Oxycodone for Cancer-Related Pain

Meta-analysis of Randomized Controlled Trials

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To evaluate the efficacy and tolerability of oxycodone in cancer-related pain, we conducted a systematic review of randomized controlled trials. Four studies, comparing oral oxycodone with either oral morphine (n=3) or oral hydromorphone (n=1), were suitable for meta-analysis. Standardized mean differences in pain scores comparing oxycodone with control groups were pooled using random-effects models. Overall, there was no evidence that mean pain scores differed between oxycodone and control drugs (pooled standardized mean difference, 0.04; 95% confidence interval [CI], −0.29 to 0.36; P=.8; I^2=62%). In meta-regression analyses, pain scores were higher for oxycodone compared with morphine (0.20; 95% CI, −0.04 to 0.44) and lower compared with hydromorphone (−0.36; 95% CI, −0.71 to 0.00), although these effect sizes were small. The efficacy and tolerability of oxycodone are similar to morphine, supporting its use as an opioid for cancer-related pain.

Arch Intern Med. 2006;166:837-843

Approximately half of all patients with advanced cancer experience moderate to severe pain.[1] Opioids are the mainstay of treatment,[2] and morphine is the opioid of choice.[3] When morphine is used appropriately, about 80% of patients will achieve adequate pain relief.[4] Approximately 20%, however, will not and may need to switch to an alternative opioid.[5] In a proportion of these patients, this is because of intolerable adverse effects associated with morphine.

Oxycodone is a semisynthetic derivative of morphine. It has been in clinical use since 1917,[6] but patterns of use have differed worldwide, perhaps reflecting a lack of clinical studies investigating its efficacy. Historically, it was most commonly used in the United States as an opioid for mild to moderate pain in low-dose combinations with acetaminophen (paracetamol) or aspirin. In such preparations, however, its use was limited, as its dose could not be increased because of potential acetaminophen or aspirin toxicity. It was also used for moderate to severe pain in Finland (mostly by parenteral administration).

Studies conducted since 1990 have suggested that, when used in single-entity formulations and with dose titration, oxycodone is as effective as morphine.[7,8] The 1996 European Association for Palliative Care guidelines recommended oxycodone as an alternative to morphine.[3] Although there has been speculation that oxycodone may have a better adverse effect profile compared with morphine,[9] there are limited data on cancer-related pain. Since 1996, oxycodone has been relaunched in different formulations and dose strengths and in modified-release preparations, increasing its potential for use in chronic cancer pain. The success of this relaunch is indicated by English Department of Health statistics,[10] which show that the percentage of annual growth in items of oxycodone prescribed from 2002 to 2003 was 43%, compared with 8% for all opioid analgesics. Annual consumption of oxycodone has increased 42-fold in the United Kingdom and 3-fold in the United States from 1999 to 2003[11] (**Figure 1**). We conducted a systematic review of the available evidence to determine the efficacy and tolerability of oxycodone for cancer-related pain.

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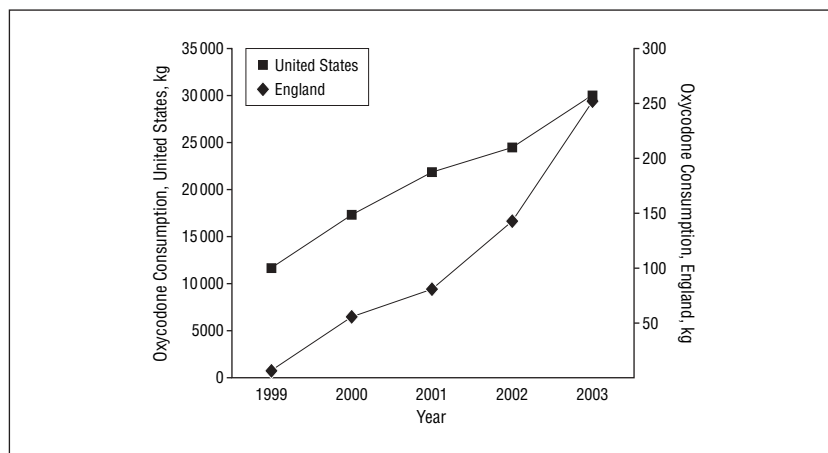
Figure 1. Consumption of oxycodone in the United Kingdom and the United States from 1999 to 2003. Data from the International Narcotics Control Board.[11]

1 Oxycodone: ME
2 Oxycodone
3 Endone
4 Proladone
5 Supeudol
6 Eukado
7 Roxicodone
8 Oxycontin
9 Oxynorm
10 Immediate Release Oxycodone
11 Eubine
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13 Neoplasms*: ME
14 Neoplasm*
15 Cancer*
16 Tumor* or Tumour*
17 13 or 14 or 15 or 16
18 Pain*: ME
19 Pain*
20 18 or 19
21 12 and 17 and 20

Figure 2. Search terms used in the systematic review of the databases. ME indicates explode MeSH (Medical Subject Headings of the National Library of Medicine) terms.

METHODS

ELIGIBILITY

We included randomized controlled trials comparing oxycodone with placebo or an active analgesic drug in patients with cancer-related pain. All routes of drug administration and all formulations of oxycodone were considered. Studies of combination oxycodone preparations (eg, oxycodone and acetaminophen) were excluded.

SEARCH STRATEGY

We searched the following electronic databases using a detailed search strategy for each: Cochrane Pain, Palliative and Supportive Care Register 2002; Cochrane Controlled Trials Register 2002: Cochrane Library current issue; MEDLINE (1966 to May 2002); EMBASE (1980 to May 2002); CancerLit (1960 to May 2002); CINAHL (1982 to May 2002); dissertation abstracts (2002); and SIGLE (2002). We searched reference lists of retrieved articles and other relevant literature such as pain or opioid reviews. We wrote to the manufacturers of oxycodone preparations (Napp Pharmaceuticals, Cambridge, England, and Purdue Pharma, Stamford, Conn), known oxycodone investigators, and subscribers of *Palliative Medicine* and selected pain journals with a request for data from unpublished trials or information about other trials we had not identified. The search strategy was repeated in April 2005, with no new studies identified. Search terms are listed in **Figure 2**.

DATA EXTRACTION

The full-text versions of potentially eligible articles were obtained and independently assessed by 2 of the investigators (C.M.R. and A.N.D.). We identified duplicate publications by reviewing study name, authors, location, study population, dates, and study design and by confirming with the study authors and Napp Pharmaceuticals (the manufacturers of oxycodone in England) that each of the included reports were indeed separate studies. We identified replication of efficacy data from trials by Kalso et al[12] and Heiskanen et al[13] contained within separate articles reporting on the pharmacokinetic outcomes from these studies. Reasons for excluding a trial were recorded.

For eligible trials, both investigators independently extracted data from the article using a specifically designed data extraction form. This form recorded the following: publication details, patient population details, nature of pain if described, interventions, outcome measures used, analgesic (efficacy) results, adverse effects, quality-of-life scores, patient preference, withdrawals, and trial quality criteria. We extracted data on reported methods of concealment of allocation[14] and the blinding of therapists, patients, and outcome assessors in each trial.

DATA ANALYSIS

Different assessment scales were used to record pain scores in the trials (**Table 1**). We expressed treatment effects as standardized weighted mean differences.[20] For the parallel group trial,[19] the standardized weighted mean difference was calculated using the Glass estimator[21] and the standard error calculated according to equation 9 of Curtin et al.[20] For crossover studies, standardized weighted mean differences were estimated according to equation 11 of Curtin et al,[20] by dividing the treatment effect by the between- plus within-subject standard deviation of the crossover differences. To estimate the standard deviation of the crossover differences, a common between-period intraclass correlation coefficient of 0.2 was estimated using individual level data available only for the trial by Heiskanen and Kalso.[18] Estimates of the variance of the crossover effect sizes were then derived by equation 14 of Curtin et al.[20] Because the trials used different control groups (morphine or hydromorphone), and because there was evidence of between-trial heterogeneity, trials were pooled using random effects meta-analysis.[22] We analyzed pain scores recorded on the final day on each study drug to ensure that steady state had been reached. Data on the presence or absence of 16 common opioid-related adverse effects were obtained from the authors of each crossover trial. We used the marginal odds ratio (OR) estimate described by Becker and Balatgas[23] to obtain ORs and their standard errors for the crossover trials. For each adverse effect, these ORs were combined with the corresponding ORs derived from the published report of the parallel group trial. The I^2 statistic was used to assess the extent of between-study variation in estimates,[24] and sources of heterogeneity were explored using meta-regression.[21] Analyses were conducted using Stata statistical software, version 8.0[25] (meta-analysis of pain outcomes) and RevMan version 4.2.7 (Nordic Cochrane Centre, Copenhagen, Denmark) (meta-analysis of adverse effects).

RESULTS

The search strategy yielded 104 references, of which 6 trials met inclu-

Table 1. Retrieved Studies

Source, Methods, and Participants	No. of Patients Entered/Completed and Withdrawals	Intervention	Outcomes Reported	Notes
Beaver et al,[15] 1978 Double-blind crossover study of hospitalized patients (mean age, 46 y)	34/28 (Completed 1 round of low and high doses for each medication) 6 Withdrawals not related to study drugs	Each patient given high- and low-dose morphine sulfate (8, 16, or 32 mg), oxycodone hydrochloride (7.5, 11, 15, 22, and 30 mg), and codeine phosphate (90 or 180 mg) intramuscularly on separate days	Intramuscular oxycodone, 0.68 times (CI, 0.32-1.07) as potent as intramuscular morphine No differences noted in adverse effects	Funded by research charity and pharmaceutical industry
Bruera et al,[16] 1998 Double-blind crossover study of patients with stable cancer pain (≥3 d of stable opioid doses)	32/23 9 Withdrawals, 5 due to adverse events (3 with morphine; 2 with oxycodone) and 4 for other reasons	7 d of each drug (crossover day 8) Dose adjustments permitted until pain control achieved Rescue dose, 10% of 24-h dose Dose titration similar in both groups Mean morphine dosage, 72.6 mg every 12 h; mean oxycodone dosage, 46.5 mg every 12 h Median morphine-oxycodone ratio, 1.5	Pain measured on VAS (10 cm) and CAT (0-4) No significant difference in pain intensity scores between treatments No statistically significant differences in mean severity of any adverse events or in patient preference	Funded by pharmaceutical company Summary statistics provided for meta-analysis
Hagen and Babul,[17] 1997 Double-blind crossover study of patients with chronic stable cancer pain (≥3 d of stable opioid doses; mean age, 56 y)	44/31 13 Withdrawals, 8 due to adverse events (6 with oxycodone; 2 with hydromorphone) and 5 for other reasons	7 d of each drug (crossover day 8) Dose adjustments permitted until pain control achieved Rescue dose, 10% of 24-h dose Dose titration similar in both groups Mean hydromorphone dosage, 30 mg per 24 h; mean oxycodone dosage, 124 mg per 24 h Hydromorphone-oxycodone ratio, 1.6	Pain measured on VAS (10 cm) and 5-point CAT (0-4) Overall mean pain intensity across all days: VAS, 28 mm (CR oxycodone) and 31 mm (CR hydromorphone) (P = .1); CAT: 1.4 (CR oxycodone) and 1.5 (CR hydromorphone) (P = .10) Nausea and sedation measured on 10-cm VAS No significant differences in nausea or sedation scores or patient preference between groups	Funded by pharmaceutical company Summary statistics provided for meta-analysis
Heiskanen and Kalso,[18] 1997 Double-blind crossover study of patients with chronic stable cancer pain (mean age, 60 y)	45/27 18 Withdrawals, 7 due to adverse events (5 with oxycodone; 2 with morphine) and 11 for other reasons	Initial open-label dose titration phase until 48 h of effective pain relief, followed by crossover sequences lasting 3-6 d Rescue dosage, ⅛ to ⅙ of 24-h dose Dose titration similar in both groups Mean morphine dosage, 180 mg in 24 h; mean oxycodone dosage, 123 mg in 24 h Morphine-oxycodone ratio, 1.5	Pain measured on 4-point verbal rating scale When stable phases were combined, pain control was better with CR morphine than with CR oxycodone Constipation was more common with oxycodone; vomiting, with morphine Nighttime acceptability was better in morphine group	Assistance from pharmaceutical company Individual patient data obtained
Kalso and Vainio,[7] 1990 Double-blind crossover study of patients with cancer pain not controlled with opioids for mild to moderate pain (mean age, 52 years)	20/19 1 Withdrawal due to adverse events on morphine	Patients titrated to pain free using a patient-controlled analgesia device with morphine or oxycodone for 48 h, then switched to oral dose (calculated from previous oral consumption) of same drug for 48 h Protocol repeated with the other drug for next 96 h Mean morphine dosage, 204 mg in 24 h; mean oxycodone dosage, 150 mg in 24 h Morphine-oxycodone ratio, 1.4	Pain measured on VAS (10 cm) Pain scores from last 24 h of each of 4 stages used in statistical analyses No statistically significant differences in pain scores between groups Oral morphine caused more nausea	Funded by research charity No further data obtained
Mucci-LoRusso et al,[19] 1998 Double-blind parallel group of patients with chronic cancer pain requiring 30 to 340 mg of oxycodone or equivalent (mean age, 59 years)	101/79 21 Withdrawals, 9 due to adverse events (3 with oxycodone and 6 with morphine), 12 for other reasons (1 patient did not receive any medication.)	Initial doses of study medication calculated from prestudy opioid requirements Dose titrated up until stable pain control for 48 h Dose titration similar in both groups Mean morphine dosage, 140 mg in 24 h; mean oxycodone dosage, 101 mg in 24 h Rescue dose, 1/6-1/8 of 24-h dose Morphine-oxycodone ratio, 1.4	Pain on 4-point CAT (0-3) Pain scores from last 48 h of study used in efficacy analyses Reduction in mean pain scores of 0.6 from baseline in both groups; no statistically significant difference between treatments noted No difference in quality of life* scores or patient preference between groups	Funded by pharmaceutical company Summary statistics provided for meta-analysis

Abbreviations: CAT, categorical scale; CI, confidence interval; CR, controlled release; VAS, visual analog scale.
*Determined according to the Functional Assessment of Cancer Treatment–General Version.

sion criteria (**Figure 3**). Of these, 1 was a single-dose study evaluating the analgesic potency and duration of action of intramuscular oxycodone against intramuscular morphine and codeine phosphate.[15] Of the remaining 5 reports, 3 crossover trials compared oral oxycodone with oral morphine[7,16,18]; 1 crossover trial compared oral oxycodone with oral hydromorphone[17]; and 1 parallel group trial compared oral oxycodone with oral morphine[19] (Table 1).

None of the eligible studies reported data in a form suitable for meta-analyses, so we contacted the authors or the sponsoring drug companies for additional data. We also requested additional data on the presence or absence of adverse effects examined by the trials. Individual patient data were obtained for the study by Heiskanen and Kalso.[18] For the studies by Bruera et al,[16] Hagen and Babul,[17] and Mucci-LoRusso et al,[19] we were provided with mean within-patient differences in pain scores (comparing the first and final study days) and an estimate of the standard deviation. Analyzable data were unavailable for the studies by Kalso and Vainio[7] (which reported no statistically significant difference in visual analog scale ratings between the morphine and oxycodone groups, but more nausea with oral morphine) and Beaver et al[15] (which demonstrated that intramuscular oxycodone was 0.68 times as potent as intramuscular morphine but had a slightly shorter duration of action). Thus, 4 studies were included in the meta-analysis.

METHODOLOGICAL QUALITY OF INCLUDED STUDIES

Only 1 trial (Heiskanen and Kalso[18]) reported on the method of concealment of allocation to treatment (the randomization code was kept by the hospital pharmacist), although information about whether restricted randomization was used in generating the allocation sequence was not available in the trial report (**Table 2**). All of the trials used matched placebo tablets to blind the patient and clinician. No studies indicated whether analysis by intention to treat was undertaken. In all included trials, patients who withdrew from the study for any reason were excluded from the final analyses reported herein. The numbers who withdrew from each trial were as follows: for Bruera et al,[16] 32 entered and 9 withdrew; for Hagen and Babul,[17] 44 entered and 13 withdrew; for Heiskanen and Kalso,[18] 45 entered and 18 withdrew; and for Mucci-LoRusso et al,[19] 101 entered and 22 withdrew (Table 1). None of the publications reported whether the outcome assessor was blinded to treatment. Each trial reported that patients in both treatment groups had their opioid doses titrated in a similar manner until stable doses were obtained. The trials were of short duration, lasting from 10 to 20 days.

PAIN INTENSITY SCORES

In pooled analyses, we found no evidence that mean pain scores differed between the oxycodone and control groups (mean difference in standardized pain scores, 0.04; 95% confidence interval [CI], −0.29 to 0.36; $P=.8$) (**Figure 4**). There was evidence of heterogeneity between the study estimates ($I^2=62\%$; heteroge-
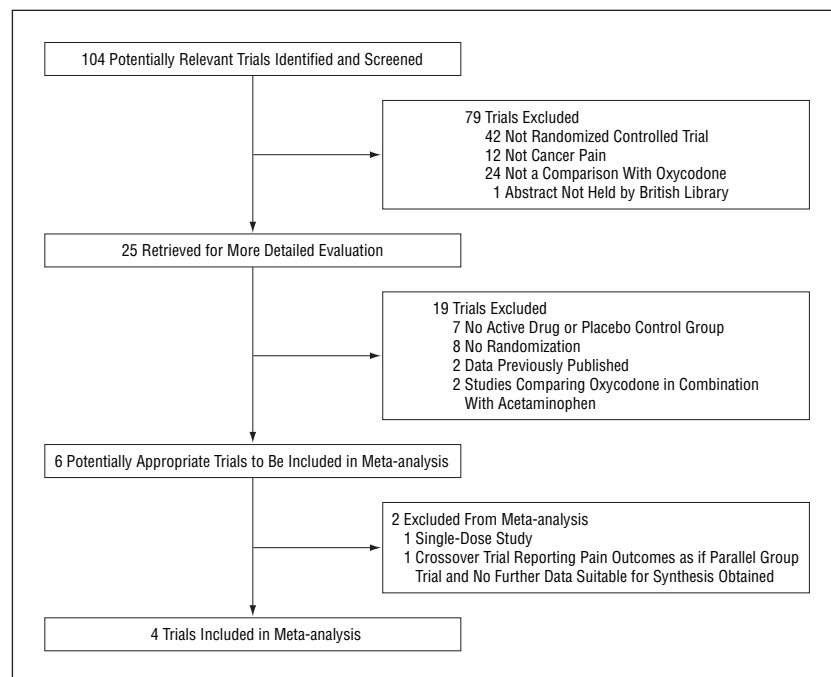


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104 Potentially Relevant Trials Identified and Screened

                    79 Trials Excluded
                       42 Not Randomized Controlled Trial
                       12 Not Cancer Pain
                       24 Not a Comparison With Oxycodone
                        1 Abstract Not Held by British Library

25 Retrieved for More Detailed Evaluation

                    19 Trials Excluded
                        7 No Active Drug or Placebo Control Group
                        8 No Randomization
                        2 Data Previously Published
                        2 Studies Comparing Oxycodone in Combination
                          With Acetaminophen

6 Potentially Appropriate Trials to Be Included in Meta-analysis

                    2 Excluded From Meta-analysis
                        1 Single-Dose Study
                        1 Crossover Trial Reporting Pain Outcomes as if Parallel Group
                          Trial and No Further Data Suitable for Synthesis Obtained

4 Trials Included in Meta-analysis
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Figure 3. Quorum statement flowchart.

Table 2. Methodological Quality of Trials Included in the Meta-Analysis*

Source	Generation of the Allocation Sequence	Method of Allocation Concealment	Masking, Patients/Clinicians†
Hagen and Babul,[17] 1997	NR	NR	Matched placebo tablets used
Heiskanen and Kalso,[18] 1997	Computer generated; unclear if restricted randomization was used	List of codes held by hospital pharmacist	Matched placebo tablets used
Bruera et al,[16] 1998	NR	NR	Matched placebo tablets used
Mucci-LoRusso et al,[19] 1998	Block randomization in 9 separate centers	NR	Matched placebo tablets used

Abbreviation: NR, not reported.
*Intention-to-treat analysis was not reported for any trial.
†Masking of outcome assessors was not reported for any trial.

neity, P=.05). The pooled standardized difference in pain scores for the 3 studies that compared oxycodone with morphine was 0.20 (95% CI, −0.04 to 0.44; I²=0%) and the standardized difference for the study that compared oxycodone with hydromorphone was −0.36 (95% CI, −0.71 to 0.00; for difference in effect estimates, P=.1). Based on the pooled standardized differences we observed and the standard deviations observed in the individual trials, we estimate that for oxycodone compared with morphine or hydromorphone, the pooled standardized differences represent only 2 to 3 mm on a 100-mm visual analog scale. It is suggested that a clinically important difference is a change of 2 points on a 0- to 10-point pain intensity scale (equivalent to 20 mm on a visual ana-

log scale),[26,27] indicating that the standardized differences we detected are unlikely to be clinically important or meaningful to patients.[27]

The results of other outcomes described in the included studies are detailed in Table 1. In summary, no differences in patient preference or quality of life were demonstrated, although the study by Heiskanen and Kalso[18] suggested that nighttime acceptability of morphine was better than that of oxycodone. Because different measures were used and the results were not reported in sufficient detail, they could not be combined in meta-analyses.

ADVERSE EFFECTS

The point estimates for the pooled ORs comparing oxycodone with con-

trol groups were 0.75 (95% CI, 0.51-1.10) for nausea and 0.72 (95% CI, 0.49-1.06) for vomiting (**Table 3**). There was substantial evidence of heterogeneity in estimates of the association of oxycodone with dry mouth and drowsiness (I²=74% and I²=71%, respectively). When the meta-analysis was repeated using only data from the trials with morphine as the control treatment, the pooled OR favored oxycodone for dry mouth (OR, 0.56; 95% CI, 0.38-0.83) and drowsiness (OR, 0.72; 95% CI, 0.47-1.1). Overall, the discontinuation rate due to adverse events was 13% (29/222) when data from all of the studies were combined; as many as 90% of patients experienced opioid-related adverse effects in each trial (**Table 4**). Discontinuation rates due to adverse events were similar in the oxycodone and control groups.

COMMENT

This study is the first we are aware of to display the accumulated evidence to date on which current prescribing of oxycodone in cancer-related pain is based. We found no clinically important differences between the analgesic efficacy or the adverse effect profile of oxycodone compared with morphine. Although only 160 patients were included in the meta-analysis, the 95% CI for the effect of oxycodone vs
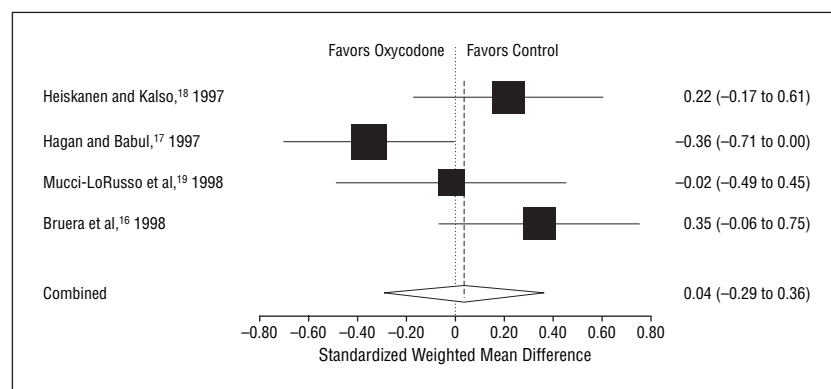

Figure 4. Standardized weighted mean differences (95% confidence intervals) in pain intensity scores in patients with cancer, comparing oxycodone minus control in all 4 trials with analyzable data.

Table 3. Adverse Effects Associated With Oxycodone vs Control Groups

Adverse Effect	Source, Estimated OR (95% CI)					Heterogeneity P Value	I² Statistic
	Bruera et al,[16] 1998	Heiskanen and Kalso,[18] 1997	Hagen and Babul,[17] 1997	Mucci-LoRusso et al,[19] 1998	Random-Effects Pooled Estimate		
Nausea	0.43 (0.19-0.99)	0.76 (0.33-1.77)	1.00 (0.54-1.87)	0.77 (0.35-1.70)	0.75 (0.51-1.10)	.47	0
Constipation	0.83 (0.31-2.19)	0.81 (0.46-1.43)	1.69 (0.92-3.13)	2.04 (0.84-4.97)	1.22 (0.76-1.95)	.18	39
Drowsiness	0.72 (0.38-1.36)	0.65 (0.29-1.43)	4.12 (1.55-10.97)	1.25 (0.54-2.92)	1.18 (0.56-2.50)	.01	71
Difficulty concentrating	0.86 (0.64-1.15)	1.00 (0.23-4.32)	1.28 (0.71-2.28)	NR	0.93 (0.72-1.21)	.49	0
Hallucinations	1.55 (0.66-3.60)	1.00 (0.06-17.15)	3.19 (0.30-33.94)	0.26 (0.01-5.95)	1.46 (0.69-3.07)	.64	0
Dry mouth	0.54 (0.27-1.05)	0.59 (0.32-1.08)	1.87 (1.04-3.35)	0.54 (0.24-1.21)	0.77 (0.40-1.46)	.01	74
Vomiting	0.34 (0.07-1.59)	0.72 (0.46-1.15)	0.86 (0.40-1.86)	NR	0.72 (0.49-1.06)	.57	0
Agitation	1.93 (0.71-5.26)	2.05 (0.27-15.51)	1.00 (0.67-1.49)	NR	1.12 (0.78-1.61)	.41	0
Dizziness	0.46 (0.21-0.99)	1.14 (0.58-2.25)	1.80 (0.91-3.56)	0.59 (0.24-1.47)	0.89 (0.48-1.66)	.04	63
Poor sleep	1.17 (0.59-2.31)	1.00 (0.06-17.15)	0.48 (0.25-0.91)	2.25 (0.14-36.92)	0.79 (0.42-1.48)	.25	27
Twitching	1.36 (0.65-2.85)	*	1.16 (0.49-2.76)	NR	*	.67	0
Fatigue	1.00 (0.50-2.00)	2.05 (0.17-24.52)	0.72 (0.29-1.79)	NR	0.92 (0.54-1.58)	.69	0
Itch	0.85 (0.41-1.75)	1.00 (0.52-1.91)	1.44 (0.86-2.43)	0.98 (0.37-2.57)	1.12 (0.80-1.56)	.65	0
Dreams	1.26 (0.46-3.46)	0.49 (0.04-5.84)	1.31 (0.57-3.05)	NR	1.21 (0.65-2.27)	.76	0
Headache	1.41 (0.55-3.59)	1.00 (0.23-4.31)	0.54 (0.27-1.09)	1.90 (0.43-8.40)	0.93 (0.51-1.68)	.28	22
Sweating	1.36 (0.65-2.83)	1.12 (0.58-2.15)	0.78 (0.39-1.57)	1.09 (0.15-8.03)	1.05 (0.71-1.56)	.75	0

Abbreviations: CI, confidence interval; I², statistic used to assess the extent of between-study variation in estimates; NR, not reported; OR, odds ratio.
*Not estimable because no individuals had discordant adverse effects.

Table 4. Percentage of Study Completers Experiencing Opioid Adverse Effects During Studies

	% of Study Completers by Study Drug							
	Oxycodone				Morphine			Hydromorphone
Adverse Effect	Heiskanen and Kalso,[18] 1997	Bruera et al,[16] 1998	Mucci-LoRusso et al,[19] 1998	Hagen and Babul,[17] 1997	Heiskanen and Kalso,[18] 1997	Bruera et al,[16] 1998	Mucci-LoRusso et al,[19] 1998	Hagen and Babul,[17] 1997
Nausea	53	56	42	64	53	74	48	68
Vomiting	31	9	0	26	35	22	2	29
Constipation	53	70	35	74	49	70	21	61
Dry mouth	35	74	33	74	47	83	48	68
Drowsiness	49	87	31	90	57	87	31	61
Dizziness	20	39	21	35	24	56	31	26
Difficulty concentrating	4	52	NR	58	4	56	NR	55
Fatigue	2	83	NR	77	0	83	NR	55
Poor sleep	0	65	2	39	0	56	2	55
Vivid dreams	2	26	NR	39	0	22	NR	32
Hallucinations	0	30	0	0	0	17	4	6
Headache	4	43	10	39	4	30	6	55
Agitation	0	70	NR	32	2	52	NR	32
Twitching	2	48	NR	29	2	35	NR	29
Itching	22	35	20	55	24	43	21	45
Sweating	35	61	4	55	31	48	4	61

Abbreviation: NR, not reported.

morphine is narrow and excludes any clinically important differences between these 2 drugs, in that the upper limit of the CI (standardized difference, 0.44) is consistent with a difference of only 6 mm on a 100-mm visual analog scale and the lower limit (−0.04) is consistent with a difference of 0.5 mm. For oxycodone vs hydromorphone, the equivalent figures are 0 and 6 mm, respectively. These differences are much lower than those that are suggested to be clinically meaningful (a change of 20 mm on a 100-mm visual analog scale[26,27]).

Our findings highlight the paucity of data in this area, and the results have to be interpreted with caution. The study reports did not allow us to be confident about the internal validity of the trials. Only the trial by Heiskanen and Kalso[18] reported an attempt to conceal treatment allocation, stating that the hospital pharmacist held the codes. This does not necessarily guarantee that concealment of allocation was successful in preventing bias, as most concealment processes can potentially be subverted[28] and no attempt to assess whether bias was indeed avoided (eg, using the methods of Berger and Exner[29]) was reported in any of the included studies. Inadequate or unclear concealment of treatment allocation is associated with exag-

geration of treatment effects[30] and is therefore unlikely to explain the absence of clinically important differences between the oxycodone and control groups found in our meta-analysis. In each of the included studies, patients who withdrew for any reason were not included in the final analyses comparing pain scores between the oxycodone and control groups (Table 1), possibly resulting in attrition bias, which might further threaten the validity of the individual studies. However, because the discontinuation rates due to adverse events were similar for the oxycodone and control groups in all studies, it seems unlikely that the potential for attrition bias explains the results of our meta-analysis.

The percentage of patients experiencing adverse effects and discontinuing treatment due to adverse events was considerable and in line with discontinuation rates from other studies of opioids in cancer and noncancer populations.[31-33] The prevalence of adverse effects was higher in studies that directly questioned patients about adverse effects compared with those that relied on self-reporting. Because the presence of adverse effects is one of the reasons patients are unwilling to continue or increase doses of medication for pain relief,[34] these findings reemphasize the need for active questioning about and

aggressive management of opioid-related adverse effects. However, the short duration of these studies also meant that useful data about long-term adverse events such as aberrant drug-seeking behavior were not obtained. Although we would not have expected aberrant drug-seeking behavior to be a significant problem, as this adverse event appears to be rare in the cancer population,[35] evidence from trials might help to dispel the fear of addiction that often hampers good pain control.[34]

The small number of studies retrieved and the short duration of the studies are perhaps a reflection of the difficulties of conducting clinical trials in this group of patients.[36,37] High attrition rates due to worsening of the underlying disease or intercurrent illness mean that investigators try to minimize losses to follow-up by designing trials of short duration. Although this approach can provide robust short-term data, it means that results on longer-term efficacy or rates of adverse effects are often not available. Short-term data on comparative effectiveness and adverse events, however, provide important information for clinicians managing cancer pain, to inform patients of the likelihood of beneficial and immediate adverse effects and to reinforce the need for appropriate management of these early adverse effects so that ad-

equate dose titration can be achieved and satisfactory pain relief obtained.

The studies recruited outpatients from general cancer or palliative care patient populations, with mixed types of pain from a variety of cancers. Where reported, the patients were treated as outpatients, although daily contact was made. It seems likely that the patient population in the trials is representative of patients with cancer-related pain seen in usual practice (Table 1). It is unclear whether these results are of relevance to patients with chronic noncancer pain, which represents a larger group of patients for whom opioids are considered. Previous systematic reviews[32,38] have examined the efficacy of opioids in various types of noncancer pain, but only 1 review[33] has attempted to compare relative efficacies of different opioids. These reviews have confirmed the efficacy of opioids in a variety of chronic pain conditions and have demonstrated that adverse effects are as common as in cancer populations. To our knowledge, no studies comparing oxycodone with other opioids for moderate to severe pain have been conducted in patients with noncancer pain, but there is no clinical or pharmacologic reason to believe that one opioid would be more effective than another in one setting (eg, cancer patients) compared with another (eg, patients with chronic noncancer pain).

Morphine, in both normal- and modified-release formulations, has been the first-line opioid in England for the management of moderate to severe cancer pain. In this review, we did not find any important differences between oxycodone and morphine. Oxycodone is almost 4 times more expensive than morphine in England, and there is less general experience of its use. Thus, there is no reason to challenge the recommendation to use morphine as a first-line agent for cancer pain. There is a need, however, for larger trials of longer duration designed to obtain comparative efficacy and adverse event data for opioids for moderate to severe pain in cancer and noncancer populations.

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Correction

Error in Table. In the Review Article by Reid et al titled "Oxycodone for Cancer-Related Pain: Meta-analysis of Randomized Controlled Trials," published in the April 24 issue of the ARCHIVES (2006;166:837-843), an error occurred on page 839 in Table 1. In that table, in the row pertaining to the study by Hagen and Babul,[17] 1997, and the column titled "Intervention," the hydromorphone-oxycodone ratio should have been listed as 0.24 rather than 1.6.