Annals of Internal Medicine | Review

Systematic Review: Opioid Treatment for Chronic Back Pain: Prevalence, Efficacy, and Association with Addiction

Bridget A. Martell, MD, MA; Patrick G. O'Connor, MD, MPH; Robert D. Kerns, PhD; William C. Becker, MD; Knashawn H. Morales, ScD; Thomas R. Kosten, MD; and David A. Fiellin, MD

Background: The prevalence, efficacy, and risk for addiction for persons receiving opioids for chronic back pain are unclear.

Purpose: To determine the prevalence of opioid treatment, whether opioid medications are effective, and the prevalence of substance use disorders among patients receiving opioid medications for chronic back pain.

Data Sources: English-language studies from MEDLINE (1966–March 2005), EMBASE (1966–March 2005), Cochrane Central Register of Controlled Clinical Trials (to 4th quarter 2004), PsychInfo (1966–March 2005), and retrieved references.

Study Selection: Articles that studied an adult, nonobstetric sample; used oral, topical, or transdermal opioids; and focused on treatment for chronic back pain.

Data Extraction: Two investigators independently extracted data and determined study quality.

Data Synthesis: Opioid prescribing varied by treatment setting (range, 3% to 66%). Meta-analysis of the 4 studies assessing the efficacy of opioids compared with placebo or a nonopioid control did not show reduced pain with opioids (*g*, −0.199 composite standardized mean difference [95% CI, −0.49 to 0.11]; $P = 0.136$). Meta-analysis of the 5 studies directly comparing the efficacy of different opioids demonstrated a nonsignificant reduction in pain from baseline (*g*, −0.93 composite standardized mean difference [CI, −1.89 to −0.03]; $P = 0.055$). The prevalence of lifetime substance use disorders ranged from 36% to 56%, and the estimates of the prevalence of current substance use disorders were as high as 43%. Aberrant medication-taking behaviors ranged from 5% to 24%.

Limitations: Retrieval and publication biases and poor study quality. No trial evaluating the efficacy of opioids was longer than 16 weeks.

Conclusions: Opioids are commonly prescribed for chronic back pain and may be efficacious for short-term pain relief. Long-term efficacy (≥16 weeks) is unclear. Substance use disorders are common in patients taking opioids for back pain, and aberrant medication-taking behaviors occur in up to 24% of cases.

Ann Intern Med. 2007;146:116-127. www.annals.org
For author affiliations, see end of text.

Back pain is the second leading symptom seen by physicians in the United States (1). Chronic back pain (that is, pain lasting more than 3 months) (2) occurs in 5% to 8% of community-dwelling persons (3, 4) and is reported in 19% of working adults (5).

Clinicians treating chronic back pain choose from a range of options, including exercise therapy, nonsteroidal antiinflammatory medications, tricyclic antidepressants, acupuncture, and electrical stimulation. Although these treatments may be effective, patients often experience ongoing pain. Concerns regarding nonsteroidal antiinflammatory medications (6, 7) can lead clinicians to consider opioid treatment. However, the potential for tolerance and withdrawal, combined with concerns about misuse and opioid dependence (8), may lead clinicians to restrict the prescription of opioids (9).

This systematic review and meta-analysis addresses the following questions: 1) What is the prevalence of opioid treatment in patients with chronic back pain? 2) Are opioid medications effective in treating chronic back pain? and 3) What is the prevalence of substance use disorders among patients receiving opioid medications for chronic back pain?

Methods

Data Sources

We conducted a search of the following databases: MEDLINE (1966–March 2005), EMBASE (1966–March 2005), Cochrane Central Register of Controlled Clinical Trials (through the fourth quarter of 2004), and PsychInfo (1966–March 2005) and limited the search to English-language and human studies. We used Medical Subject Headings (MeSH) and text words in MEDLINE (**Appendix Table 1**, available at www.annals.org). Separate searches were conducted for the 3 clinical questions and were combined into a master library. We examined selected literature reviews and bibliographies for additional studies. Opinions from leading pain experts regarding potential unidentified manuscripts were also solicited.

Study Selection

Studies were included if they provided data on 1 of our 3 clinical questions and met the following criteria: 1) adult (≥18 y) patients; 2) nonobstetric sample; 3) no preexisting diagnosis of opioid dependence (8); 4) focus on

See also:

Print
Editors' Notes 117

Web-Only
Appendix Tables
CME quiz
Conversion of figures and tables into slides

opioids for chronic back pain; and 5) use of oral, topical, or transdermal opioid preparations. For studies reporting on the efficacy of opioids, we required that the duration of back pain be at least 3 months. For studies of prevalence, we relied on the study author's operational definition of chronic back pain. For studies investigating the prevalence of addictive behaviors, we required that studies investigated aberrant medication-taking behaviors in patients prescribed opioids for treatment for back pain, assessed any type of substance use disorder concurrent with treatment for chronic back pain, or described lifetime prevalence of substance use disorders that may have preceded treatment for back pain.

Two reviewers applied these criteria to all identified abstracts. When they could not determine eligibility based on the abstract, the full article was reviewed. Discordant eligibility determinations were resolved by consensus.

Quality Assessment

Study quality was assessed by using standardized instruments (10, 11). Two reviewers independently scored the quality of all studies; differences were resolved by consensus. Quality descriptions (for example, "excellent") were based on designations created by the authors who developed the quality instrument. For observational studies, a quality score of 12 or greater was considered excellent (10). We included all cross-sectional studies that reported prevalence and their quality scores. For clinical trials, a score of 10 or greater is considered excellent (11). Opioid efficacy trials that did not achieve a score of 10 or greater are not given detailed consideration in this report.

Data Synthesis and Analysis

We provide descriptive data on the prevalence of opioid treatment, substance use disorders, and aberrant medication-taking behaviors. We used SAS software, version 9.1 (SAS Institute, Inc., Cary, North Carolina), to perform a meta-analysis of the studies that reported on the efficacy of opioids. Only studies that provided a measure of effect size were included. We used opioid equianalgesic conversion charts to compare medications across studies (12).

One outcome measure was extracted from each study. Whenever possible, we extracted the outcome measure recommended by the pain expert consensus panel IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) statement (13). In some cases, the reported measure of pain intensity differed across studies. For example, the visual analogue scale ranged from 0 to 100 mm, and the Brief Pain Inventory was measured on a 0- to 10-point scale. In addition, binary studies reported outcome measures as a proportion to show a decrease in pain. For these reasons, a standardized effect size was used. We calculated a Hedges' *g* estimate of the effect size for continuous measures, consisting of the difference in mean change in pain from baseline between 2 groups divided by a pooled estimate of the standard error (14, 15). Our estimate of the effect size for binary outcomes used the Cox approach that divides the log odds ratio by the constant, 1.65 (16, 17). For studies that compared opioids with placebo or nonopioid medications, the comparison was the difference between control and treatment groups. For observational studies or studies comparing 2 opioids, the comparison was the change in pain intensity from baseline. We pooled studies with 2 opioid groups when they resulted in similar estimates.

Determining the homogeneity of the standardized mean difference across studies is equal to testing the equality of means (15). For large samples, the test statistic, which is a function of Cochran *Q* statistic, follows a chi-square distribution: Degrees of freedom are equal to the number of studies minus one (15). If the null hypothesis of equal means is rejected, we estimated a random-effects model. Otherwise, the fixed-effects solution is presented. In addition, the I^2 statistic is reported as an index of study heterogeneity (18). Defined as the maximum of [0, $(Q - df)/Q$], I^2 is the proportion of total variance in the pooled estimate. A value of 0.5 or greater indicates substantial heterogeneity.

Pooled standardized mean differences were estimated based on a subset of studies to evaluate the sensitivity of the results. In particular, the influence of an outlying study or studies with binary outcomes was removed in 2 separate assessments. In addition, the relationships between the standardized mean difference and variables potentially causing variability across studies (for example, randomized vs. nonrandomized study, continuous vs. binary outcome, sample size, comparator group [placebo vs. active control], quality, and study duration) were examined independently using inverse–variance-weighted linear regression or meta-regression (19).

Context

Patients with low back pain often request pain medication, and many physicians prescribe opioids despite concerns about drug dependence.

Contribution

Opioid prescribing rates in 11 studies varied widely (3% to 66%). In 4 short-term randomized trials, pain relief was similar with opioids and either active treatment or placebo. In poor-quality, heterogeneous studies, the prevalence of substance abuse disorders in patients taking long-term opioids for back pain varied from 5% to 24%.

Caution

Study quality was weak overall.

Implications

Opioids seem to have limited, if any, short-term value in chronic low back pain. Evidence about developing substance abuse is too limited to draw any conclusions.

—The Editors

Role of the Funding Sources

The Robert Wood Johnson Foundation's Program of Research Integrating Substance Use in Mainstream Healthcare, the National Institute on Drug Abuse, and the National Institute on Alcohol Abuse and Alcoholism funded this study through a grant administered by the Treatment Research Institute, which had no role in designing, conducting, or reporting the study.

RESULTS

Literature Search Results

The search identified 2378 abstracts. After we excluded duplicates ($n = 752$), 1626 abstracts remained. Of these, we excluded 1592 abstracts for the following reasons: The association between opioid medication and chronic back pain was not specifically assessed ($n = 1068$ [65%]); the study opioids were not administered orally, topically, or transdermally ($n = 185$ [11%]); the prevalence of addiction or substance use disorders in patients receiving opioid medications was not addressed ($n = 184$ [11%]); obstetric patients were included ($n = 45$ [3%]); the efficacy of opioids in treatment for chronic back pain was not assessed ($n = 89$ [6%]); and there was a lack of a focus on adults ($n = 21$ [1%]). Four additional manuscripts (20–23) were obtained through bibliographies. Therefore, 38 studies were included in the final analysis. The percentage agreement was 95% (665 of 700) between 2 reviewers regarding eligibility based on an evaluation of 700 abstracts.

Figure 1 shows a flow diagram for study exclusion. Of the 38 studies, 14 (37%) addressed the prevalence of opioid prescribing, 18 (47%) addressed the efficacy of opioids, and 9 (24%) addressed the prevalence of substance use disorders or aberrant medication-taking behaviors in patients who were prescribed opioids. Three of the 14 studies that reported the prevalence of opioid prescribing did not provide a denominator for back pain patients in the sample and therefore were excluded (24–26). Three studies addressed prevalence of opioid prescribing and efficacy of opioids; however, quality scores resulted in exclusion in at least 1 category (26–28). Three studies regarding the efficacy of opioids were excluded because they reported quality scores less than 10 (27, 29, 30). One study was reviewed in abstract form because the full manuscript was not available (21).

What Is the Prevalence of Opioid Treatment for Patients with Chronic Back Pain?

Description and Quality of Studies Reporting Prevalence of Opioid Treatment

Of the 11 studies describing the prevalence of opioid treatment for chronic back pain, most used a cross-sectional design (**Table 1**). Studies were conducted in various settings, including 4 multidisciplinary or specialty groups (28, 31–33), 4 pain treatment centers (27, 34–36), 1 across all disciplines (37), 1 in community-dwelling elderly persons (38), and 1 in a primary care group (39).

Four of 11 studies (36%) had quality rating scores of 12 or more (28, 31, 34, 35) of a maximum possible score of 27 (range, 7 to 16) (**Appendix Table 2**, available at www.annals.org). The most common concern was lack of internal validity due to limitations that are common in observational studies (for example, failure to adjust for confounding variables). In addition, recall bias was a concern in studies that used surveys or questionnaires (37, 38).

Results of Studies Reporting Prevalence of Opioid Treatment

The proportion of patients who were prescribed opioids for chronic back pain ranged from 3% to 66%. The ranges of prevalence rates were similar for higher-quality (scores ≥12) and lower-quality studies. Prevalence estimates were highest in specialty treatment centers (range, 11% to 66%) and lowest in primary care centers (range, 3% to 31%).

Four studies sought to describe the characteristics of patients who were receiving opioids for chronic back pain compared with those who were not receiving these medications (31, 34–36) (**Table 1**). Two studies found that patients were more likely to be prescribed opioids if they reported greater disability, poorer functioning, greater distress and suffering, and higher functional disability scores than if they had higher pain severity scores (34, 36). One study conducted in spine specialty clinics found that patients receiving opioids were more likely to have neurologic signs, dermatomal pain distributions, and pain radiation (31).

In summary, opioid prescribing for chronic back pain varies substantially by treatment setting, ranging from 3% to 66%, and is more common in patients with impaired functional status.

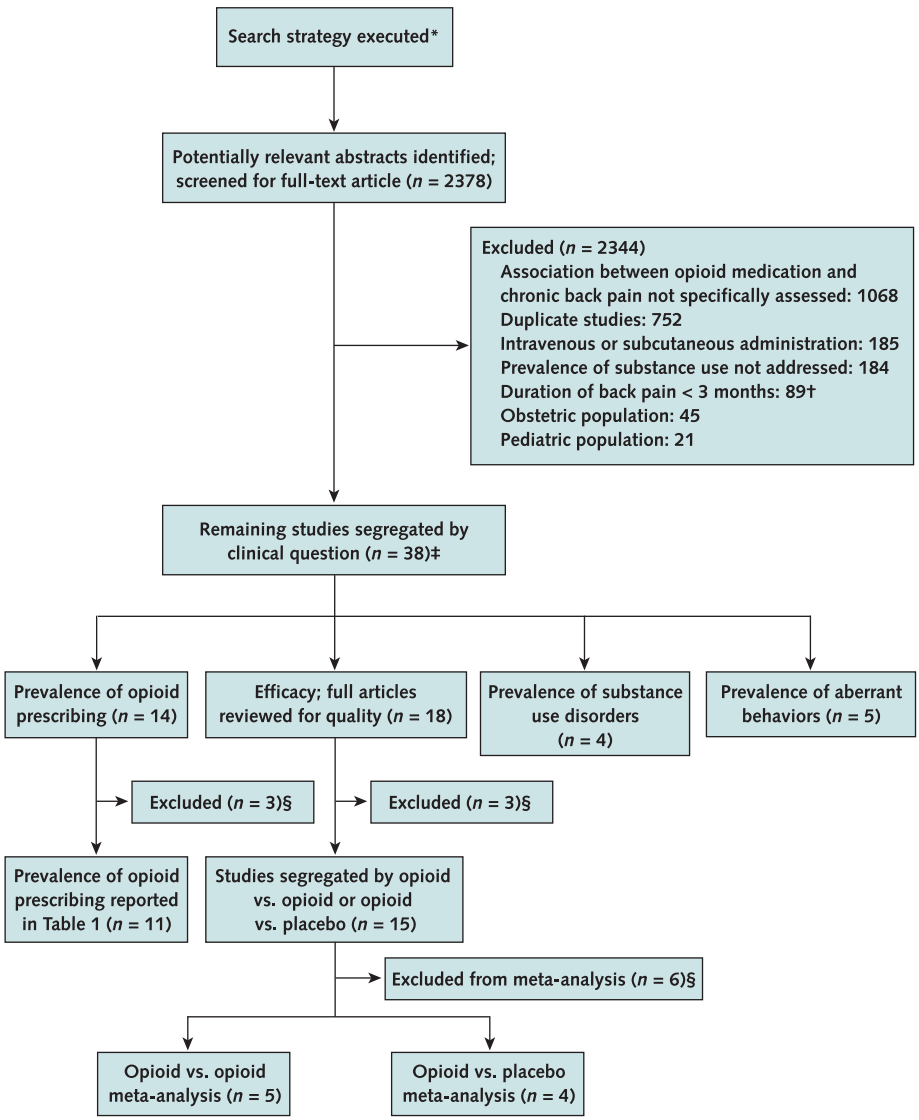
Are Opioids Effective for Treatment for Chronic Back Pain?

The 15 studies of the efficacy of opioids for chronic back pain (**Tables 2** and **3**) offered information on 1008 patients. Eight (53%) studies used a randomized, double-blind trial design (20, 21, 40–43, 45, 46), 4 were placebo-controlled (20, 21, 41, 43), and 2 used a crossover design (42, 46). Pharmaceutical companies sponsored 11 of the 15 (73%) trials.

Description and Quality of Trials Comparing Opioids with Nonopioids or Placebo

In these 6 trials, the quality scores were considered excellent (range, 14 to 18; possible maximum score, 20), and all eligible patients had moderate pain as evidenced by baseline assessments (**Table 2** and **Appendix Table 3**, available at www.annals.org). Most trials failed to describe pretrial analgesia and used divergent primary pain outcome measures. The mean study duration was 64 days (range, 7 days to 16 weeks). Overall patient retention was 67% to

Figure 1. **Study inclusion flow diagram.**



*See the Appendix. †Strictly defined only for efficacy trials. ‡3 studies addressed both prevalence of prescribing and efficacy (reference 26–28). §See text for reasons for exclusion.

99%. The average (SD) opioid dose, in morphine units, was 73 mg/d (SD, 89) (range, 30 to 232 mg/d) (21, 40, 41, 44). Oxymorphone and topical morphine do not have a published equianalgesic conversion and are not included in this calculation (41, 43). All studies reported a substantial reduction in pain scores: Opioids were superior to placebo and active nonopioid comparators.

Meta-analysis of Studies Evaluating Opioids for Chronic Back Pain: Studies Comparing Opioid Medications with Nonopioids or Placebo

Four of the 6 studies comparing an opioid medication with a nonopioid or placebo were included in the meta-analysis (**Figure 2**) (21, 40, 41, 44). One crossover trial was excluded because we were not able to compute a comparative standardized mean difference from the reported data (43). Another study was excluded because baseline pain measurements were not provided (42). Two studies compared 2 experimental conditions with a control group (41, 44). In this instance, the 2 experimental groups were pooled to provide only 1 estimate. A test of equality of study means was not rejected at the 0.05 significance level (chi-square = 1.08; $P = 0.782$; $I^2 = 0$). Analysis of active treatment compared with placebo revealed a composite standardized mean difference (g, −0.199 [95% CI, −0.49 to 0.11]; $P = 0.136$), which reflects a nonsignificant reduction in pain in patients receiving opioid treatment compared with those receiving nonopioids or placebo (**Figure 1**).

In a sensitivity analysis, there was no association in standardized mean difference estimates: Study quality,

Table 1. **Studies Reporting on the Prevalence of Opioid Prescribing in Patients with Chronic Nonmalignant Back Pain***

Study, Year (Reference)	Study Type	Study Setting	Patient Inclusion	Prevalence of Opioid Prescription for Chronic Back Pain	Quality Score†
Fillingim et al., 2003 (34)	Cross-sectional	Multidisciplinary pain clinic	Spinal pain ≥3 mo	43% (67/156) of men, 39% (33/84) of women for low back pain; 57% (89/156) of men, 50% (42/84) of women for spinal pain	16
Deyo et al., 1988 (35)	Cross-sectional	Multidisciplinary outpatient pain center in Texas	Back pain >4 mo in pain clinic enrollees or recruits for pain treatment trial	41% (25/61) in pain clinic sample; 0% (0/55) in clinical trial group (baseline)	13
Mahowald et al., 2005 (28)	Cross-sectional	Minneapolis Orthopedic Spine Clinic	Spine clinic patients who received ≥1 opioid prescription over past 3 years	66% (152/230) from a specialty spine clinic	12
Fanciullo et al., 2002 (31)	Cross-sectional	23 specialty spine clinics across the United States	Patients seen between 1995 and 1998	3% (649/25 479) (observational database)	12
Pitkala et al., 2002 (38)	Cross-sectional mailed survey	Surveys mailed in 1999 to Finnish households	Home-dwelling elderly persons age 75 y, 80 y, and 85 y in Helsinki, Finland	3% (57) for back and/or joint pain	11
Coste and Venot, 1999 (39)	Cross-sectional study using pharmacy database	Primary care practices in France	1992 prescriptions for intervertebral disc disease, unspecified disorder of back, and peripheral enthesopathy	3% (575/23 080) of prescriptions for low-back pain	10
Nyiendo et al., 2001(32)	Cross-sectional	14 multispecialty clinics in Oregon	Pain between 12th rib and gluteal fold, pain >6 wk	31% (96/309)	9
Hart et al., 1995 (37)	Cross-sectional	National Ambulatory Medical Care Survey for 1980, 1981, 1985, 1989, and 1990; 3000 office-based physician practices were included	ICD-9 codes for "definite" low back pain and "possible" low back pain; back pain primary diagnosis for visit	15% (range, 11%–19% of all back pain visits)	8
France et al., 1984 (27)	Observational case series	Academic multidisciplinary pain clinic	Patients who required long-term opioids after program enrollment	11% (16) of patients with chronic back pain completing 3 wk of an inpatient stay; required opioids at 1-year follow-up	8
Long et al., 1996 (33)	Observational cohort	National Low Back Pain Study including 8 academic neurosurgical or orthopedic specialty referral centers	Primary symptom of low back pain, not more than 1 surgery, eighth-grade reading level, and fluent in the English language	28% (655/2374); specialty pain clinic	8
Turk and Okifuji, 1997 (36)	Cross-sectional	University of Washington tertiary care pain treatment center	Consecutive patients evaluated at pain treatment center	40% (17/42); specialty pain clinic	8

* ICD-9 = International Classification of Diseases, Ninth Revision.
† Scoring instrument is from reference 10.

sample size, study duration, and opioid dose were equal. The 1 study with a binary outcome (40) was removed to assess the sensitivity of the pooled estimate. This study had little influence on the pooled standardized mean difference (*g*, −0.24 [CI, −0.73 to 0.25]; $P = 0.169$).

In summary, when comparing the effect of opioid medications with placebo or active control conditions, opioids have limited efficacy in treating chronic back pain.

Description and Quality of Trials Comparing Opioids

Nine of the trials that tested the efficacy of an opioid against an opioid comparator had quality scores of 10 or greater (**Appendix Table 4**, available at www.annals.org). These trials tended not to adequately describe pretrial analgesia, were of short duration, and tested a range of opioids (**Table 3**). Of studies in which an examination of the equianalgesic opioid dose was possible, the average (SD) morphine-equivalent dose was 63 mg (SD, 15) (range, 30 to 82 mg) for the experimental group and 49 mg (SD, 22) (range, 16 to 62 mg) for the comparison group (20, 45–47). Although only 1 study was powered for equivalency (52), 3 compared the effects of opioids with the effects of other opioids rather than with the baseline condition (20, 45, 46). All studies reported a substantial reduction in pain scores: The index opioid was superior to the baseline condition and the active opioid comparator. Although most studies used an intention-to-treat analysis, 2 stratified their samples into a "responder" group, which was used as the reportable sample (20, 47).

Meta-analysis of Studies Evaluating Opioids for Chronic Back Pain: Comparing Opioids

Five of the 9 studies comparing 2 or more opioids were included in the meta-analysis (45, 48–51). Two studies (45, 47) had 2 or more experimental conditions; in 1 instance, we were able to pool the observed estimates (45). In the other instance, the estimates resulted from separate clinical trials and were too disparate to allow a pooled analysis (47). Three studies were excluded because they lacked a follow-up outcome measure (20), a baseline pain measurement (46), or an appropriate comparator group (52). A test of equality of study means was not rejected at the 0.05 significance level (chi-square = 3.39; $P = 0.495$; $I^2 = 0$). Our analysis evaluated the change in pain measurements from baseline to after opioid treatment. Meta-analysis revealed a composite standardized mean difference (*g*, −0.93, [CI, −1.89 to −0.03]; $P = 0.055$), reflecting a nonsignificant reduction in pain with opioid treatment compared with baseline (**Figure 3**). One report that could

not be pooled because of disparate estimates from 2 clinical trials (47) demonstrated a statistically significant reduction in pain scores from baseline with controlled-release and immediate-release oxycodone. The standardized mean differences were −5 (CI, −6.20 to −3.80) and −2.55 (CI, −3.29 to −1.80), respectively.

In a sensitivity analysis, there was no association between standardized mean difference and study type (randomized vs. nonrandomized), study duration, study quality, sample size, or medication dose.

In summary, compared with patients' baseline pain scores, we cannot definitively conclude that opioids provide efficacy.

Overall Quality of Studies Reporting Efficacy of Opioid Treatment

All 15 studies reporting the efficacy of opioid medication for chronic back pain had quality scores of 10 or greater (**Appendix Table 3** and **Appendix Table 4**, available at www.annals.org). Although their quality scores were considered excellent, the heterogeneous designs of these studies made interpretation challenging. Studies varied markedly regarding the sample selected (opioid-naive vs. opioid-experienced), causes of back pain (nociceptive and mechanical with and without radiculopathy), length of opioid treatment, type of opioid medication, use of rescue medications during the trial, and primary outcome instru-

Table 2. **Studies Evaluating the Efficacy of Opioid Medication for the Treatment of Chronic Nonmalignant Back Pain Using Nonopioid Medications or Placebo as Comparators***

Study, Year (Reference)	Study Type	Study Drug(s) and Dose	Patients Enrolled/ Evaluable	Medications taken before Study Randomization	Study Duration	Outcome Measure Instrument	Results	Quality Score†
Kuntz and Brossel, 1996 (40)	Randomized, double-blind	Acetaminophen/ caffeine (500/50 mg) (PC) vs. acetaminophen/ dextropropoxyphene (400/30 mg) (PD)	57/62 PC 55/62 PD	Not described	7 d	VAS‡ and Huskisson VAS‡	Reduction in pain (>50%) was seen in 51.2% of PC and in 47.0% of PD patients	17
Hale et al., 2005 (41)§	Randomized, placebo-controlled, double-blind	Efficacy of extended-release oxymorphone (10 to 110 mg) vs. controlled-release oxycodone (20 to 220 mg) vs. placebo	330/217 (139 completed the trial)	Receiving stable opioid and analgesia < 600 mg morphine equivalent before randomization	7 to 14 d titration with 18-d evaluable period	VAS‡ 4-point categorical scale, BPI, PGA, Kaplan–Meier time-to-failure estimates, use of rescue medications	VAS least-squares mean difference was statistically significant with extended release oxymorphone (−18.21 [95% CI, −25.83 to −10.58]) and controlled-release oxycodone (−18.55 [CI, −26.12 to −10.98]) compared with placebo	17
Muller et al., 1998 (42)§	Randomized, double-blind, crossover	Efficacy and tolerability of acetaminophen/ codeine (500 mg/30 mg every 8 h) (PC) vs. tramadol 50 mg every 8h (T)	55/52 (T) and 55/54 (PC)	Not defined; 24-h washout	7 d for each treatment	3-point medication rating scale; yes/no, medication continuation‡, quality of sleep, VAS, and treatment preference	PC was at least as effective as T; 80% "good" response for PC and 81% "good" response for T; 50% continue PC; 40% continue T	16
Tennant et al., 1993 (43)	Open-label followed by randomized, placebo-controlled, double-blind, crossover	Pain relief with topical morphine (1.0 to 3.0 mg daily application) vs. placebo cream	26/26 open-label; 9/9 double-blind	Used opioids daily	90 d	PRRS‡; pain-free movement	Mean length pain relief morphine cream longer than placebo (7.8 ± 9.5 h vs. 6.6 ± 9.8 h); 4/9 pain-free movement morphine vs. 0/9 placebo	16
Richards et al., 2002 (21)§‖	Randomized, placebo-controlled, double-blind	Controlled-release oxycodone (10 mg every 12 h) vs. placebo	110 (unknown denominator)	4% opioids, 39% NSAIDs, 57% both	90 d	BPI‡, SF-36, RDQ	Controlled-release oxycodone demonstrated a statistically significant decrease in average pain intensity and pain relief scores compared with placebo (4.6 vs. 5.4 [$P = 0.03$] and 47.2 vs. 36.3 [$P = 0.05$])	15
Jamison et al., 1998 (44)§	Randomized, open-label	Long-term safety and efficacy of oxycodone (20 mg) or oxycodone plus sustained-release morphine (maximum 20 mg morphine equivalents every day) compared with naproxen (1000 mg)	36/35	Not specified; 1-mo washout	16-wk prescription; 16-wk continuation; 12-wk detoxification	CPEQ, SF-36, SCL-90, medication diary, and helpfulness rating	Average pain in set dose and titrated dose showed a statistically significant difference compared with naproxen (59.8 ± 16.6 and 54.9 ± 15.9 vs. 65.5 ± 19.1, respectively) ($P = 0.05$); no primary outcome measure was defined	15

* BPI = Brief Pain Inventory; CPEQ = Comprehensive Pain Evaluation Questionnaire; NSAID = nonsteroidal anti-inflammatory drug; PC = paracetamol codeine; PD = paracetamol dextroproxyphene; PGA = Physician Global Assessment; PRRS = Pain Relief Rating Scale; RDQ = Roland Disability Questionnaire; SCL-90 = Symptom Checklist-90; SF-36 = Short Form-36 Health Status Questionnaire; T = reference; VAS = visual analogue pain scale.
† Average score from 2 independent reviews. Scoring instrument is from reference 11.
‡ Primary outcome measure instrument identified in study design.
§ Pharmaceutical industry–sponsored.
‖ Published abstract.

Table 3. **Studies Evaluating the Efficacy of Opioid Medication for the Treatment of Chronic Nonmalignant Back Pain Using Other Opioids as Comparator Medications***

Study, Year (Reference)	Study Type	Study Drugs and Dose	Patients Enrolled/ Evaluable	Medications Taken before Study Randomization	Study Duration	Outcome Measure Instrument	Results	Quality Score†
Thurel et al., 1991 (45)‡	Randomized, double-blind	Acetaminophen/codeine (1500 mg/90 mg every 8 h) (PC); vs. acetaminophen/ dextropropoxyphene (1200 mg/120 mg every 8 h) (PD)	50/49	Type of analgesia not defined, but 56% were treated successfully; 22% did not respond; 22% no previous medication	14 d	VAS§; 3-category impairment of activity scale; number of pain awakenings per night	Medications were similar in efficacy PC group from 72.2 ± 2.1 to 31.3 ± 4.6 and PD group from 70.8 ± 2.6 to 26.8 ± 4.5; not powered as an equivalency trial	17
Hale et al., 1999 (46)‡	Randomized, double-blind, crossover	Similar efficacy of controlled-release oxycodone (10 mg every 12 h) vs. immediate-release oxycodone (5 mg, 4 times/d)	57/47 (37 completed)	All patients were receiving maximum doses of nonopioids with or without opioid medications before study; 50% continued nonopioid therapy	14 d (7 d each crossover)	PIS (4-point)†	Overall pain intensity 1.2 ± 0.1 SEM controlled-release vs 1.1 ± 0.1 SEM immediate-release not substantially different; biased population: only those achieving analgesia with oxycodone were randomly assigned	16
Hale et al., 1997 (20)‡	Randomized, placebo-controlled, double-blind	Controlled-release oxycodone 100 mg (average, 200 mg/d) vs. as-required dose of codeine/APAP 30/325 mg (average, 71 mg/d)	104/82	None of these patients was taking medications 24 to 96 h before randomization	5 d	PIS (4-point) acceptability of therapy score (5-point)	Mean sum pain intensity better in controlled-release oxycodone formulation (6.1 ± 0.6 vs. 8.6 ± 0.7); compared as-needed codeine/ acetaminophen in placebo group with oxycodone controlled-release codeine	15
Salzman et al, 1999 (47)‡	Randomized, open-label	Stable pain control for immediate-release vs. controlled-release formulation of oxycodone (maximum for either drug, 80 mg/d)	57/47 (37 completed and 10 nonresponders)	88% used opioids before the study; conversion ratios were used to convert doses to oxycodone	10 d	PIS (4-point scale) and Kaplan–Meier time to stable pain control	Immediate-release and controlled-release formulations resulted in less pain compared with baseline in the responder group. 2.3 ± 0.1 SEM to 1.2 ± 0.1 for immediate-release and 2.4 ± 0.1 to 1.0 ± 0.2 for controlled-release groups	14
Gammaitoni et al., 2003 (48)‡	Nonrandomized, open-label	Evaluate the analgesic effectiveness and safety of oxycodone/ acetaminophen (7.5/325 mg vs. 10/325 mg formulations) maximum dose of either formulation, 20/650 mg	33/33 (28 completed the trial)	25% were receiving an opioid or opioid combination as needed before study entrance	4 wk	BPI§; NPI (4-point); BPI; and NASS lumber spine questionnaire	Compared with baseline: worst pain: 7.7 ± 1.5 vs. 5.6 ± 2.1; least pain: 4.4 ± 2.1 vs. 2.6 ± 1.9; pain right now: 6.6 ± 2.2 vs. 3.8 ± 2.4; average pain: 6.4 ± 1.3 vs. 4.4 ± 2.1	14
Simpson et al., 1997 (51)‡	Open-label crossover comparison of transdermal fentanyl and short-acting opioid	Efficacy of transdermal fentanyl (average dose, 25 μg/h)	68/50 (50 completed the trial)	100% were taking oral opioids before study entrance	30 d	VAS; ODQ; PDI; and VSH	VAS declined from 79.8 ± 30.0 to 44.2 ± 26.7 with transdermal fentanyl treatment; primary efficacy measure was not defined	13
Schofferman, 1999 (49)	Open-label, observational	Effect of opioids on pain and function (various dosing regimens)	33/28 (7/33 [25%] nonresponders)	Not described; patients had to have not responded to "adjuvant medication" in addition to other interventions	Phase I: 6 to 12 wk; phase II: 32 wk	NRS§ and OSW	6- to 12-wk trial; NRS improved from 8.6 to 5.9 and OSW improved from 64 to 54; 32-mo follow up NRS improved from 8.5 to 4.9 and OSW improved from 64 to 50	12
Ringe et al., 2002 (50)‡	Open-label, observational	Efficacy and safety of transdermal fentanyl (25 μg–100 μg/h)	64/49 (15 [23%] withdrew before 30 d)	Not described; however, patients were eligible for the study only if pain required "strong" opioids	30 d	PIS at rest (11-point scale)§; quality of life (5-point scale) satisfaction with therapy (5-point scale)	Statistically significant difference comparing baseline with pain at rest after 30 d (7.7 ± 2 to 4.0 ± 2.7) pain at movement (8.5 ± 1.3 to 5.0 ± 2.1)	11
Zenz et al., 1992 (52)	Open-label	Evaluate the pain reduction and patient function of opioid treatment for chronic pain; opioid-naive patients (n = 19) received sustained-release dihydrocodone. Previous opioid exposure received buprenorphine (n = 57). If no response, patients received morphine (n = 23); one received methadone	100/100 (24/100 back pain) 23/100 (back pain not substratified); 60 patients discontinued over course of 1 year	Opioid-naive (19%) and opioid-experienced patients	14 d 1 y	VAS % reduction§, Karnofsky Performance Scale	For back pain 12 (50%) had good pain relief (>50% reduction on 100% scale); 7 (29%) had partial pain relief (<50%, >25%); and 5 (21%) had no relief (<25%)	10

* APAP is the European equivalent of acetaminophen. BPI = Brief Pain Inventory; NASS = North American Spine Society; NPI = Neuropathic Pain Score; NRS = Numerical Rating Scales; ODQ = Oswestry Disability Questionnaire; OSW = Oswestry Low Back Disability Scale; PC = paracetamol codeine; PD = paracetamol dextroproxyphene; PIS = Pain Intensity Scale; PRRS = Pain Relief Rating Scale; RODQ = Revised Oswestry Disability Questionnaire; VAS = visual analogue pain scale; VSH = Verran and Snyder-Halpern Sleep Scale.

† Average score from 2 independent reviews. Scoring instrument is from reference 11.

‡ Pharmaceutical industry–sponsored.

§ Primary outcome measure instrument identified in study design.

ments. Most trials had small samples: 10 of the 15 (67%) had 55 or fewer evaluable patients at study completion. Finally, only 1 study addressed concerns regarding statistical power (52).

What Is the Prevalence of Substance Use Disorders among Patients Receiving Opioid Medications for Chronic Back Pain?

Description and Quality of Studies Reporting Prevalence of Substance Use Disorders

Overall, studies reporting the prevalence of current substance use disorders in chronic back pain patients receiving opioids ranged from 3% to 43%, with a lifetime prevalence as high as 54% (**Table 4**) (22, 23, 26, 53). The mean quality score for these studies was 11 of 27 (range, 7 to 16), which indicated generally poor study quality (**Appendix Table 5** and **Appendix Table 6**, available at www.annals.org). The studies were heterogeneous and varied with respect to clinical practice location, methods used to assess abuse disorders, and the presence and composition of a control group. Only 2 studies diagnosed a substance use disorder by using a validated instrument (22, 23). In the study with the highest quality score (16 of 27), current and lifetime prevalence estimates of substance use disorders in patients receiving opioids for chronic back pain did not differ markedly from those of the group not receiving opioids (current, 23% for both groups; lifetime, 54% vs. 52%, respectively) (**Table 4**) (22).

Description and Quality of Studies Reporting Prevalence of Aberrant Medication-Taking Behaviors

Of the 5 studies that reported prevalence of aberrant medication-taking behaviors, the current prevalence estimates ranged from 5% to 24% (25, 28, 54, 55, 57) (**Table 4**). The mean quality score was 8 (range, 6 to 11), which indicated poor quality. In all but 1 study, there was inadequate controlling for potential clinical concerns, such as recognizing behaviors that may be the result of inadequate pain control. Also, no studies provided estimates of random variability. These studies used various assessment measures, but only 1 study attempted to use a combination of behaviors that might be consistent with medication abuse (54).

Two studies (54, 57) assessed patient characteristics that may be associated with increased prevalence of addictive behaviors. Ready and colleagues (57) found that women were more likely than men to underestimate opioid use. Reid and coworkers (54) showed that more co-occurring medical diseases, higher lifetime prevalence of substance use disorders, and younger age were associated with an increased number of substance-abusing behaviors.

Figure 2. **Results of meta-analysis of opioid efficacy with nonopioids or placebo comparisons**

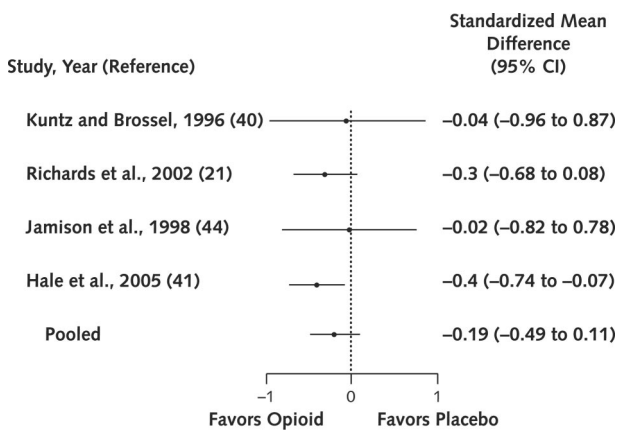
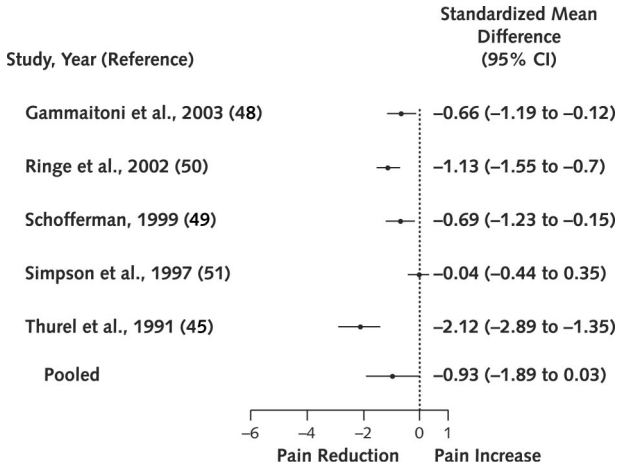


Figure 3. **Results of meta-analysis of opioid efficacy with opioid comparisons**



Discussion

Our review and meta-analysis has revealed that opioids are commonly prescribed for but may only be efficacious for short-term treatment for chronic back pain (<16 weeks). Limited information also indicates that up to one quarter of patients who are receiving these medications exhibit aberrant medication-taking behaviors that may be interpreted as signs of abuse. Prevalence rates of lifetime or current substance use disorders varied, with estimates up to 56%.

Our findings are not consistent with previous reviews on the efficacy of opioids for chronic back pain. Opioids, in some instances, have been found to be efficacious for treatment for painful conditions (58–61). Our review, however, found that the evidence in favor of opioids is not always consistent, and when supportive, only supports this treatment for short periods (for example, <4 months). Long-term trials of opioid efficacy for chronic back pain are lacking, and there is other evidence that indicates that

Table 4. **Studies Reporting on the Prevalence of Aberrant Medication-Taking Behaviors or Substance Use Disorders in Patients Receiving Opioids for Chronic Nonmalignant Back Pain***

Study, Year (Reference)	Study Type	Study Setting	Patient Selection	Patients Evaluated, *n*	Substance Use Disorder and Assessment Measure Used	Lifetime Prevalence of Substance Use Disorder	Prevalence of Current Aberrant Medication-Taking Behavior or Substance Use Disorder	Quality Score†
Brown et al., 1996 (22)	Observational case–control	Wisconsin family practice clinic	Random among patients seen >3 times for back pain in 1 year and reported back pain in past month	61	CIDI-SAM	54% pain group and 52% comparison group	23% for both groups	16
Breckenridge and Clark, 2003 (53)	Observational case–control from 2001–2002	Palo Alto VA Health Care System, which comprises a tertiary referral hospital, 2 long-term inpatient facilities, and 9 primary and specialty outpatient clinics (50 000 patients)	ICD-9 codes associated with back pain as primary diagnosis and at least 1 prescription for opioid per month and/or NSAID in 6-mo period	4325 single-prescription opioid group (and/or NSAID) 100 randomly selected charts were chosen for each group (opioid or NSAID groups) from a total of 4325 single prescription records	Substance abuse and psychiatric diagnosis physician assigned; strict diagnosis criteria may not have been applied	Not assessed	43% in opioid group and 13% in nonopioid group. Unclear whether this is lifetime or current substance abuse ($P <$ 0.001).	11
Mahowald et al., 2005 (28)	Cross-sectional	Minneapolis Orthopedic Spine Clinic	All patients in spine clinic who received at least 1 opioid prescription during previous 3 years	230 charts were identified, 174 interviewed; cohort divided into 45 no opioid, 72 short-term opioid, and 58 long-term opioid	For lifetime prevalence substance abuse: self-report during interview For current prevalence: dose escalation that could not be explained by worsening underlying pain process	45%, 43%, and 46% of short-term opioid, long-term opioid, and no treatment opioid (control), respectively, reported a history of substance abuse	3 (5%) patients in opioid groups exhibited abuse behaviors	11
Reid et al., 2002 (54)	Cross-sectional	2 general medicine clinics	Noncancer pain patients with 6 or more months of opioid prescriptions during 1-year period	98	≥1 of the following: early refill, lost prescriptions, or multiple prescription sources	Not defined for low back pain patients specifically	24% prescription opioid abuse in patients with low back pain of nontraumatic origin	11
Adams et al., 2001 (25)	Cross-sectional chart review	12 University of Wisconsin primary care clinics representing 83 000 patients	Seen in clinic at least once in a 3-month preceding audit date Used opioids for treatment for chronic pain for 3 mo before audit date	267 charts were reviewed (58 failed inclusion criteria) 209 in cohort; 91 (44%) low back pain and 34 (16%) upper back or neck pain	Toxicology screening	Not reported	5% and 6% of low back pain and upper back pain patients, respectively, had drug toxicology screens ordered by primary care providers as a measure of substance abuse	9
Polatin et al., 1992 (23)	Cross-sectional	Functional restorative program in Texas	200 chronic low back pain patients entering program	200	DSM III-R SCID	36% lifetime prevalence of substance abuse	19%	9
Bramley-Moore et al., 1998 (26)	Cross-sectional	Pharmacy records form New South Wales, Australia prescribers	Applications to prescribe opioids for more than 2 mo to the same patient	1500; of those 422 for chronic nonmalignant pain; of those 156 for back pain	As defined by 1966 "Poisons Act" of New South Wales	Not described	30 (19%) and 5 (3%) of back pain patients were classified as "addict" or "possibly addict"	7
Manchikanti et al., 2004 (55)	Cross-sectional	Interventional pain management referral center	Consecutive patients referred with pain for ≥2 y	100	Positive results on urine toxicology screening for a nonprescribed opioid	Not defined for low back pain patients specifically	Not defined for low back pain patients specifically	6
Ready et al., 1982 (57)	Case series	University of Washington Clinical Inpatient Pain Service	Admissions to clinical pain service during 1979	63 admissions; of those 53 chronic pain with medications reported; of those 21 chronic back pain	Self-report vs. observed prescribing	Not reported	Reported daily use, 1.86 narcotic equivalents, observed daily use, 3.64 narcotic equivalents ($P <$ 0.01)	5

* CIDI-SAM = Composite International Diagnostic Interview Substance Abuse Module; ICD-9 = International Classification of Diseases, Ninth Revision; NSAID = nonsteroidal anti-inflammatory drug; DSM III-R SCID = Diagnostic and Statistical Manual of Mental Disorders Structured Clinical Interview; VA = Veterans Affairs.
† Scoring instrument is from reference 10.

the long-term efficacy of opioids for chronic pain may be limited (62, 63).

We noted substantial concerns regarding the quality of the literature in this field. There are few high-quality observational studies examining the prevalence of opioid prescribing in patients with chronic back pain. In addition, we are concerned about sampling bias because of variability in strategies used to determine the prevalence in patients with chronic back pain.

Although the included trials that examined the efficacy of opioids in treating chronic back pain achieved high scores on external validity (**Tables 2** and **3** and **Appendix Table 3** and **Appendix Table 4**, available at www.annals.org), these studies performed less well in other areas: They

frequently did not provide complete information about study design or information on follow-up. Studies used a range of recruitment strategies, drew on diverse patient populations, had small samples with short periods of follow-up, used an array of diagnostic criteria, and used various functional outcomes. In addition, in many studies, an improvement in pain intensity was not necessarily associated with improved functional status. Sampling bias also may have affected findings because most patients enrolled in these trials had persistent, moderate back pain despite previous therapeutic interventions. Finally, most trials in this area were sponsored by pharmaceutical companies, which raises concern regarding reporting and interpretation of the data (64, 65).

There are few high-quality studies examining the prevalence of substance use disorders among patients receiving opioids despite practicing clinicians' general concern of the potential for opioid abuse in this population. Only 1 of the 7 studies had an acceptable quality score. Of the 7 studies identified, only 2 (22, 23) used a comprehensive and structured clinical assessment concerning behaviors associated with opioid dependence among the population studied, despite the existence of published assessment instruments (66–68). Studies also were not explicit in separating iatrogenic opioid dependence from preexisting substance use disorders. Because of the potential difficulty of assessing addictive behavior in patients with pain, the true prevalence of the diagnosis in these studies may still be unknown.

As with any systematic review or meta-analysis, publication and retrieval biases can limit the validity of the results. We limited our search to published manuscripts and English-language abstracts. We have attempted to control for retrieval bias by using well-defined searches, comparing our retrievals with those of other reviews, and through expert review. Although a hand-search and inclusion of studies published in other languages may have increased our yield, we believe we have identified the most pertinent literature (69).

The results of our review have implications for future research. Studies investigating the prevalence of opioid prescribing by clinicians ideally would include large observational cohorts inclusive of multispecialty practices and diverse populations of patients with chronic back pain.

Attempts to reach consensus on the most appropriate efficacy trial designs have begun (13). General guidelines aimed at improving the reporting and design of these clinical trials have been published (70–72). Included in these suggestions are studies that use standardized scales to independently measure pain intensity and functional status and, as such, can be used as measures that predict efficacy. Useful studies would be designed to include a placebo that can mimic the common side effects of the opioid that is being administered. In addition, trials should be of a longer duration to reflect the way in which opioids are used clinically (56). Lastly, studies investigating medications combined with such treatments as physical therapy; psychological coping skills training; and medications designed to target specific symptoms, such as neuropathic pain, should be developed to identify the most effective strategies to treat chronic back pain.

Finally, high-quality cohort studies using validated instruments for assessing the prevalence of substance use disorders (66–68, 73) should be used to clearly define the risks for these disorders among patients receiving long-term opioid therapy. Despite the acceptance of opioid treatment as routine care for chronic back pain, this systematic review cannot provide unequivocal evidence that opioids are efficacious for such treatment. In addition, well-designed trials describing the true prevalence of substance use disorders among patients receiving opioids for chronic back pain are lacking. This is a conundrum for the practicing physician. With reports of increased abuse of prescription opioids, especially with long-acting formulations, (74) physicians, policymakers, and regulators are concerned that long-term opioid therapy can result in dependence. There are guidelines for physicians whose goal in prescribing opioids is to treat the painful condition while preventing and monitoring medication-related problems (22, 61, 75–77). In addition, national guidelines exist to assist physicians in clinical management decisions (78, 79).

The clinical care of patients with chronic back pain is complicated, and there are various treatments. On the basis of recent attention to the treatment for pain and concerns regarding the adverse affects of nonsteroidal anti-inflammatory medications, it would be expected that an increasing number of patients with chronic back pain will receive opioid medications. The findings in this review suggest that clinicians should reconsider treating chronic back pain with opioid medications, and consider other treatments with similar benefit yet fewer long-term adverse effects. In addition, because of the state of the science in this field and the limitations we have noted, future research is needed to guide this common and often vexing management issue.

From Yale University School of Medicine, New Haven, Connecticut; VA Connecticut Health Care System, West Haven, Connecticut; and University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

Grant Support: Dr. Martell was supported by a Veterans Administration Career Development Award during the conduct of this study.

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: David A. Fiellin, MD, Yale University, 333 Cedar Street, PO Box 208025, New Haven, CT 06520-8025; e-mail, david.fiellin@yale.edu.

Current author addresses are available at www.annals.org.

References

1. **Deyo RA, Weinstein JN.** Low back pain. N Engl J Med. 2001;344:363-70. [PMID: 11172169]
2. **van Tulder MW, Scholten RJ, Koes BW, Deyo RA.** Nonsteroidal anti-inflammatory drugs for low back pain: a systematic review within the framework of the Cochrane Collaboration Back Review Group. Spine. 2000;25:2501-13. [PMID: 11013503]
3. **Cassidy JD, Carroll LJ, Côté P.** The Saskatchewan health and back pain survey. The prevalence of low back pain and related disability in Saskatchewan adults. Spine. 1998;23:1860-6; discussion 1867. [PMID: 9762743]
4. **Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA.** The epidemiology of chronic pain in the community. Lancet. 1999;354:1248-52. [PMID: 10520633]
5. **National Center for Health Statistics.** Accessed at www.cdc.gov/nchs/data/hus/hus05.pdf on 24 April 2006.
6. Dangerous drugs? Med Lett Drugs Ther. 2004;47:97. [PMID: 15583525]
7. **Brett AS.** Perspective on the Vioxx recall. J Watch. 2004;24:157-8.
8. **American Psychiatric Association.** Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Assoc; 1994.
9. **Zacny J, Bigelow G, Compton P, Foley K, Iguchi M, Sannerud C.** College on Problems of Drug Dependence taskforce on prescription opioid non-medical use and abuse: position statement. Drug Alcohol Depend. 2003;69:215-32. [PMID: 12633908]
10. **Downs SH, Black N.** The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52:377-84. [PMID: 9764259]
11. **Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al.** Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1-12. [PMID: 8721797]
12. 2005 Physicians Desk Reference. Philadelphia: Thomson Pdr.; 2005.
13. **IMMPACT.** Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113:9-19. [PMID: 15621359]
14. **Hedges LV, Olkin I, eds.** Statistical Methods for Meta-Analysis. Orlando: Academic Pr; 1985.
15. **Normand SL.** Meta-analysis: formulating, evaluating, combining, and reporting. Stat Med. 1999;18:321-59. [PMID: 10070677]
16. **Cox DR.** The Analysis of Binary Data. London: Chapman and Hall; 1970.
17. **Sánchez-Meca J, Marín-Martínez F, Chacón-Moscoso S.** Effect-size indices for dichotomized outcomes in meta-analysis. Psychol Methods. 2003;8:448-67. [PMID: 14664682]
18. **Higgins JP, Thompson SG.** Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539-58. [PMID: 12111919]
19. **Sutton AJ, Abrams KR, Jones DF.** Methods for Meta-Analysis in Medical Research. New York: J Wiley; 2000.
20. **Hale ME, Speight KL, Harsanyi Z, Iwan T, Slagle NS, Lacouture PG, et al.** Efficacy of 12 hourly controlled-release codeine compared with as required dosing of acetaminophen plus codeine in patients with chronic low back pain. Pain Res Manag. 1997;2:33-8.
21. **Richards P, Zhang P, Friedman M, Dhanda R.** Controlled-release oxycodone relieves moderate to severe pain in a 3-month study of persistent moderate to severe back pain [Abstract]. Pain Med. 2002;3:176.
22. **Brown RL, Patterson JJ, Rounds LA, Papasouliotis O.** Substance abuse among patients with chronic low back pain. J Family Practice. 1996;43:152-60. [PMID: 8708625]
23. **Polatin PB, Kinney RK, Gatchel RJ, Lillo E, Mayer TG.** Psychiatric illness and chronic low-back pain. The mind and the spine—which goes first? Spine. 1993;18:66-71. [PMID: 8434327]
24. **Sørensen HT, Rasmussen HH, Møller-Petersen JF, Ejlersen E, Hamburger H, Olesen F.** Epidemiology of pain requiring strong analgesics outside hospital in a geographically defined population in Denmark. Dan Med Bull. 1992;39:464-7. [PMID: 1424820]
25. **Adams NJ, Plane MB, Fleming MF, Mundt MP, Saunders LA, Stauffacher EA.** Opioids and the treatment of chronic pain in a primary care sample. J Pain Symptom Manage. 2001;22:791-6. [PMID: 11532592]
26. **Bramley-Moore SR, Wodak AD, Day RO, Lauchlan RL.** Patterns of analgesic prescribing for patients with chronic non malignant pain in NSW. Aust J Hosp Pharm. 1998;28:83-8.
27. **France RD, Urban BJ, Keefe FJ.** Long-term use of narcotic analgesics in chronic pain. Soc Sci Med. 1984;19:1379-82. [PMID: 6152361]
28. **Mahowald ML, Singh JA, Majeski P.** Opioid use by patients in an orthopedics spine clinic. Arthritis Rheum. 2005;52:312-21. [PMID: 15641058]
29. **Dellemijn PL.** Opioids in non-cancer pain: a life-time sentence? Eur J Pain. 2001;5:333-9. [PMID: 11558990]
30. **Libretto SE.** Use of transdermal fentanyl in patients with continuous non-malignant pain: a case report series. Clin Drug Invest. 2002;22:473-83.
31. **Fanciullo GJ, Ball PA, Girault G, Rose RJ, Hanscom B, Weinstein JN.** An observational study on the prevalence and pattern of opioid use in 25, 479 patients with spine and radicular pain. Spine. 2002;27:201-5. [PMID: 11805668]
32. **Nyiendo J, Haas M, Goldberg B, Lloyd C.** A descriptive study of medical and chiropractic patients with chronic low back pain and sciatica: management by physicians (practice activities) and patients (self-management). J Manipulative Physiol Ther. 2001;24:543-51. [PMID: 11753326]
33. **Long DM, BenDebba M, Torgerson WS, Boyd RJ, Dawson EG, Hardy RW, et al.** Persistent back pain and sciatica in the United States: patient characteristics. J Spinal Disord. 1996;9:40-58. [PMID: 8727456]
34. **Fillingim RB, Doleys DM, Edwards RR, Lowery D.** Clinical characteristics of chronic back pain as a function of gender and oral opioid use. Spine. 2003;28:143-50. [PMID: 12544931]
35. **Deyo RA, Bass JE, Walsh NE, Schoenfeld LS, Ramamurthy S.** Prognostic variability among chronic pain patients: implications for study design, interpretation, and reporting. Arch Phys Med Rehabil. 1988;69:174-8. [PMID: 2964814]
36. **Turk DC, Okifuji A.** What factors affect physicians' decisions to prescribe opioids for chronic noncancer pain patients? Clin J Pain. 1997;13:330-6. [PMID: 9430814]
37. **Hart LG, Deyo RA, Cherkin DC.** Physician office visits for low back pain. Frequency, clinical evaluation, and treatment patterns from a U.S. national survey. Spine. 1995;20:11-9. [PMID: 7709270]
38. **Pitkala KH, Strandberg TE, Tilvis RS.** Management of nonmalignant pain in home-dwelling older people: a population-based survey. J Am Geriatr Soc. 2002;50:1861-5. [PMID: 12410908]
39. **Coste J, Venot A.** An epidemiologic approach to drug prescribing quality assessment: a study in primary care practice in France. Med Care. 1999;37:1294-307. [PMID: 10599610]
40. **Kuntz D, Brossel R.** [Analgesic effect and clinical tolerability of the combination of paracetamol 500 mg and caffeine 50 mg versus paracetamol 400 mg and dextropropoxyphene 30 mg in back pain]. Presse Med. 1996;25:1171-4. [PMID: 8949620]
41. **Hale ME, Dvergsten C, Gimbel J.** Efficacy and safety of oxymorphone extended release in chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study. J Pain. 2005;6:21-8. [PMID: 15629415]
42. **Müller FO, Odendaal CL, Müller FR, Raubenheimer J, Middle MV, Kummer M.** Comparison of the efficacy and tolerability of a paracetamol/codeine fixed-dose combination with tramadol in patients with refractory chronic back pain. Arzneimittelforschung. 1998;48:675-9. [PMID: 9689426]
43. **Tennant F, Moll D, DePaulo V.** Topical morphine for peripheral pain [Letter]. Lancet. 1993;342:1047-8. [PMID: 8105274]
44. **Jamison RN, Raymond SA, Slawsby EA, Nedeljkovic SS, Katz NP.** Opioid therapy for chronic noncancer back pain. A randomized prospective study. Spine. 1998;23:2591-600. [PMID: 9854758]
45. **Thurel C, Bardin T, Boccard E.** Analgesic efficacy of an association of 500-mg paracetamol plus 30-mg codeine versus 400-mg paracetamol plus 30-mg dextropropoxyphene in repeated doses for chronic lower back pain. Curr Ther Res. 1991;50:463-73.
46. **Hale ME, Fleischmann R, Salzman R, Wild J, Iwan T, Swanton RE, et al.** Efficacy and safety of controlled-release versus immediate-release oxycodone: randomized, double-blind evaluation in patients with chronic back pain. Clin J Pain. 1999;15:179-83. [PMID: 10524470]
47. **Salzman RT, Roberts MS, Wild J, Fabian C, Reder RF, Goldenheim PD.** Can a controlled-release oral dose form of oxycodone be used as readily as an immediate-release form for the purpose of titrating to stable pain control? J Pain Symptom Manage. 1999;18:271-9. [PMID: 10534967]
48. **Gammaitoni AR, Galer BS, Lacouture P, Domingos J, Schlagheck T.** Effectiveness and safety of new oxycodone/acetaminophen formulations with reduced acetaminophen for the treatment of low back pain. Pain Med. 2003;4:21-30. [PMID: 12873275]
49. **Schofferman J.** Long-term opioid analgesic therapy for severe refractory lumbar spine pain. Clin J Pain. 1999;15:136-40. [PMID: 10382928]

50. **Ringe JD, Faber H, Bock O, Valentine S, Felsenberg D, Pfeifer M, et al.** Transdermal fentanyl for the treatment of back pain caused by vertebral osteoporosis. Rheumatol Int. 2002;22:199-203. [PMID: 12215866]
51. **Simpson RK Jr, Edmondson EA, Constant CF, Collier C.** Transdermal fentanyl as treatment for chronic low back pain. J Pain Symptom Manage. 1997; 14:218-24. [PMID: 9379069]
52. **Zenz M, Strumpf M, Tryba M.** Long-term oral opioid therapy in patients with chronic nonmalignant pain. J Pain Symptom Manage. 1992;7:69-77. [PMID: 1573287]
53. **Breckenridge J, Clark JD.** Patient characteristics associated with opioid versus nonsteroidal anti-inflammatory drug management of chronic low back pain. J Pain. 2003;4:344-50. [PMID: 14622692]
54. **Reid MC, Engles-Horton LL, Weber MB, Kerns RD, Rogers EL, O'Connor PG.** Use of opioid medications for chronic noncancer pain syndromes in primary care. J Gen Intern Med. 2002;17:173-9. [PMID: 11929502]
55. **Manchikanti L, Damron KS, McManus CD, Barnhill RC.** Patterns of illicit drug use and opioid abuse in patients with chronic pain at initial evaluation: a prospective, observational study. Pain Physician. 2004;7:431-7. [PMID: 16858484]
56. **Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL.** Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med. 2005;352:1324-34. [PMID: 15800228]
57. **Ready LB, Sarkis E, Turner JA.** Self-reported vs. actual use of medications in chronic pain patients. Pain. 1982;12:285-94. [PMID: 6123102]
58. **Chou R, Clark E, Helfand M.** Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review. J Pain Symptom Manage. 2003;26:1026-48. [PMID: 14585554]
59. **Schnitzer TJ, Ferraro A, Hunsche E, Kong SX.** A comprehensive review of clinical trials on the efficacy and safety of drugs for the treatment of low back pain. J Pain Symptom Manage. 2004;28:72-95. [PMID: 15223086]
60. **Eisenberg E, McNicol ED, Carr DB.** Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. JAMA. 2005;293:3043-52. [PMID: 15972567]
61. **Clark ME, Young RW, Cole BE.** Opioid Therapy for Chronic Non-Cancer Pain: Cautions, Concerns, Misconceptions and Potential Myths Boca Raton, FL: CRC Pr; 2005.
62. **Compton P, Athanasos P, Elashoff D.** Withdrawal hyperalgesia after acute opioid physical dependence in nonaddicted humans: a preliminary study. J Pain. 2003;4:511-9. [PMID: 14636819]
63. **Ossipov MH, Lai J, King T, Vanderah TW, Porreca F.** Underlying mechanisms of pronociceptive consequences of prolonged morphine exposure. Biopolymers. 2005;80:319-24. [PMID: 15795927]
64. **Lexchin J, Bero LA, Djulbegovic B, Clark O.** Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ. 2003;326: 1167-70. [PMID: 12775614]
65. **Fries JF, Krishnan E.** Equipoise, design bias, and randomized controlled trials: the elusive ethics of new drug development. Arthritis Res Ther. 2004;6: R250-5. [PMID: 15142271]
66. **Chabal C, Erjavec MK, Jacobson L, Mariano A, Chaney E.** Prescription opiate abuse in chronic pain patients: clinical criteria, incidence, and predictors. Clin J Pain. 1997;13:150-5. [PMID: 9186022]
67. **Trafton JA, Oliva EM, Horst DA, Minkel JD, Humphreys K.** Treatment needs associated with pain in substance use disorder patients: implications for concurrent treatment. Drug Alcohol Depend. 2004;73:23-31. [PMID: 14687956]
68. **Compton P, Darakjian J, Miotto K.** Screening for addiction in patients with chronic pain and "problematic" substance use: evaluation of a pilot assessment tool. J Pain Symptom Manage. 1998;16:355-63. [PMID: 9879160]
69. **Moher D, Fortin P, Jadad AR, Jüni P, Klassen T, Le Lorier J, et al.** Completeness of reporting of trials published in languages other than English: implications for conduct and reporting of systematic reviews. Lancet. 1996;347: 363-6. [PMID: 8598702]
70. **Altman DG, Schulz KF, Mohler D, Egger M, Davidoff F, Elbourne D, et al.** The revised CONSORT statement for the reporting randomized trials: explanation and elaboration. Ann Intern Med. 2001;134:663-694. [PMID: 11304107]
71. **Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al.** Improving the quality of reporting of randomized controlled trials. The CONSORT statement. JAMA. 1996;276:637-9. [PMID: 8773637]
72. **Mohler D, Schulz KF, Altman DG.** The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet. 2001;357:1191-1194. [PMID: 11323066]
73. **Manchikanti L, Pampati V, Damron KS, McManus CD.** Evaluation of variables in illicit drug use: does a controlled substance abuse screening tool identify illicit drug use? Pain Physician. 2004;7:71-5. [PMID: 16868615]
74. **Substance Abuse and Mental Health Services Administration (SAMHSA) Office of Applied Studies.** National Survey on Drug Abuse and Health. Detailed tables from the National Survey on Drug Use and Health. Rockville, MD: U.S. Department of Health and Human Service; 2004.
75. **Graven S, DeVet HCW, van Kleef M, et al.** Opioids in chronic nonmalignant pain: A criteria based review of the literature. Proceedings of the 9th World Congress on Pain: Progress in Pain Research and Management, Vienna 22-27 August 1999. International Association for the Study of Pain; Seattle: 2000;16: 554-63.
76. **Moulin Y.** [Review of wound classifications]. Infirm Que. 2001;9:53-6. [PMID: 12942809]
77. **Savage SR.** Opioid use in the management of chronic pain. Med Clin North Am. 1999;83:761-86. [PMID: 10386124]
78. **World Health Organization.** WHO's Pain Relief Ladder. Accessed at www.who.int/cancer/palliative/painladder/en/ on 12 May 2005.
79. **VA National Pain Management.** VA Office of Quality Performance: Opioid therapy for chronic pain clinical practice guidelines. Washington, DC: U.S. Department of Veterans Affairs; 2005.

Current Author Addresses: Dr. Martell: Pfizer, New Haven Clinical Research Unit, 50 Pequot Avenue, Mailstop 3000, New London, CT 06330.
Drs. Kerns and Kosten: VA Connecticut Health Care System, Psychology Service, 116B, 950 Campbell Avenue, West Haven, CT 06516.
Dr. Morales: Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, 626 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104-6021.
Drs. Fiellin, O'Connor, and Becker: Yale University, 333 Cedar Street, PO Box 208025, New Haven, CT 06520-8025.

Appendix Table 1. **Opioid Search Terms in the Literature on Chronic Nonmalignant Back Pain**

Topic	Medical Subject Heading Terms		Text Word
	Exploded	Subheadings	
Chronic pain	Pain	suffering, physical ache pain, burning pain, crushing pain, migratory pain, radiating pain, splitting	Pain$.mp Pain.mp
	Chronic disease	chronic illness chronically ill	
			Chronic pain states, non-cancer pain, pain management, chronic pain, pain syndrome, pain treatment, pain control, non-malignant pain
Low back pain	Low back pain	lumbago low back ache low back pain, mechanical low back pain, posterior compartment low back pain, postural low back pain, recurrent low backache lower back pain mechanical low back pain postural low back pain recurrent low back pain	Spinal disease$, sciatica, lumbago, back pain, low back pain
	Back pain	backache back ache back pain with radiation back pain without radiation vertebrogenic pain syndrome	
Substance abuse	Opioid-related disorders	narcotic abuse narcotic addiction narcotic dependence opiate addiction opiate dependence	Addict$, substance dependence, opi$ dependence, drug, narcotic, substance abuse
	Substance-related disorders	drug abuse drug addiction drug dependence drug habituation drug use disorders glue sniffing organic mental disorders, substance-induced substance abuse substance dependence substance use disorders drug usage substance addiction	
	Substance abuse, intravenous	drug abuse, intravenous drug abuse, parenteral intravenous drug abuse IV drug users	
	Substance withdrawal syndrome	drug withdrawal symptoms withdrawal symptoms	
Opioids	Narcotics	opiates opioids	Oxycodone, codeine, hydromorphone, meperidine, fentanyl, hydrocodone, propoxyphene, morphine, opi$, dihydromorphine, heroin, levorphanol, meperidine, oxymorphone

Appendix Table 1—**Continued**

Topic	Medical Subject Heading Terms		Text Word
	Exploded	**Subheadings**	
	Analgesics, opioid	analgesics, addictive analgesics, narcotic narcotic analgesics opioid analgesics	
	Receptors, opioid	enkephalin receptors narcotic receptors opioid receptors receptors, endorphin receptors, enkephalin receptors, narcotic receptors, opiate endorphin receptor enkephalin receptor normorphine receptors opiate receptor opiate receptors opioid receptor receptors, normorphine receptors, beta-endorphin beta-endorphin receptor	
	Methadone	amidone dolophine methadone hydrochloride phenadone physeptone	
	Buprenorphine	6029-m buprenex buprenorphinehydrochloride rx-6029-m temgesic (narcotics, opium, substance dependence)*	
Prevalence	Incidence		Prevalen$, incident$, pattern$, trend$
	Treatment outcome	Rehabilitation outcome, treatment effectiveness, treatment efficacy	effect$, efficacy

* Terms used 1966 to 1979.

Appendix Table 2. **Quality Score by Category of Reports on the Prevalence of Opioid Prescribing in Patients with Chronic Nonmalignant Back Pain**

Study, Year (Reference)	Study Type	Maximum Reporting Score*	External Validity Score†	Internal Validity and Bias Score‡	Internal Validity and Confounding Score‡	Power Score§	Total Quality Score‖
Fillingim et al., 2003 (34)	Cross-sectional	9	3	1	2	1	16
Deyo et al., 1988 (35)	Cross-sectional	7	3	2	1	0	13
Mahowald et al., 2005 (28)	Cross-sectional	6	3	1	2	0	12
Fanciullo et al., 2002 (31)	Cross-sectional	5	3	2	2	0	12
Pitkala et al., 2002 (38)	Cross-sectional mailed survey	5	3	2	1	0	11
Coste and Venot, 1999 (39)	Cross-sectional using pharmacy database	6	2	1	1	0	10
Nyiendo et al., 2001 (32)	Cross-sectional	5	3	1	0	0	9
Hart et al., 1995 (37)	Cross-sectional	4	3	1	0	0	8
France et al., 1984 (27)	Observational case series	3	3	1	1	0	8
Long et al., 1996 (33)	Observational Cohort	5	3	0	0	0	8
Turk and Okifuji, 1997 (36)	Cross-sectional	4	1	1	1	1	8

* Maximum score was 11.
† Maximum score was 3.
‡ Maximum score was 6.
§ Maximum score was 6.
‖ Scoring instrument is from reference 10.

Appendix Table 3. **Quality Score by Category of Studies Evaluating the Efficacy of Opioid Medication for the Treatment of Chronic Nonmalignant Back Pain Using Nonopioid Medications or Placebo as Comparators***

Study, Year (Reference)	Study Type†	Appropriate Comparator‡	Follow-up§	Random Assignment Maintained‡	Adequate Sample Size for Diversity‡	Outcomes/ Exposure Measured in Same Way‡	Observational Studies: Confounders Adjusted‡	Appropriate Statistics‡	Total Quality Score‖
Kuntz and Brossel, 1996 (40)	5	2	3	2	2	2	NA	1	17
Hale et al., 2005 (41)	5	2	3	2	1	2	NA	2	17
Muller et al., 1998 (42)	5	1	3	2	2	2	NA	1	16
Tennant et al., 1993 (43)	5	2	3	2	1	2	NA	1	16
Richards et al., 2002 (21)¶	5	2	1	2	1	2	NA	2	15
Jamison et al., 1998 (44)	3	2	3	2	1	2	NA	2	15

* NA = not available.
† Study types ranged from double-blind, randomized, controlled trials (score, 5) to observational studies (historical control) (score, 1).
‡ Maximum score was 2.
§ Maximum score was 3.
‖ Scoring instrument is from reference 11. Maximum score was 20.

Appendix Table 4. **Quality Score by Category of Studies Evaluating the Efficacy of Opioid Medication for the Treatment of Chronic Nonmalignant Back Pain Using Other Opioids as Comparator Medications***

Study, Year (Reference)	Study Type†	Appropriate Comparator‡	Follow-up§	Random Assignment Maintained‡	Adequate Sample Size for Diversity‡	Outcomes/Exposure Measured in the Same Way‡	Observational Studies: Confounders Adjusted†	Appropriate Statistics‡	Total Quality Score‖
Thurel et al., 1991 (45)	5	1	3	2	2	2	NA	2	17
Hale et al., 1999 (46)	5	1	3	2	1	2	NA	2	16
Hale et al., 1997 (20)	4	1	3	2	1	2	NA	2	15
Salzman et al., 1999 (47)	3	1	3	1	1	2	NA	2	14
Gammaitoni et al., 2003(48)	2	1	3	1	1	2	2	2	14
Simpson et al., 1997 (54)	2	1	3	1	1	2	1	2	13
Schofferman, 1999 (49)	2	1	3	1	1	2	1	1	12
Ringe et al., 2002 (50)	2	1	2	NA	1	2	1	2	11
Zenz et al., 1992 (52)	2	1	2	NA	1	2	1	1	10

* NA = not available.
† Study types ranged from double-blind, randomized, controlled trials (score, 5) to observational studies (historical control) (score, 1).
‡ Maximum score was 2.
§ Maximum score was 3.
‖ Scoring instrument is from reference 11. Maximum score was 20.

Appendix Table 5. **Quality Score by Category of Studies Reporting on the Prevalence of Substance Use Disorders in Patients Receiving Opioids for Chronic Nonmalignant Back Pain**

Study, Year (Reference)	Study Type	Maximum Reporting Score*	External Validity†	Internal Validity and Bias‡	Internal Validity and Confounding‡	Power§	Total Quality Score‖
Brown et al., 1996 (22)	Observational case–control	9	3	2	2	0	16
Breckenridge and Clark, 2003 (53)	Observational case–control from 2001–2002	7	0	2	2	0	11
Polatin, 1992 (23)	Cross-sectional	6	0	2	1	0	9
Bramley-Moore et al., 1998 (26)	Cross-sectional	4	1	1	1	0	7

* Maximum score was 11.
† Maximum score was 3.
‡ Maximum score was 6.
§ Maximum score was 1.
‖ Scoring instrument is from reference 10.

Appendix Table 6. **Quality Score by Category of Studies Reporting on the Prevalence of Aberrant Medication-Taking Behaviors in Patients Receiving Opioids for Chronic Nonmalignant Back Pain**

Study, Year (Reference)	Study Type	Maximum Reporting Score*	External Validity†	Internal Validity and Bias‡	Internal Validity and Confounding‡	Power§	Total Quality Score‖
Mahowald et al., 2005 (28)	Cross-sectional	4	3	1	3	0	11
Reid et al., 2002 (54)	Cross-sectional	6	3	2	0	0	11
Adams et al., 2001 (25)	Cross-sectional chart review	4	2	0	2	0	8
Manchikanti et al., 2004 (73)	Cross-sectional	5	0	1	0	0	6
Ready et al., 1982 (57)	Case series	4	1	1	0	0	6

* Maximum score was 11.
† Maximum score was 3.
‡ Maximum score was 6.
§ Maximum score was 1.
‖ Scoring instrument is from reference 10.