min	Minute
mL	Milliliter
mo	Month
MOS	Medical Outcomes Study
N	Sample size (entire sample)
n	Subgroup sample size
NA	Not applicable
NR	Not reported
NRS	11-point Likert Numeric Rating Scale
NS	Not significant
NSD	No significant difference
OA	Osteoarthritis
OR	Odds ratio
OROS	Osmotic release oral system
P	*P* value
P	Placebo
PCT	Placebo-controlled trial
PGA	Patient Global Assessment
PGIC	Patient Global Impression of Change
PPY	Per person year
qd	Once daily
QOL	Quality of life
RCT	Randomized controlled trial
RR	Relative risk
SB	Single-blind
SD	Standard deviation
SE	Standard error

Abbreviation	Term
SR	Sustained release
SSRIs	Selective serotonin reuptake inhibitors
tid	Three times daily
VAS	Visual analog scale
vs.	Compared with (versus)
WD	Withdrawal
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
XR	Extended release
y	Year

Evidence Table 1. Update 6: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Hale, 2007 U.S. Poor	Adults meeting ACR criteria for OA of the knee or hip for ≥3 months before enrolment with a mean daily pain rating at the affected joint of moderate to severe, despite chronic se of stable doses (at least 30 days with no regimen change) of NSAIDs or other non steroidal, non opioid therapies.	A. OROS hydromorphone QD max dose 64 mg B. ER oxycodone BID max dose 80/80mg for 6 weeks (parallel)	Analgesics: ASA: 21% Tramadol: 11.3% Propoxyphene/acetaminophen: 7.3% Hydrocodone/acetaminophen: 4.0%	Age: 63.6 years Female: 69.4% Ethnicity: White 85.5% Black: 4.8% Other: 5.6%	Mean weight: 91.2kg Affected joint Knee: 79.8% Hip: 20.2% Mean Pain intensity at screening: 2.5

Evidence Table 1. Update 6: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes	Harms
Hale, 2007 U.S. Poor	140	55/1/124	OROS Hydromorphone vs ER oxycodone Mean change from baseline in pain relief: 0.8 vs 0.75; 95% CI, -0.35 to ∞ Mean change in pain intensity score: -6.0 vs -4.0; 95% CI, -0.53 to ∞ Time to third day of moderate to complete pain relief, mean (SD) days: 6.2 (4.00) vs 5.5 (2.57); 95% CI, -0.31 to ∞ Mean (SD) change (improvement) from baseline in patient global evaluation: 1.2 (1.01) vs 1.0 (1.33), P=NS between groups Proportion of patients rated treatment effectiveness as good, very good and excellent: 67.2% vs 66.7% Mean (SD) improvement in investigator global evaluation: 1.2 (1.01) vs 1.1 (1.16) Proportion of investigators rated treatment effectiveness as good, very good and excellent: 71.9% vs 70.0% Mean (SD) change in WOMAC total score from baseline: -2.0 (1.90) vs -1.8 (2.14) Mean (SD) change in WOMAC pain subscale score from baseline: -2.1 (1.96) vs -2.0 (2.03) Mean (SD) change in WOMAC stiffness score from baseline: -2.2 (2.37) vs -2.2 (2.72) Mean (SD) change in WOMAC physical function subscale score: -1.9 (1.99) vs -1.7 (2.1) Sleep disruption and daytime somnolence: 25.7 (17.82) vs 35.3 (22.56), P<0.012 Change from baseline on MOS sleep problems index I: -13.3 (21.10) vs -5.2 (22.09), P<0.045 Change from baseline on MOS sleep problem index II: -13.0 vs -7.0, P=NS (data interpreted from graph)	OROS Hydromorphone vs ER oxycodone Proportion of patients with any AE: 78.9% vs 79.1%, P=NS Proportion of patients with SAE: 4.2% vs 1.5% Nausea: 35.2% vs 29.9% Constipation: 29.6% vs 25.4% Somnolence: 25.4% vs 17.9% Vomiting: 16.9% vs 11.9% Dizziness (excluding vertigo): 14.1% vs 22.4% Headache: 5.6% vs 10.4%

Evidence Table 1. Update 6: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Hale, 2007 U.S. Poor	OROS Hydromorphone vs ER oxycodone Total withdrawals: 39.4% vs 39.1% Withdrawals due to AE: 35.2% vs 32.8%	Unclear. Study protocol developed by Knoll Pharmaceutical Company, NJ. Conduct of the study supported by Alza Corporation, CA. Assistance in preparing the first draft of the manuscript by Pharma Genesis Inc., PA	Non-inferiority study

Evidence Table 1. Update 6: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Katz, 2010 (J Pain) U.S. Fair	Adult patients with chronic pain due to OA of the knee or hip as designated by ACR criteria requiring treatment of the affected joint with non opioid analgesics or had received opioid therapy equivalent to ≤40mg/d of oral morphine	A. ERMS max dose 20-160mg BID B. ALO-01 20-80mg for 14 days (Crossover)	Acetaminophen used as rescue medication. Proportion of rescue medication used, ERMS vs ALO-01: 57.7% vs 50.7%	Median age: 57.0 (range 28 to 83 years) Female: 68.5% White: 88.3%	Mean weight: 90.2kg Mean BMI: 32.4kg/m^2 Location of OA pain Right knee: 11.7% Left hip: 4.5% Right hip: 11.7%

Evidence Table 1. Update 6: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes	Harms
Katz, 2010 (J Pain) U.S. Fair	72	3/0/72	ERMS vs ALO-01 Mean in-clinic pain intensity score change from baseline: 0.3 vs 0.2 (data from graph), P=NS Mean daily pain score summed over 14 days (Data from graph): Worst: 43 vs 42.5, Least: 20 vs 19.5, Average: 29.5 vs 29, Current: 28 vs 27.5, p=NS No significant difference between ERMS and ALO-01 in change from baseline in WOMAC pain, physical function and composite index subscales. WOMAC stiffness score at day 14: 12.3 vs 2.5, P=0.02 Proportion of patients rating treatment good, very good or excellent: 78.9% vs 91.5%	ERMS vs ALO-01 Constipation: 12.7% vs 15.5% Nausea and somnolence: 8.5% vs 9.9% Vomiting: 4.2% vs 8.5% Dizziness: 7.0% vs 1.4% Headache: 8.5% vs 4.2% Dry mouth: 1.4% vs 0.0% Pruritus: 1.4% vs 1.4% Fatigue: 0.0% vs 2.8% Pruritus generalized: 2.8% vs 0.0% Muscle spasms: 4.2% vs 4.2%

Evidence Table 1. Update 6: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Katz, 2010 (J Pain) U.S. Fair	ERMS vs ALO-01 Total withdrawals: 2.8% vs 2.7% Withdrawals due to AE: 2.8% vs 2.7%	King Pharmaceuticals	

Evidence Table 2. Update 6: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N
Afilalo, 2010 United States, Canada, New Zealand, and Australia Fair	Men and women ≥40 years of age with a diagnosis of OA of the knee according to ACR criteria, functional capacity class I-III, and pain at the reference joint requiring the use of analgesics (non-opioids or opioids at doses equivalent to ≤160 mg oral morphine/day) for ≥3 months prior to screening. Patients were dissatisfied with their current analgesic therapy and had an average baseline pain intensity NRS score of ≥5 during the 3 days preceding randomization, based on a patient-rated 11-point numerical rating scale.	A: Tapentadol ER 100-250 mg BID (maintenance period) B: Oxycodone HCl CR 20-50 mg BID (maintenance period) C: Placebo 15 weeks (3-week titration period and 12-week maintenance period)	Paracetamol ≤1000 mg/day; maximum, 3 consecutive days when deemed necessary for the relief of pain unrelated to the index joint osteoarthritis pain. Medications such as SSRIs were allowed for patients with diagnosed, controlled psychiatric or neurological conditions if taken at a stable dose for ≥3 months prior to randomization.	Age: 58.3 years (SD 9.8) Female: 60.4% White: 75.5% Black: 12.9% Hispanic: 7.6% Other: 4%	Weight: 97.5 kg BMI: 34.3 kg/m2 Age group: <65 years: 74.1% ≥65 years: 25.9% Baseline pain category: Mild: 0.2% Moderate: 16.4% Severe: 83.3%	1030

Evidence Table 2. Update 6: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Afilalo, 2010 United States, Canada, New Zealand, and Australia Fair	521/8/1023	Placebo vs Tapentadol ER vs Oxycodone CR (P-values are versus placebo unless otherwise noted) Change from baseline in average pain intensity: Tapentadol ER compared to placebo vs Oxycodone CR compared to placebo, LS mean difference vs placebo: Week 12 of maintenance period: -0.7 (95% CI, -1.04 to -0.33) vs -0.3 (95% CI, -0.68 to 0.02) Overall maintenance period: -0.7 (95% CI, -1.00 to -0.33) vs -0.3 (95% CI, -0.67 to 0.00) ≥30% reduction in average pain intensity at week 12 of the maintenance period: 35.9% vs 43.0% (P=0.058) vs 24.9% (P=0.002) ≥50% reduction in average pain intensity at week 12 of the maintenance period: 24.3% vs 32.0% (P=0.027) vs 17.3% (P=0.023, placebo superior) Health status index, mean change from baseline to endpoint: 0.1 (SE 0.02, LSM 0.12) vs 0.2 (SE 0.02, LSM 0.17; P=0.004) vs 0.1 (SE 0.02, LSM 0.11, P=0.449) WOMAC Index of OA Questionnaire subscale, LSM change from baseline: Global WOMAC score: -0.91 (SE 0.054) vs -1.12 (SE 0.054; P=0.0047) vs -1.08 (SE 0.068; P=0.0381) Pain subscale: -0.88 (SE 0.055) vs -1.16 (SE 0.055. P<0.001) vs -1.05 (SE 0.070; P=0.051) Physical function subscale: -0.83 (SE 0.055) vs -1.04 (SE 0.055; P=0.006) vs -1.04 (SE 0.070; P=0.019) Stiffness subscale: -1.00 (SE 0.063) vs -1.17 (SE 0.063; P=0.053) vs -1.10 (SE 0.080; P=0.321) EuroQol-5 Dimension questionnaire (ITT analysis population): Patients reporting "no problem at study end": Mobility: 16.3% vs 25.0% vs 16.7% Self-care: 75.1% vs 81.1% vs 80.1% Usual activities: 26.1% vs 33.7% vs 27.2% Pain/discomfort: 5.6% vs 9.0% vs 4.7% Anxiety/depression: 71.8% vs 70.9% vs 69.6% SF-36 scores, LS mean change from baseline (ITT analysis population): Physical functioning: 5.4 vs 10.7 (P<0.001) vs 7.3 (P=0.200) Role-physical: 12.1 vs 18.0 (P=0.029) vs 6.8 (P=0.050) Bodily pain: 13.1 vs 18.6 (P<0.001) vs 11.6 (P=0.297) General health: 1.7 vs 2.4 (P=0.407) vs 0.9 (P=0.361) Vitality: 6.8 vs 8.6 (P=0.168) vs 1.3 (P<0.001) Social functioning: 7.0 vs 9.7 (P=0.089) vs 2.7 (P=0.008) Role-emotional: 7.8 vs 4.8 (P=0.248) vs 0.1 (P=0.004) Mental health: 3.5 vs 2.3 (P=0.270) vs -0.1 (P<0.001) Mental component summary: 2.0 vs 0.9 (P=0.089) vs -1.0 (P<0.001) Physical component summary: 3.5 vs 6.2 (P<0.001) vs 3.7 (P=0.675) PGIC: Very much improved: 8.4% (23/273) vs 20.2% (52/258) vs 13.5% (27/200) Much improved: 27.1% (74/273) vs 38.4% (99/258) vs 33.5% (67/200) Minimally improved: 23.4% (64/273) vs 20.9% (54/258) vs 26.5% (53/200) No change: 24.2% (66/273) vs 12.8% (33/258) vs 9.5% (19/200) Minimally worse: 11.0% (30/273) vs 3.1% (8/258) vs 10.0% (20/200) Much worse: 4.0% (11/273) vs 3.9% (10/258) vs 6.5% (13/200) Very much worse: 1.8% (5/273) vs 0.8% (2/258) vs 0.5% (1/200) Improvements in PGIC scores: tapentadol ER P<0.001; oxycodone CR P=0.018

Evidence Table 2. Update 6: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Afilalo, 2010 United States, Canada, New Zealand, and Australia Fair	Placebo vs Tapentadol ER vs Oxycodone CR Incidence of treatment-emergent AEs: 206 (61.1%) vs 261 (75.9%) vs 299 (87.4%) **Gastrointestinal disorders:** 88 (26.1%) vs 148 (43.0%) vs 230 (67.3%) Constipation: 22 (6.5%) vs 65 (18.9%) vs 126 (36.8%) Nausea: 23 (6.8%) vs 74 (21.5%) vs 125 (36.5%) Vomiting: 11 (3.3%) vs 18 (5.2%) vs 61 (17.8%) Dry mouth: 8 (2.4%) vs 22 (6.4%) vs 15 (4.4%) Diarrhea: 20 (5.9%) vs 16 (4.7%) vs 17 (5.0%) **Nervous system disorders:** 84 (24.9%) vs 138 (40.1%) vs 164 (48.0%) Somnolence: 14 (4.2%) vs 37 (10.8%) vs 67 (19.6%) Dizziness: 16 (4.7%) vs 61 (17.7%) vs 65 (19.0%) Headache: 56 (16.6%) vs 51 (14.8%) vs 50 (14.6%) **General and administration site disorders:** 37 (11.0%) vs 65 (18.9%) vs 66 (19.3%) Fatigue: 15 (4.5%) vs 37 (10.8%) vs 35 (10.2%) **Skin and subcutaneous disorders:** 12 (3.6%) vs 50 (14.5%) vs 71 (20.8%) Pruritus: 4 (1.2%) vs 24 (7.0%) vs 43 (12.6%) **Musculoskeletal and connective tissue disorders:** 59 (17.5%) vs 36 (10.5%) vs 36 (10.5%) Back pain: 22 (6.5%) vs 7 (2.0%) vs 5 (1.5%) Arthralgia: 17 (5.0%) vs 10 (2.9%) vs 6 (1.8%) PAC-SYM: LS mean change from baseline was significantly lower in the tapentadol ER group than the oxycodone CR group for the overall PAC-SYM score (P<0.001), and the overall abdominal (P<0.001), overall rectal (P=0.018), and overall stool subscale scores (P<0.001), indicating a worsening of constipation symptoms with oxycodone CR treatment compared with tapentadol ER treatment. COWS (evaluated at treatment discontinuation was for patients who did not use opioids following discontinuation of study medication): **COWS assessments completed ≥2 days to <5 days after the last intake of study medication:** No opioid withdrawal: 100% (23/23) vs 82.9% (29/35) and 86.5% (32/37) Mild opioid withdrawal: 0% (0/23) vs 17.1% (6/35) vs 13.5% (5/37) **COWS assessments completed ≥5 days after last intake of study medication:** No opioid withdrawal: 91.5%(54/59) vs 98.6%(69/70) vs 85.7%(72/84) Mild opioid withdrawal: 8.5% (5/59) vs 1.4% (1/70) vs 11.9% (10/84) Moderate opioid withdrawal: 0% (0/59) vs 0% (0/70) vs 2.4% (2/84)	Placebo vs Tapentadol ER vs Oxycodone CR Total withdrawals: 130 (38.6%) vs 147 (42.7%) vs 221 (64.6%) Due to AEs: 22 (6.5%) vs 66 (19.2%) vs 147 (43%)	Johnson & Johnson Pharmaceutical Research and Development	There were discrepancies between the numbers of withdrawals (total and due to AE) reported in the text and in Figure 1, so the values from the text were abstracted.

Evidence Table 2. Update 6: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N
Hale, 2010 United States Fair	Males and females 18-75 years of age with a documented diagnosis of moderate-to-severe chronic LBP for ≥3 hours per day, 20 days per month for 6 months, and had their pain classified as non-neuropathic (classes 1 and 2) or neuropathic (classes 3, 4, 5, and 6) based on the Quebec Task Force Classification of Spinal Disorders. All patients were required to be on daily opioid treatment with 60-320 mg oral morphine equivalent (12-64 mg hydromorphone) per day within 2 months prior to the screening visits, and on stable doses of all prior analgesics for at least 2 weeks prior to the screening visit.	A: OROS hydromorphone ER QD B: Placebo Only patients who found OROS hydromorphone efficacious and tolerable during the 2-4 week open-label conversion and titration phase were randomized to the DB phase. Patients who were randomized to placebo had hydromorphone tapered down over the first 2 weeks of the 12-week DB phase. (See Comments for complete design information.)	ASA ≤325 mg/day for cardiovascular prophylaxis; Hydromorphone (2, 4, and 8 mg) as rescue medication (unrestricted for the first 3 days and then restricted to two tablets per day after day 3 of the conversion/titration phase) Overall percentage of patients requiring rescue medication at least once over the course of the DB phase, hydromorphone ER vs placebo: 96.2% vs 97.0%	Age: 48.6 years (SD 10.6) Female: 50.4% White: 84.6% Black: 8.6% Hispanic: 5.3% Other: 1.5%	Weight: 91.8 kg BMI: 31.2 kg/m2 Mean stable daily hydromorphone ER dose: 37.8 mg (SD 17.4) Etiology: Non-neuropathic LBP: 64.3% Neuropathic LBP: 35.3%	268 (out of 459 patients who entered open-label phase)

Evidence Table 2. Update 6: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Hale, 2010 United States Fair	DB phase: 158/5/266 Open-label titration phase: 191/8/NA	<u>Hydromorphone vs Placebo</u> Median change in weekly patient diary NRS scores from baseline to endpoint: 0.2 vs 1.6; P<0.001 Change from baseline in mean pain intensity NRS scores: 0.4 vs 1.2; P<0.001 Median change in weekly Roland Morris Disability Questionnaire scores: 0 vs 1.0; P<0.005 PGA of treatment: Poor: 3.5% vs 14.2% Fair: 14.9% vs 22.5% Good: 41.3% vs 35.2% Very good: 27.6% vs 20.3% Excellent: 11.1% vs 6.3% Ad hoc analyses: 30% pain reduction: 60.6% vs 42.9%; P<0.01 50% pain reduction: 42.4% vs 24.1%; P<0.005 Discontinuations due to treatment failure occurred sooner (p<0.001) and more frequently among patients in the placebo group compared with patients in the hydromorphone ER group.

Evidence Table 2. Update 6: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Hale, 2010 United States Fair	Open-label dose conversion/titration phase (all patients taking Hydromorphone) vs Hydromorphone (DB phase) vs Placebo At least one AE: 247 (55.3%) vs 64 (47.8%) vs 73 (54.5%) Serious AE: 6 (1.1%) vs 6 (4.5%) vs 4 (3%) Treatment-related AE: 192 (43%) vs 36 (26.9%) vs 43 (32.1%) Treatment-related serious AE: 1 (0.2%) vs NR vs NR Constipation: 69 (15.4%) vs 10 (7.5%) vs 5 (3.7%) Nausea: 53 (11.9%) vs 12 (9.0%) vs 10 (7.5%) Vomiting: 29 (6.5%) vs 8 (6.0%) vs 6 (4.5%) Somnolence: 39 (8.7%) vs 1 (0.7%) vs 0 (0%) Headache: 35 (7.8%) vs 7 (5.2%) vs 10 (7.5%) Drug withdrawal syndrome: 22 (4.9%) vs 13 (9.7%) vs 16 (11.9%) Arthralgia: 9 (2.0%) vs 8 (6.0%) vs 3 (2.2%) Diarrhea: 13 (2.9%) vs 5 (3.7%) vs 9 (6.7%) Back Pain: 13 (2.9%) vs 6 (4.5%) vs 8 (6.0%) Insomnia: 13 (2.9%) vs 7 (5.2%) vs 5 (3.7%)	Hydromorphone vs Placebo Total withdrawals: 68 (50.7%) vs 90 (67.2%); P<0.01 Due to AE: 7 (5.2%) vs 3 (2.2%) Due to opioid withdrawal symptoms: 3 (2.2%) vs 7 (5.2%) Open-label dose conversion/titration phase (all patients taking Hydromorphone) Total withdrawals: 191 (41.6%) Due to AE: 60 (13.1%) Due to opioid withdrawal symptoms: 3 (0.65%)	Neuromed and Covidien Pharmaceuticals	During the 2- to 4-week dose-conversion/titration phase, patients received hydromorphone ER 12-64 mg (only two dose increases were permitted per week). Patients were initially converted to a dose of once-daily hydromorphone ER that was approximately 75% of the equianalgesic dose of their previous total daily opioid dose. Only patients who met the following predefined stability criteria were eligible to enter the DB phase: patients were taking ≥12 mg and ≤64 mg of hydromorphone ER per day; patients remained on the same dose without change for at least 7 consecutive days (stable dose period); patients took a mean of ≤2 tablets of rescue medication hydromorphone IR per day during the stable dose period; patients had adequate pain control as indicated by a mean pain intensity score ≤4 on the pain intensity NRS during the stable dose period; patients answered 'yes' to the question 'Has this medication helped your pain enough so that you would continue to take the medication?'; patients had no side-effects that were intolerable or that could impact their ability to complete the study. Patients who did not meet these stability criteria underwent premature discontinuation procedures and were discontinued from the study.

Evidence Table 2. Update 6: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N
Hanna, 2008 Europe and Australia Fair	Patients with moderate to severe painful diabetic neuropathy for at least 3 months despite receiving their maximum tolerated dose of gabapentin for at least one month, as confirmed by a Michigan Neuropathy Screening Instrument assessment score of ≥2.5 at the screening visit.	A: Oxycodone prolonged-release (OxyContin®) tablets BID + gabapentin B: Placebo + gabapentin For 12 weeks Dosing schedule: All patients started the study on the lowest dose of medication (5 mg) and continued their treatment with gabapentin at a stable frequency and dose (maximum tolerated). The Investigator titrated the patients' oxycodone prolonged-release tablets or matched placebo in a stepwise manner, i.e. increased or reduced the medication by one dose level (permitted for the entire duration of the 12 week DB phase).	Paracetamol as escape medication; patients taking stable doses of NSAIDS and tricyclic antidepressants started at least 3 weeks prior to screening were permitted to continue; ASA for cardiovascular indication (max 300 mg/d) and any other medication not excluded by study exclusion criteria. See article for detailed list of concomitant medications and percentage of patients taking them.	Age: 60.1 years Female: 36% Caucasian: 99% Asian: <1% Other: <1%	Weight: 90.77 kg	338

Evidence Table 2. Update 6: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Hanna, 2008 Europe and Australia Fair	79/0/328	Oxycodone + gabapentin vs Placebo + gabapentin Change from baseline in the mean Box Scale-11 pain scores at endpoint (using LOCF): 2.1 (SD 2.61) vs 1.5 (SD 2.38); Treatment difference P=0.002, Overall treatment difference 0.55 (95% CI, 0.15 to 0.95), P=0.007; Treatment x period difference P=0.004 Mean escape medication use (tablets) at endpoint using LOCF: 1.6 (SD 2.09) vs 2.1 (SD 2.41); Treatment difference -0.48 (95% CI, -0.91 to -0.05), P=0.029 Global assessment of pain relief: Patients rating study drug as good or very good at relieving pain and better than their pre-study medication: 56% vs 41% Patients rating treatment as better or much better than pre-study medication: 74% vs 47% Patients rating their treatment as good or very good for overall treatment of pain: 60% vs 40% Global assessment of pain analysis: P=0.003 The McGill pain questionnaire total pain intensity score, sensory pain score, total affective pain score (all P<0.001), VAS pain for "pain last week" (P=0.001), and present pain intensity (P=0.002) were all statistically significantly lower in the oxycodone group. Results of the EuroQol EQ-5D questionnaire were not significant (but showed oxycodone to be slightly superior). The BPI scores (mean pain intensity and mean pain interference) were statistically significantly lower in the oxycodone group (P < 0.001).

Evidence Table 2. Update 6: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Hanna, 2008 Europe and Australia Fair	Oxycodone + gabapentin vs Placebo + gabapentin Any treatment emergent AE: 147 (88%) vs 119 (71%) Cardiac disorders: 6 (4%) vs 4 (2%) Gastrointestinal disorders: 91 (54%) vs 45 (27%) Constipation: 45 (27%) vs 10 (6%) Nausea: 43 (26%) vs 18 (11%) Vomiting: 16 (10%) vs 7 (4%) Ear/labyrinth disorders: 13 (8%) vs 7 (4%) Eye disorders: 8 (5%) vs 2 (1%) Fatigue: 31 (18%) vs 14 (8%) Infections and infestations: 50 (30%) vs 30 (18%) Injury, poisoning and procedural complications: 12 (7%) vs 16 (10%) Investigations: 17 (10%) vs 16 (10%) Metabolism and nutrition disorders: 15 (9%) vs 4 (2%) Musculoskeletal and connective tissue disorders: 31 (18%) vs 26 (16%) Nervous system disorders: 81 (48%) vs 39 (23%) Dizziness: 25 (15%) vs 6 (4%) Headache: 17 (10%) vs 17 (10%) Somnolence: 37 (22%) vs 9 (5%) Psychiatric disorders: 29 (17%) vs 16 (10%) Renal and urinary: 7 (4%) vs 4 (2%) Skin and subcutaneous tissue disorders: 34 (20%) vs 19 (11%) Surgical/medical procedures: 9 (5%) vs 5 (3%) Vascular disorders: 8 (5%) vs 4 (2%)	Oxycodone + gabapentin vs Placebo + gabapentin Total withdrawals: 37 (22%) vs 42 (26%) Due to AE: 9 (24%) vs 27 (64%)	Mundipharma Research Limited	

Evidence Table 2. Update 6: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N
Katz, 2010 (Postgrad Med) U.S. Fair	Men and women ≥21 years with OA of the hip or knee who were otherwise in generally good health were eligible if they required treatment of chronic joint pain within the last 90 days and were unable to consistently control join pain with either non-opioid analgesics, tramadol or another opioid at a dose equivalent to ≤40 mg/day of oral morphine.	MS-sNT (EMBEDA) start dose 20 mg, max dose 160 mg/d in open label phase A: MS-sNT effective dose as identified in the open label titration phase B: Placebo 45 days open label dose titration,12 week DB phase and 2 week tapering phase	Rescue medication with acetaminophen ≤500 mg every 6 hours. ASA ≤325 mg for cardiovascular prophylaxis.	Age: 54.5 years Female: 58.4% White: 72.4% Black: 17.2% Asian: 7% American Indian or Alaska Native: 1.7% Other: 1.7% Hispanic ethnicity (reported separately): 22.1%	Primary area of OA: Right hip: 12.8% Left hip: 9.6% Right knee: 46.5% Left knee: 31.1% Prior opioid use: Opioid naïve: 73.8% Opioid experienced: 24.4%	344

Evidence Table 2. Update 6: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Katz, 2010 (Postgrad Med) U.S. Fair	61/5/343	MS-sNT (EMBEDA) vs placebo Mean (SD) change from baseline: Diary BPI pain score: -0.2 (1.9) vs 0.3 (2.1), P=0.045 Diary pain score - average pain: 0.3 (1.9) vs 0.9 (1.9), P=0.003 vs placebo Diary pain score - current pain: 0.4 (2.0) vs 0.9 (2.1), P=0.026 vs placebo WOMAC composite index : 1.6 (18.0) vs 5.8 (16.8), P=0.031 vs placebo WOMAC pain: 1.4 (18.9) vs 5.7 (17.1), P=0.023 WOMAC stiffness: 1.1 (21.1) vs 5.3 (22.0), P=0.063 WOMAC physical function: 2.3 (18.4) vs 6.2 (17.8), P=0.064 BDI: -1.4 (4.5) vs -0.9 (3.9), P=0.675

Evidence Table 2. Update 6: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Katz, 2010 (Postgrad Med) U.S. Fair	MS-sNT (EMBEDA) vs placebo Proportion of patients with any AE: 53.2% vs 48.6%; P=0.391 Proportion of patients with treatment-emergent AE: 32.7% vs 26.0% Most common treatment-emergent AEs: Constipation: 7.0% vs 4.0% Nausea: 11.7% vs 7.5% Somnolence: 1.2% vs 2.9% Vomiting: 7.05 vs 2.3% Dizziness: 1.8% vs 1.7% Pruritus: 0.6% vs 0.6% Headache: 7.0% vs 3.5% Dry mouth: 1.8% vs 1.2% Diarrhea: 12.3% vs 12.1% Rhinorrhea: 2.3% vs 6.9%	MS-sNT (EMBEDA) vs placebo Total withdrawals: 35.7% vs 43.4% Due to AE: 10.5% vs 7.5%	King Pharmaceuticals	

Evidence Table 2. Update 6: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N
Munera, 2010 U.S. Fair	Men and women ≥18 years with radiologic evidence of OA of the knee or hip who had received opioid therapy in the previous year for OA pain or whose OA pain was inadequately controlled with NSAIDs.	A: BTDS max dose 20 µg/h B: Placebo 1 week run-in followed by 4 week DB	ASA ≤325 mg as an antithrombotic.	Age: 61 years Female: 67% White: 85.1% Black: 8.9% Hispanic: 5.1% Other: 1%	Predominant pain site: Hip: 45.1% Knee: 54.9%	315

Evidence Table 2. Update 6: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Munera, 2010 U.S. Fair	160/4/311	BTDS vs placebo % of patients who met criteria for successful pain management: 44% vs 32%; OR 1.66, P=0.036 % of patients with knee OA who had successful treatment: 45% vs 30%; P=0.028, OR 2.18; 95% CI, 1.1 to 4.4 % of patients with hip OA who had successful treatment: 42% vs 35%; P=NS, OR 1.44; 95% CI, 0.7 to 3.1 Change from baseline in average pain intensity at day 28, LSM (± SEM): -1.84 (0.22) vs -1.40 (0.21); P=NS Change from baseline in diary pain intensity score, average of days 22-28 LSM (± SEM): -1.76 (0.20) vs -1.53 (0.18); P=NS Patient satisfaction score at day 28 LSM (± SEM): 1.3 (0.11) vs 1.0 (0.11); P=0.046 Patient's with positive investigator's assessment: 45% vs 31%; P=0.003

Evidence Table 2. Update 6: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Munera, 2010 U.S. Fair	BTDS vs Placebo Proportion of patients with any AE: 70% vs 53% Nausea: 27% vs 8% Headache: 22% vs 15% Dizziness: 20% vs 14% Somnolence: 15% vs 5% Pruritus at site: 13% vs 15% Vomiting: 11% vs 3% Constipation: 10% vs 2%	BTDS vs placebo Overall withdrawal: 55% vs 47% Due to AE: 24% vs 11%	Purdue Pharma L.P.	

Evidence Table 3. Update 6: Quality assessment of trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Afilalo, 2010 U.S., Canada, New Zealand, and Canada	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hale, 2007 U.S.	Unclear	No	BMI lower in placebo group, more women in treatment group; pain scores similar	Yes	No- open label	No- open label	No- open label
Hale, 2010 U.S.	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hanna, 2008 Europe and Australia	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Katz, 2010 (J Pain) U.S.	Yes	Yes	Unclear; crossover study, not reported by order of randomization	Yes	Yes	Yes	Yes
Katz, 2010 (Postgrad Med) U.S.	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Munera, 2010 U.S.	Unclear	Unclear	Yes	Yes	Unclear, described as double blind	Yes	Yes

Evidence Table 3. Update 6: Quality assessment of trials

Author, Year Country	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality Rating
Afilalo, 2010 U.S., Canada, New Zealand, and Canada	Yes (except for WOMAC, where 38.7% analyzed)	Unclear	Unclear/yes/unclear	No: overall 521/1030 withdrew; differential: 39.5% placebo, 64.9% oxycodone.	Fair
Hale, 2007 U.S.	No (>5% enrolled not included in ITT)	Unclear	Unclear	No: 83/140 completed (60%); not differential	Poor
Hale, 2010 U.S.	Yes (266/268, 99.3%)	Unclear	No	No: 158/268 (59%); 67% placebo vs 51% treatment withdrew	Fair
Hanna, 2008 Europe and Australia	Yes 328/338 (97%) analyzed; used LOCF	Unclear	Unclear	No: overall 79/338 withdrew (23%); reasons differed	Fair
Katz, 2010 (J Pain) U.S.	Yes	Unclear	Unclear/yes/unclear	Yes: 69/72 completed (96%), not differential	Fair
Katz, 2010 (Postgrad Med) U.S.	Yes 343/344 analyzed (99.7%)	Unclear	Unclear/yes/unclear	No: overall 39.5%; differential: 43% vs 36% and reasons differed	Fair
Munera, 2010 U.S.	Yes 311/315 (98.7%) analyzed	Unclear	Unclear/yes/unclear	No: overall 51% withdrew; reasons differed and more withdrew in treatment group (55% vs 47%)	Fair

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of 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	NR NR 256	60 (23%) 212

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of 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	Outcomes	Method of adverse event assessment and adverse events assessed
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 NR	<u>Fentanyl (A) vs. Long acting morphine (B)</u> **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)	Any treatment-related adverse event, assessment methods not clear other than a bowel function questionnaire was performed

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Rate and number of adverse events	Quality ratings and comments	Funding source and role	Other comments
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% Vomiting: 10% vs 10% Constipation: 16% vs. 22% Constipation by bowel function questionnaire: 29% vs. 48%, p<0.001 Somnolence: 18% vs 14% Dizziness: 11% vs 4% "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)	Efficacy: 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. Safety: 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. (Met 2 of 7 criteria)	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. Adverse events NR 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 NR.

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of 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, 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	NR NR 683	342 (50%) 608

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of 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	Outcomes	Method of adverse event assessment and adverse events assessed
Allan, 2005	Avg. 54.0 years 61% female Race: NR 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 NR 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 **Global assessment** investigator assessment on 3-point scale (deteriorated, unchanged, improved) **Rescue medication use** **Work status** number of days lost to work	<u>Fentanyl (A) vs. Long acting morphine (B)</u> **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	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

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Rate and number of adverse events	Quality ratings and comments	Funding source and role	Other 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: 27% 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/anticholinergics: 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)	Efficacy: FAIR. Allocation performed centrally. Groups similar at baseline, but baseline pain scores NR. 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. Safety: 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). (Met 4 of 7 criteria)	Janssen Pharmaceutical. One author employed by Janssen.	Not blinded. ITT results NR for several outcomes. 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%).

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of 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	NR NR 295	111 (37%) 295

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of 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	Outcomes	Method of adverse event assessment and adverse events assessed
Caldwell, 2002	Avg. 62.4 years 63% female 85% white 100% osteoarthritis (no further details reported) Pain duration NR	**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	Long acting morphine Q AM (A) vs. Long acting morphine Q PM (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)	Any treatment-related adverse event, assessment methods not clear

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Rate and number of adverse events	Quality ratings and comments	Funding source and role	Other 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	Efficacy: FAIR. Method of randomization NR. Method of treatment allocation NR. 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. Safety: 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. (Met 3 of 7 criteria)	NR	Out of multiple sleep measures, one found a significant different between long acting morphine A and long acting morphine C. 42% of patients were on opioids prior to trial; specific opioids or doses NR. 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 NR.

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of 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
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

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of 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	Outcomes	Method of adverse event assessment and adverse events assessed
Hale, 2005	Median age=46 years 47% female Race NR 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)	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 Interference** 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. 4/164 (2.4%) **Rescue medication use** 13.8 vs. 14.7 mg/day after first 4 days	Patients queried on nausea, vomiting, constipation, pruritus, sedation, lightheadedness, and sweating (methods not described in any more detail)

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Rate and number of adverse events	Quality ratings and comments	Funding source and role	Other comments
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%)	Efficacy: FAIR. Adequate randomization and treatment allocation. Groups reported as similar at baseline but data not clearly reported. Prior opioid use NR. Clear eligibility 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. Safety: 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. (Met 3 of 7 criteria)	Endo Pharmaceuticals Inc and Penwest Pharmaceuticals Co	Results of first randomization to long acting oxymorphone versus long acting oxycodone (titration phase) NR. Not clear how patients re-randomized to treatment phase.

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of 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	NR NR 491	222/491 (45%) 467 analyzed

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of 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	Outcomes	Method of adverse event assessment and adverse events assessed
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: NR Previous opioids: NR	Pain intensity VAS (0 to 100) WOMAC pain, stiffness, and physical function subscales SF-36 Global assessments of therapy (method NR) Sleep assessment (method NR)	Oxymorphone ER 40 mg vs Oxymorphone ER 20 mg vs Oxycodone CR 20 mg vs placebo, at week 4: Patient's global assessment (VAS): -28.6 (P=0.033 vs placebo) vs -23.2 (P=NS) vs -25.4 (P=NS) vs -19.5 Quality of life (SF-36) physical component: 4.5 (P=0.018 vs placebo) vs 3.4 (P=NS) vs 4.0 (P=0.038 vs placebo) vs 1.8 Quality of life (SF-36) mental component: -0.4 (P=0.06 vs placebo) vs 1.5 (P=NS) vs -0.8 (P=0.022 vs placebo) vs 0.22 Overall quality of sleep (VAS): 18.2 (P=0.01 vs placebo) vs 13.8 (P=NS) vs 15.3 (P=0.036 vs placebo) vs 7.7	Electrocardiogram, physical examination, vital signs, and clinical laboratory assessments; methods not described

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Rate and number of adverse events	Quality ratings and comments	Funding source and role	Other comments
Matsumoto, 2005	Sustained-release oxymorphone 40 mg BID (n=114) vs. sustained-release oxymorphone 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. 5% (34/124) Any adverse events: 91% vs. 95% vs. 88% vs. 57%	See Evidence Table 10	Endo Pharmaceuticals Inc. and Penwest Pharmaceuticals	

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of 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	IR rescue medication (morphine for patients randomized to extended-release morphine, oxycodone for those randomized to sustained-release oxycodone). Adjuvant pain medications such as acetaminophen, NSAIDs, anxiolytics, antidepressants, corticosteroids, anticonvulsants and neuroleptics were allowed if the doses were anticipated to remain stable during the duration of the study.	NR NR 112	5/112 (4%) dropped out due to non-compliance 52/112 (46%) 97/112 (87%) analyzed

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of 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	Outcomes	Method of adverse event assessment and adverse events assessed
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 (NR) 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	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 NR, 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)	Clinical observations and assessments of AEs entered on a case report form. Incidence, severity and drug relationship of AEs were assessed and summarized. Categorized as mild, moderate, or severe. Investigator assessed.

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Rate and number of adverse events	Quality ratings and comments	Funding source and role	Other comments
Nicholson, 2006	Extended-release morphine (Kadian) once daily versus sustained-release oxycodone twice daily Any adverse event: NR 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)	See Evidence Table 10	Alpharma Branded Products Division	

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of 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 NR)	NR NR 18	1/18 (5.6%) 18

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of 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	Outcomes	Method of adverse event assessment and adverse events assessed
Niemann, 2000	Median age=47 years 33.3% female Race NR Median duration of chronic abdominal pain=9 years Etiology of chronic pancreatitis Alcohol abuse=17(94.4%) Sjögren's syndrome=1(5.6%)	Preference recorded at end of study (assessment method NR, categorical scale used) Global pain control assessment of last two weeks of trial periods compared to last month prior to study entry (assessment method NR, 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	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	NR

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Rate and number of adverse events	Quality ratings and comments	Funding source and role	Other comments
Niemann, 2000	NR	Efficacy: FAIR. Method of randomization NR. Method of treatment allocation NR. 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.	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

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of 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
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)	30 to 70 years, persistent, moderate to severe chronic low back pain judged appropriate for chronic opioid therapy, suboptimal response to non-opioids, pain score >4 on a 0 to 10 scale	Treated with a sustained-release opioid, used a sustained-release opioid in last 6 months, previously unresponsive or intolerant to opioids, serious diagnosed medical condition that would interfere with ability to complete study, back surgery in the past 6 months, more than 2 surgeries for back pain, or back surgery or steroid injection expected during the first 12 to 13 weeks of the trial	Ibuprofen, up to 2400 mg/day	NR NR 392	3% (11/392) 220/392 (56%) did not complete trial 266/392 (68%) analyzed

Evidence Table 4. Original Report through Update 5: Data abstraction and quality assessment of 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	Outcomes	Method of adverse event assessment and adverse events assessed
Rauck, 2006 and 2007	Median age: 50 vs. 50 Female gender: 64% vs. 58% Non-white race: 24% vs. 18% Duration of back pain: median 7 vs. 6 years Cause of back pain mechanical: 76% vs. 85% Baseline pain: 6.5 vs. 6.6	Brief Pain Inventory: VAS (0 to 10) Ibuprofen rescue doses Pittsburgh Sleep Quality Index SF-12: 15-item ordinal scale Work Limitations Questionnaire	Extended-release morphine (Avinza) once daily versus sustained-release oxycodone (OxyContin) twice daily Brief Pain Inventory score (0 to 10, mean improvement from baseline): -3.1 vs. -2.8 (p NR) Proportion with >2 point improvement in BPI: 55% (73/132) vs. 44% (59/134) (p=0.03) Pittsburgh Sleep Quality Index (mean improvement from baseline): 33% vs. 17% (p=0.006) Rescue medication use: 2,595 vs. 3,154 doses (p<0.0001) SF-12 Physical Component Summary (mean improvement from baseline): 23% vs. 19% (NS) SF-12 Mental Component Summary (mean improvement from baseline): 23% vs. 16% (NS) Work Limitations Questionnaire (mean demands score, 0 to 100): 22.1 vs. 20.9 Withdrawal (lack of efficacy): 5% (10/203) vs. 3% (6/189)	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 4. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid with a long-acting opioid

Author, Year	Rate and number of adverse events	Quality ratings and comments	Funding source and role	Other comments
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: 87% vs. 89% Dizziness: 58% vs. 64% Drowsiness: 85% vs. 84% Dry mouth: 82% vs. 76% Itchiness: 65% vs. 57% Nausea: 50% vs. 47% Vomiting: 24% vs. 19% Withdrawal (overall): 46% (93/203) vs. 42% (79/189(Withdrawal (adverse events): 19% (38/203) vs. 14% (27/189)	See Evidence Table 10	Ligand Pharmaceuticals Inc and Organon Pharmaceuticals USA Inc.	

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of 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

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of 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	Outcomes
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.	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)).

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality ratings and comments
Caldwell, 1999	Any adverse event at least possibly related to study medication, spontaneously reported by patients	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 (9%) vs. 5/37 (14%) vs. 3/36 (8%), NS	Efficacy: 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. Safety: 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. (Met 3 of 7 criteria)

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Funding source and role	Other comments
Caldwell, 1999	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. 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.

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of 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
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

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of 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	Outcomes
Gostick, 1989	16 (26%) 42	Avg. 52 years 56% female Race not reported Osteoarthritis 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.	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

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality ratings and comments
Gostick, 1989	Methods not reported	Long-acting dihydrocodeine vs. short-acting dihydrocodeine Bowel movement less frequently than once every two days: 23/61 (37.7%) vs. 21/61 (34.4%) Daily use of laxatives: 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")	Efficacy: 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. Safety: 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. (Met 2 of 7 criteria)

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Funding source and role	Other comments
Gostick, 1989	Not specified. One author employed by Napp Pharmaceutical, maker of long acting dihydrocodeine.	

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of 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

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of 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	Outcomes
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.	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)

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality ratings and comments
Hale, 1997	Any adverse event reported by >5% of either treatment group	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%)	Efficacy: 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 received acetaminophen only while group B received acetaminophen plus codeine. Follow up for 5 days. Safety: 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. (Met 2 of 7 criteria)

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Funding source and role	Other comments
Hale, 1997	Purdue Frederick sponsored study. 1 author (corresponding) employed by Purdue.	Groups received different rescue medications. Not clear if rescue medication was blinded as well. 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 5. Original Report through Update 5: Data abstraction and quality assessment of 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, 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
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 intensity >40 on scale of 0 to 100, unsuccessful response to traditional pain treatment	Cancer, acute osteomyelitis or acute bone disease, spinal stenosis and neurogenic 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 Not reported 36

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of 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	Outcomes
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	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).
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)	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

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality ratings and comments
Hale, 1999	Any adverse event at least possibly related to study medication, assessed at each contact, assessment methods not clear	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%)	Efficacy: 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. Safety: 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. (Met 3 of 7 criteria)
Jamison, 1998	Pre-specified set of adverse events assessed on 0 to 10 scale by weekly phone interview	Long-acting morphine + short-acting oxycodone vs. short-acting oxycodone (proportion reported weekly, sample sizes not clear) Dry mouth: 35% vs. 26% Drowsiness: 39% 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%)	Efficacy: 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. Safety: 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. (Met 5 of 7 criteria)

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Funding source and role	Other comments
Hale, 1999	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. 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	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). Higher adverse events in long-acting morphine + short-acting oxycodone arm, but they also received higher average doses of opioids.

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of 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
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 x-ray, 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 dihydrocodeine or 8 dextropropoxyphene/paracetamol per day.	Not permitted	Not reported Not reported 86
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

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of 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	Outcomes
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).	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.
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	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) **Achievement 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)

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality ratings and comments
Lloyd, 1992	Any adverse event, assessed by patient diary	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%)	Efficacy: 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. Safety: 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. (Met 3 of 7 criteria)
Salzman, 1999	Any adverse event reported by >10% of one treatment group and at least possibly related to study medication, assessed by daily patient diary	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%)	Efficacy: 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. Safety: 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. (Met 3 of 7 criteria)

Evidence Table 5. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid with a short-acting opioid

Author, Year	Funding source and role	Other comments
Lloyd, 1992	Not reported. However 5th author appears to be an employee of Napp Laboratories (maker of long acting dihydrocodeine) 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. 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	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 (results from 48 cancer patients not abstracted). This study is the 10 day open-label titration phase that preceded the study reported by Hale. 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 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

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 (titrated) 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	NR NR 46	13 (28%) 30

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Outcomes
Arkinstall. 1995	Avg. 55.1 years 57% female Race NR 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	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)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality rating and comments
Arkinstall. 1995	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	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%)	Efficacy: 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 NR. Contamination was not allowed. Groups received similar care except for study drug. Follow up for 7 days per arm. Safety: 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. (Met 4 of 7 criteria)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Funding source and role	Other comments
Arkinstall. 1995	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). Adverse events NR 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 NR); withdrawal symptoms may have occurred in placebo group that could not be distinguished from adverse events. NR 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.

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

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
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 comorbidities	Nonopioid drugs other than gabapentin permitted	86 Unclear 57	16 (28%) 54

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Outcomes
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	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

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality rating and comments
Gilron, 2005	Any reported adverse event	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% Cognitive dysfunction: 2% vs. 2% vs. 7% vs. 2% Nausea: 5% vs. 0% vs. 0% vs. 7%	Efficacy: GOOD. Results adjusted for treatment carryover effects Safety: FAIR. Adverse events not pre-specified or defined. Inadequate description of adverse event assessment technique. No analysis of confounders. (Met 4 of 7 criteria)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Funding source and role	Other comments
Gilron, 2005	Canadian Institutes for Health Research provided funding; gabapentin provided by Pfizer and morphine by Aventis-Pharma	Results of initial intervention NR. 44% of patients and 33% of research nurses correctly guessed morphine treatment. Adverse events NR for initial 5 week intervention period. Withdrawals due to adverse events not clear.

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

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	NR NR 160	44 (28%) 159

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Outcomes
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 NR	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)	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 (post-baseline 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

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality rating and comments
Gimbel, 2003	Investigator assessed for adverse events at each visit, and reported events graded for severity and probability of relationship to study drug	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%)	Efficacy: GOOD Safety: FAIR. Adverse events not pre-specified or defined. Inadequate description of adverse event assessment technique. No analysis of confounders. (Met 4 of 7 criteria)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Funding source and role	Other comments
Gimbel, 2003	Purdue Pharma provided funding and one of the authors employed by them.	

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

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/Gould, 2009	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	NR 251 244 enrolled in open-label titration 143 randomized	3/143 (2%) withdrawal due to protocol violation 76/143 (53%) did not complete trial Number analyzed: 142/143

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Outcomes
Hale, 2007/Gould, 2009	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) Pain Quality Assessment Scale: 20 domains rated 0 (no pain) to 10 (most pain sensation imaginable)	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) Pain Quality Assessment Scale items, mean (SD): Paroxysmal: Post-titration: 2.01 (1.59) vs 2.03 (1.43) Post-treatment: 2.40 (2.05) vs 4.33 (2.76); F for time effect for oxymorphone: 61.65 (P<0.0022); F for time x treatment effect for oxymorphone: 31.02 (P<0.0022) Surface: Post-titration: 1.18 (1.24) vs 1.18 (1.15) Post-treatment: 1.27 (1.33) vs 2.07 (2.06); F for time effect for oxymorphone: 15.67 (P<0.0022); F for time x treatment effect for oxymorphone: 10.23 (P<0.0022) Deep: Post-titration: 2.27 (1.39) vs 2.32 (1.53) Post-treatment: 2.67 (1.94) vs 4.34 (2.63); F for time effect for oxymorphone: 56.20 (P<0.0022); F for time x treatment effect for oxymorphone: 25.18 (P<0.0022)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality rating and comments
Hale, 2007/Gould, 2009	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 weeks of treatment.	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%	See Evidence Table 10

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Funding source and role	Other comments
Hale, 2007/Gould, 2009	Endo Pharmaceuticals Inc	

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

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 carbamazepine 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

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Outcomes
Harke, 2001	Avg. 55 years 51% female Race NR (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)	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)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality rating and comments
Harke, 2001	NR	NR	Efficacy: FAIR. Randomization method not discussed. Treatment allocation concealment NR. Treatment groups appear similar prior to the RCT conducted before the RCT of interest to this report, however, demographics are NR 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.

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Funding source and role	Other comments
Harke, 2001	NR	The method used to report the results is unusual and makes interpretation difficult.

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

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 NR 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

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Outcomes
Huse, 2001	Avg. 50.6 years 16% female Race NR Phantom Limb Pain 2 upper limb 9 lower limb 1 both Prior opioid use NR 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	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.

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality rating and comments
Huse, 2001	Any reported adverse event, recorded in daily patient diary	Long-acting morphine vs. placebo (results for initial intervention NR), 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 NR	Efficacy: FAIR. Randomization method NR. Treatment allocation concealment adequate. Baseline statistics of treatment groups NR. 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. Safety: 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. (Met 4 of 7 criteria)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Funding source and role	Other comments
Huse, 2001	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. Not clear how dose of morphine titrated during intervention.

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

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 NR	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	NR 326 325 enrolled in open-label titration 205 randomized	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

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Outcomes
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	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)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality rating and comments
Katz, 2007	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.	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%	See Evidence Table 10

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Funding source and role	Other comments
Katz, 2007	Endo Pharmaceuticals Inc	

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

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 NR	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	516 408 370	172/370 (46%) did not complete trial Number analyzed: 357/370 (96%) 1 withdrawal due to protocol violation

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Outcomes
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: NR 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)	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)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality rating and comments
Kivitz, 2006	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.	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%	See Evidence Table 10

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Funding source and role	Other comments
Kivitz, 2006	Endo Pharmaceuticals Inc and Penwest Pharmaceuticals Co	Duration and severity of baseline pain unclear

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

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 NR	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 NR 416	217/416 (52%) did not complete trial Number analyzed: 399/416

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Outcomes
Langford, 2006	Mean age: 66 vs. 66 years Female gender: 65% vs. 68% Non-white race: NR Baseline pain score (0 to 100 mm): 73 vs. 73 Duration of pain: NR 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	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)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality rating and comments
Langford, 2006	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)	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)	See Evidence Table 10

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Funding source and role	Other comments
Langford, 2006	Janseen-Cilag	Population restricted to those needing surgery and failing weak opioids.

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

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 pregnancy	Non-opioids and co-analgesics allowed; step II opioids also allowed	997 NR 49	12 (24%) 48 included in ITT analyses

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Outcomes
Maier, 2002	Avg. 52.3 years 54% female Race NR 4 postherpetic neuralgia 11 neuralgia 12 radiculopathy or neuropathy 6 other neuropathic pain 12 low back pain 3 other nociceptive pain Prior opioid use NR 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)	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 NR prior to crossover

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality rating and comments
Maier, 2002	20 symptoms or complaints rated on 0 (none) to 3 (severe) scale; some central nervous system and gastrointestinal symptoms pre-specified	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%	Efficacy: FAIR. Not clear if randomization adequate ("random generator") and allocational concealment not described. Baseline characteristics NR 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. Safety: 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. (Met 3 of 7 criteria)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Funding source and role	Other comments
Maier, 2002	Mundipharma GmbH provided funding.	Most patients and investigators knew when they were receiving morphine. Not clear how lost to follow-up handled in safety analysis. Only withdrawal due to adverse events reported prior to crossover.

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

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 NR	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	NR NR 109	1 withdrawal due to protocol violation 73/109 (67%) did not complete trial Number analyzed: 107/109 (98%)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Outcomes
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)	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)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality rating and comments
Markenson, 2005	Safety was evaluated by vital signs and physical examinations, reports of adverse events, and the number and percentage of patients who discontinued from the study due to adverse events.	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)	See Evidence Table 10

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Funding source and role	Other comments
Markenson, 2005	Purdue Pharma	

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

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	NR 33 19	8 (42%) 11 completed both phases

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Outcomes
Morley, 2003	Avg. 57.0 years 32% female Race NR 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	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

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality rating and comments
Morley, 2003	Not specified	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	Efficacy: FAIR. Not clear if randomization adequate (eight replications of a Latin Square Design) and allocation concealment not described. Baseline characteristics NR 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. Safety: 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). (Met 1 of 7 criteria)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Funding source and role	Other comments
Morley, 2003	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). Not clear how lost to follow-up handled in safety analysis. Adverse events reported on day of or day after taking methadone or placebo.

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

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, musculoskeletal 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	NR 103 61	18 (30%) 46

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Outcomes
Moulin, 1996	Avg. 40.4 years 59% female Race NR 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 coccygeal 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	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.

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality rating and comments
Moulin, 1996	Any reported adverse event, assessed by weekly or biweekly adverse effects questionnaire	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 NR	Efficacy: 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. Safety: 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. (Met 4 of 7 criteria)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Funding source and role	Other comments
Moulin, 1996	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). Data NR 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 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

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	NR NR 103	37 (36%) 66

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Outcomes
Peloso, 2000	Avg. 61.6 years 62% female Race NR 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	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)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality rating and comments
Peloso, 2000	Any reported adverse event, assessed by weekly non-directed adverse events questionnaire	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 NR) 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 NR	Efficacy: 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. Safety: FAIR. Not clear if selection of patients biased, number eligible NR. 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. (Met 3 of 7 criteria)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Funding source and role	Other comments
Peloso, 2000	No mention of funding is made. Purdue Frederick (maker of long acting codeine) employs 2 of the authors.	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 NR. High withdrawal rate, not clear how withdrawn patients accounted for in adverse event rates.

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

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	NR NR 133	70 (53%) 133

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Outcomes
Roth, 2000	Avg. 62 years 74% female Race NR 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"	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)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality rating and comments
Roth, 2000	Any adverse event reported in >10% of patients, assessed by spontaneous patient reported or observed by investigators at each weekly visit	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%)	Efficacy: FAIR. Randomization technique NR. 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. Safety: 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. (Met 5 of 7 criteria)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Funding source and role	Other comments
Roth, 2000	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. 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 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

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 codeine/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	NR 100 81	22 (27%) 81 (100%) analyzed

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Outcomes
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**: categorical 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)	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-Digit Modalities Test Quality of Life: No differences in Multidimensional Pain Inventory

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality rating and comments
Rowbotham, 2003	Not specified. Reported withdrawal due to adverse events, and serious adverse events	High-dose levorphanol vs. low-dose levorphanol (sample sizes for adverse event assessment not clear): Withdrawal due to adverse event: 25/81 overall, NR 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	Efficacy: FAIR. Methods of randomization and allocation concealment not described, blinding methods not described. High loss to follow-up, but all enrolled patients analyzed. Safety: 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. (Met 4 of 7 criteria)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Funding source and role	Other comments
Rowbotham, 2003	National Institute on Drug Abuse and the National Institute of Neurological Disorders and Stroke	

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

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, 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	NR NR 50	11 (22%) 38

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Outcomes
Watson, 1998	Avg. 70 years 58% female Race NR Postherpetic neuralgia 63% thoracic 26% trigeminal 5% cervical 3% other 45% on narcotics 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.	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)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality rating and comments
Watson, 1998	Most frequently reported adverse event, assessed by weekly questionnaire	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 NR	Efficacy: 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. Safety: 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. (Met 3 of 7 criteria)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Funding source and role	Other comments
Watson, 1998	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. 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 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

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)	NR NR 107	71/107 (66%) 104/107 (97%) analyzed

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Population characteristics	Method of outcome assessment and timing of assessment	Outcomes
Watson, 2003	Avg. 70 years 47% female Race NR Prior opioid use NR 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	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
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: NR	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	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)

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Method of adverse event assessment and adverse events assessed	Rate and number of adverse events	Quality rating and comments
Watson, 2003	Events spontaneously reported by patients and observed by investigators recorded at each visit.	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)	Efficacy: 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. Safety: 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). (Met 3 of 7 criteria)
Zautra, 2005	Safety assessments included vital signs, physical examinations, reports of adverse events, and the number of and percentage of patients who discontinued the study due to adverse events.	Sustained-release oxycodone vs. placebo Withdrawal (adverse events): 36% (20/55) vs. 4% (2/49)	See Evidence Table 10

Evidence Table 6. Original Report through Update 5: Data abstraction and quality assessment of randomized controlled trials comparing a long-acting opioid to placebo or nonopioid

Author, Year	Funding source and role	Other comments
Watson, 2003	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. Not clear how withdrawals handled in safety analysis. Analyzed for carry-over effect: none found. Most investigators and patients could identify active intervention.
Zautra, 2005	Supported in part by Purdue Pharma LP	

Evidence Table 7. Original Report through Update 5: Data abstraction and quality assessment of observational studies

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)
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

Evidence Table 7. Original Report through Update 5: Data abstraction and quality assessment of observational studies

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	NR NR 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 NR. 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 NR; Diagnosis, duration of pain NR 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)
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 NR 56% of non-cancer pain patients had ischemic leg pain 44% other non-cancer pain Pain duration NR	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 NR. (0)

Evidence Table 7. Original Report through Update 5: Data abstraction and quality assessment of observational studies

Author, Year	Funding sources and role of funder	Rate and number of adverse events	Comments
Ackerman, 2004	Janssen (transdermal fentanyl) One author employed by funder, NR 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	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 NR.
Bach, 1991	NR	Oral long-acting morphine vs. sublingual buprenorphine: Any adverse event: 33/114 (28.9%) vs. 19.3% (29/150) Individual adverse events NR according to indication for treatment	Tabulated results exclude 189 patients with cancer pain. Individual side effects NR for non-cancer pain patients. Not clear if mean doses of medications equipotent between long-acting morphine and buprenorphine.

Evidence Table 7. Original Report through Update 5: Data abstraction and quality assessment of observational studies

Author, Year	Type of study, Setting	Medications evaluated (dose, duration)	Eligibility criteria	Exclusion criteria	Other pain medications used or allowed
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 7. Original Report through Update 5: Data abstraction and quality assessment of observational studies

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)
Caldwell, 2002	184 screened 184 eligible 181 enrolled	52% (86/181) discontinued or withdrew prematurely 181 analyzed for adverse events	Age, gender, race NR Characteristics and duration of osteoarthritis pain NR for patients enrolling in open-label extension	Any adverse event, assessment methods not clear	POOR. Not clear if selection of patients biased, number eligible NR. 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 7. Original Report through Update 5: Data abstraction and quality assessment of observational studies

Author, Year	Funding sources and role of funder	Rate and number of adverse events	Comments
Caldwell, 2002	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 7. Original Report through Update 5: Data abstraction and quality assessment of observational studies

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 non-cancer 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 + oxycodone 1/20 (5%) morphine SR alone Doses NR Pain duration NR	Patients with chronic non-cancer pain and a prior history of substance abuse who were managed on opioids for any period of time	None	NR

Evidence Table 7. Original Report through Update 5: Data abstraction and quality assessment of observational studies

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 NR Neuropathic pain: 58% radiculopathy 19% post-traumatic neuralgia 6% post-herpetic neuralgia 4% phantom pain 6% central pain 6% post-rhizotomy pain Pain duration NR	Any adverse event, assessment methods not clear, severity graded on 0-100 VAS	POOR. Not clear if selection biased; number eligible in prior trial NR. 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 NR	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 NR. (0)

Evidence Table 7. Original Report through Update 5: Data abstraction and quality assessment of observational studies

Author, Year	Funding sources and role of funder	Rate and number of adverse events	Comments
Dellemijn, 1998	Janssen (transdermal fentanyl) Author not employed by funder, NR 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	NR	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 7. Original Report through Update 5: Data abstraction and quality assessment of observational studies

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 NR (range 30 to 120 mg/day) Duration NR	Patients with chronic non-cancer pain on methadone	NR	NR

Evidence Table 7. Original Report through Update 5: Data abstraction and quality assessment of observational studies

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	NR NR 236 enrolled	110(46.6%) withdrawn 236 analyzed	avg. 66.2 years 31% female Race NR 50.8% neuropathic pain Pain duration NR	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 NR. 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 NR 73% chronic back pain 18% neuropathy 9% chronic headaches Pain duration NR	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 NR. (0)

Evidence Table 7. Original Report through Update 5: Data abstraction and quality assessment of observational studies

Author, Year	Funding sources and role of funder	Rate and number of adverse events	Comments
Franco, 2002	NR	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	NR	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.

Evidence Table 7. Original Report through Update 5: Data abstraction and quality assessment of observational studies

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	NR
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

Evidence Table 7. Original Report through Update 5: Data abstraction and quality assessment of observational studies

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	NR	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	
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 NR. 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)

Evidence Table 7. Original Report through Update 5: Data abstraction and quality assessment of observational studies

Author, Year	Funding sources and role of funder	Rate and number of adverse events	Comments
Hartung, 2007	NR	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 Comorbidity Index, concomitant drugs (benzodiazepines, sedative hypnotics, muscle relaxants, short-acting opioids), history of opioid dependence, abuse, or enrollment in a substance abuse treatment program
Milligan, 2001	Janssen (transdermal fentanyl) One author employed by Janssen, NR 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%)	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.

Evidence Table 7. Original Report through Update 5: Data abstraction and quality assessment of observational studies

Author, Year	Type of study, Setting	Medications evaluated (dose, duration)	Eligibility criteria	Exclusion criteria	Other pain medications used or allowed
Ringe, 2002	Prospective cohort Germany Multicenter	Transdermal fentanyl (titrated) Mean dose NR 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%)
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

Evidence Table 7. Original Report through Update 5: Data abstraction and quality assessment of observational studies

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)
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)
Roth, 2000	133 screened 133 eligible 106 enrolled	60 withdrew 106 analyzed for adverse events	NR, 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	NR NR 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 NR. Not clear if assessors blinded. Adequate duration of follow-up, 90 days. (5)

Evidence Table 7. Original Report through Update 5: Data abstraction and quality assessment of observational studies

Author, Year	Funding sources and role of funder	Rate and number of adverse events	Comments
Ringe, 2002	Janssen-Cilag GmbH	Transdermal fentanyl: Patients with at least one adverse event: 25(39%) Withdrawal due to adverse events: 13(20.3%)	
Roth, 2000	Purdue (sustained release oxycodone) One author employed by funding source, NR 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	Janssen (transdermal fentanyl) One author employed by funder, NR 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 8. Update 5: Quality assessment of trials

Author	Year	Randomization method adequate?	Allocation concealment method adequate?	Groups similar at baseline?	Inclusion criteria specified?	Exclusion criteria specified?	Outcome assessors masked?	Care provider masked?
Hale	2007	Method not described	Method not described	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Katz	2007	Yes	Method not described	Yes	Yes	Yes		Yes
Kivitz	2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Langford	2006	Yes	Yes	Yes	Yes	Yes	Unclear, reported as double blind	Yes
Markenson	2005	Yes	Yes	Yes	Yes	Yes	Unclear, reported as double blind	Yes
Matsumoto	2005	Yes	Method not described	Yes	Yes	Yes	Yes	Yes
Nicholson	2006	Yes	Method not described	Yes Females 61% vs. 40%, p<0.05	Yes	Yes	No	No
Rauck (ACTION Trial)	2006, 2007	Method not described	Yes	No	Yes	Yes	No	No
Zautra	2005	Method not described	Method not described	Yes	Yes	Yes	Unclear, reported as double blind	Yes

Evidence Table 8. Update 5: Quality assessment of trials

Author	Patients masked?	Attrition reported?	Withdrawal rate differential or high?	Loss to follow-up differential or high?	ITT analysis?	Post- randomization exclusions?	Rating
Hale	Unclear, reported as double blind	Yes	Yes	No	Yes	Yes	FAIR
Katz	Yes	Yes	Yes	No	Yes	Unable to determine	FAIR
Kivitz	Yes	Yes	Yes	No	Yes	Unable to determine	GOOD
Langford	Yes	Yes	Yes	No	Unable to determine	Unable to determine Discrepancy between number randomized and number in each randomization group	FAIR
Markenson	Yes	Yes	Yes	No	Yes	Yes	FAIR
Matsumoto	Yes	Yes	Yes	No	Yes	Yes	FAIR
Nicholson	No	Yes	Yes	Yes (6%)	No	Yes	FAIR
Rauck (ACTION Trial)	No	Yes	Yes	Unable to determine	No	Unable to determine	POOR
Zautra	Yes	Yes	Yes	No	Yes	No	FAIR