REVIEW

Efficacy and Safety of Opioid Agonists in the Treatment of Neuropathic Pain of Nonmalignant Origin

Systematic Review and Meta-analysis of Randomized Controlled Trials

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Context In the United States, an estimated 2 million persons have neuropathic pain that is often resistant to therapy. The use of opioids for neuropathic pain remains controversial, in part because studies have been small, have yielded equivocal results, and have not established the long-term risk-benefit ratio of this treatment.

Objective To assess the efficacy and safety of opioid agonists for the treatment of neuropathic pain based on published randomized controlled trials (RCTs).

Data Sources We searched MEDLINE (1966 to December 2004) and the Cochrane Central Register of Controlled Trials (fourth quarter, 2004) for articles in any language, along with reference lists of reviews and retrieved articles, using a combination of 9 search terms for RCTs with 32 terms for opioids and 15 terms for neuropathic pain.

Study Selection Trials were included in which opioid agonists were given to treat central or peripheral neuropathic pain of any etiology, pain was assessed using validated instruments, and adverse events were reported. Studies in which drugs other than opioid agonists were combined with opioids or opioids were administered epidurally or intrathecally were excluded.

Data Extraction Data were extracted by 2 independent investigators and included demographic variables, diagnoses, interventions, efficacy, and adverse effects.

Data Synthesis Twenty-two articles met inclusion criteria and were classified as short-term (less than 24 hours; n=14) or intermediate-term (median=28 days; range=8-56 days; n=8) trials. The short-term trials had contradictory results. In contrast, all 8 intermediate-term trials demonstrated opioid efficacy for spontaneous neuropathic pain. A fixed-effects model meta-analysis of 6 intermediate-term studies showed mean post-treatment visual analog scale scores of pain intensity after opioids to be 14 units lower on a scale from 0 to 100 than after placebo (95% confidence interval [CI], −18 to −10; $P<.001$). According to number needed to harm (NNH), the most common adverse event was nausea (NNH, 3.6; 95% CI, 2.9-4.8), followed by constipation (NNH, 4.6; 95% CI, 3.4-7.1), drowsiness (NNH, 5.3; 95% CI, 3.7-8.3), vomiting (NNH, 6.2; 95% CI, 4.6-11.1), and dizziness (NNH, 6.7; 95% CI, 4.8-10.0).

Conclusions Short-term studies provide only equivocal evidence regarding the efficacy of opioids in reducing the intensity of neuropathic pain. Intermediate-term studies demonstrate significant efficacy of opioids over placebo for neuropathic pain, which is likely to be clinically important. Reported adverse events of opioids are common but not life-threatening. Further RCTs are needed to establish their long-term efficacy, safety (including addiction potential), and effects on quality of life.

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IN THE UNITED STATES, AN ESTIMATED 2 million persons have neuropathic pain.[1] This may result from a large variety of insults to the peripheral or central somatosensory nervous system, including trauma, inflammation, ischemia, and metabolic and neoplastic disorders. Common examples of peripheral neuropathic pain include diabetic neuropathy, postherpetic neuralgia (PHN), and trigeminal neuralgia. Central neuropathic pain includes central poststroke pain, pain in multiple sclerosis, and post–spinal cord injury pain. The main clinical characteristics of neuropathic pain are continuous or intermittent spontaneous pain, typically described as burning, aching, or shooting in quality, and abnormal sensitivity of the painful site to normally innocuous stimuli such as light touch by garments, running water, or even wind (allodynia).[2] Neuropathic pain, like many other forms of chronic pain, often has negative effects on quality of life. Pharmacotherapy of neuropathic pain has generally involved the use of antidepressants or anticonvulsants, but even with the current generation of these drugs, effective analgesia is achieved in less than half of this population.[3]

Clinical trials to assess the efficacy of opioids for reducing neuropathic pain have been reported for more than 15 years. Yet large variability in trial design in terms of the type of the neuropathic pain syndrome treated, the type of opioid administered, and the dura-

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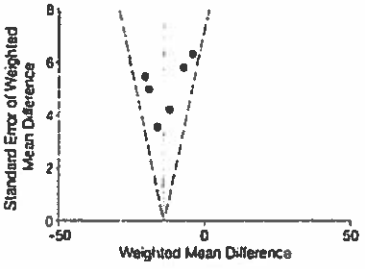
Figure 1. Funnel Plot of Intermediate-term Efficacy Studies



Plot shows standard error of effect estimate vs effect estimate for each study (fixed-effects model). Vertical dotted line indicates overall effect estimate; dashed lines, 95% confidence intervals; and dots, individual studies

tion of treatment has yielded contradictory results. Studies that have suggested efficacy have had small study populations, raising questions about the validity of the results. Lack of definitive evidence regarding the efficacy of opioids in reducing neuropathic pain in general, and central neuropathic pain in particular, as well as concerns about adverse effect profiles and potential for abuse, addiction, hormonal abnormalities, dysfunction of the immune system, and, in some cases, paradoxical hyperalgesia,[1-8] discourage use of opioids in the treatment of neuropathic pain.[9]

Given growing interest in and concerns regarding prescribing of opioids to patients with neuropathic pain, we conducted a systematic review of published randomized controlled trials (RCTs) to answer 2 questions: (1) What is the efficacy of opioid agonists in relieving neuropathic pain? and (2) What is the nature and occurrence of adverse effects caused by opioid agonists in patients with neuropathic pain?

METHODS

Search Strategy

We searched for pertinent articles in any language using the MEDLINE database (1966 to December 2004), the Cochrane Central Register of Controlled Trials (fourth quarter, 2004), and the reference lists of reviews and retrieved articles. We did not contact authors for original data and did not consider abstracts or unpublished reports. We combined 9 search terms for RCTs with 32 terms for opioids and 15 terms for neuropathic pain.

Inclusion and Exclusion Criteria

We reviewed abstracts of all citations and retrieved studies based on the following inclusion criteria: (1) design was randomized, blinded, controlled trial; (2) opioid agonists (but not partial agonists or agonist-antagonists) were given to treat central or peripheral neuropathic pain of any etiology; (3) 1 or more opioid agonists or different doses of the same opioid agonist were compared with placebo, each other, or another class of medications used for neuropathic pain (eg, antidepressants); (4) drugs were administered by any of the following routes: orally, rectally, transdermally, intravenously, intramuscularly, or subcutaneously; (5) neuropathic pain was assessed with validated pain measurement tools; and (6) adverse events were reported. Men and women of all ages and races/ethnicities were included.

We excluded studies in which (1) patients with both neuropathic and other types of pain (eg, nociceptive) were enrolled and responses of the 2 groups of patients were not differentiated; (2) drugs other than opioid agonists were combined with opioids (eg, codeine with acetaminophen); (3) opioids were administered epidurally or intrathecally; (4) tramadol was used as the active drug, because although tramadol interacts to some degree with opioid receptors, it is not regarded as a pure opioid agonist. The efficacy of tramadol in relieving neuropathic pain has been recently reviewed.[10]

Data Extraction

Information on study design, methods, interventions, pain outcomes, and adverse effects was extracted from each article. In addition, diagnoses, patient inclusion and exclusion criteria, numbers of patients enrolled and completing the study, and functional assessments were extracted into a standardized table by 2 independent investigators (E.E. and E.D.M.) who were not blinded to study authors. Discrepancies in extracted data were resolved by discussion prior to including data in the analysis.

Analyses focused on differences in pain intensity, pain relief, and the incidence and severity of adverse effects. When possible we normalized all data to a 0- to 100-mm visual analog scale (VAS). No attempt was made to convert surrogate outcomes (eg, global evaluations or preferences, amount of rescue medication used) to a VAS. For studies in which surrogate outcomes were the only results available, they are described herein as such. The number of patients experiencing adverse events was extracted from trials in which patients were asked about or observed for specific adverse effects, such as constipation. Withdrawals or dropouts were noted if described.

Assessment of Methodological Quality

Studies that met inclusion criteria were graded for methodological quality using a scale reported by Jadad et al.[11] Jadad scores are based on the description of randomization, blinding, and withdrawals and can range from 0 to 5, where higher scores indicate better methodological quality.

Statistical Analysis

We performed statistical analyses of included trials using the Cochrane Collaboration's Review Manager software (RevMan), version 4.2.7 (Oxford, England: Cochrane Collaboration). Whenever possible, results from the trials were combined to calculate differences in postintervention pain intensity or pain relief and to calculate relative risks (RRs) for adverse effects, along with 95% confidence intervals (CIs). We evaluated heterogeneity between and within trials using the χ^2 test.[12] Because studies that were combined appeared to be homogeneous, a fixed-effects model was used for all analyses. A funnel chart of the intermediate-term trials (FIGURE 1) was consistent with absence of publication bias. P values less than .05 were considered significant.

RESULTS

Overview of Included Studies

The literature search yielded 1995 citations, of which 44 were selected for retrieval. Twenty-two[13-34] of the 44 articles met inclusion criteria and provided data on 670 opioid-treated patients with neuropathic pain. We divided the trials into 2 categories according to study duration. The first group consisted of 14 short-term trials,[13-26] in which opioids were administered mostly as brief intravenous infusions and outcomes were measured for less than 24 hours. The number of patients in each of these studies was generally small (median, 13; range, 7-53). The second group consisted of 8 intermediate-term trials,[27-34] in which opioids were administered orally over longer periods, between 8 and 56 days (median, 28 days), generally to larger numbers of patients (median, 47; range, 12-157). A QUOROM (Quality of Reporting of Meta-analyses) flow diagram (FIGURE 2) shows an overview of the study selection process.

Excluded Studies

Three controlled trials[35-37] of opioids for neuropathic pain failed to meet 1 or more of the inclusion criteria. First, an RCT conducted over 7 days[35] compared morphine with placebo in a mixed group of patients with various neuropathic and nociceptive pain syndromes. The authors reported that "the number of responders was significantly higher in patients with neuropathic than with nociceptive pain." However, efficacy and adverse effects of the 2 types of pain were combined into a single outcome, thereby precluding separate analyses of data for the 2 subgroups. That study was therefore excluded. Second, a short-term, placebo-controlled trial[36] showed that only 4 of the 14 tested patients with multiple sclerosis and central neuropathic pain were categorized as "responders" to intravenous morphine. The study was nonrandomized and single-blinded. Third, in an RCT,[37] 5 different doses of buprenorphine (0.033-0.166 mg) were randomly administered to 21 patients with postthoracotomy neuropathic pain 1 month after surgery, with reduction of pain by 50% in each of the patients. However, buprenorphine is a partial μ receptor agonist, with different pharmacological properties than those of the full μ opioid agonist class.

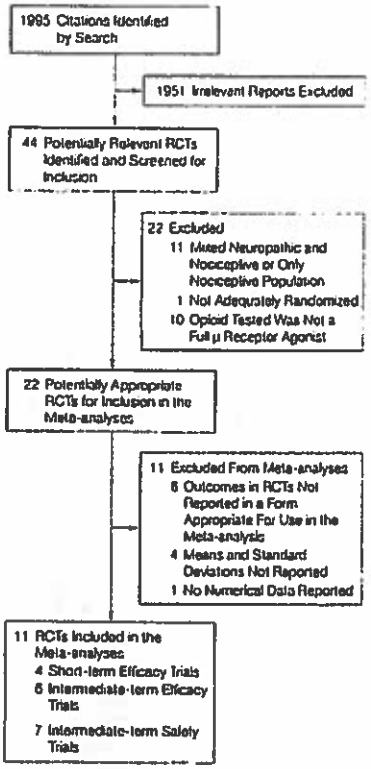
Study Quality

The quality of the short- and intermediate-term studies as judged by the Jadad score is presented in TABLE 1 and TABLE 2, respectively. The median overall score was 4 (range, 2-5) indicating generally good methodological quality. The Jadad scores of intermediate-term studies were nonsignificantly higher than those of short-term studies (median, 5 vs 4). Inadequate description of the randomization process (in 8 trials) was the most common shortfall in the short-term trials. In the intermediate-term trials, 6 trials scored 5 points, 1 scored 3,[28] and 1 scored 2.[29] Inadequate description of adverse events, reasons for dropout, methods of randomization, and blinding led to the lower scores of the latter 2 studies.

Short-term Studies

Fourteen RCTs using a crossover design provided adequate data regarding efficacy of acute exposure to opioids in 267 patients with neuropathic pain (Table 1). Drugs were administered intravenously in 12 trials, orally in 1 trial,[26] and intramuscularly in 1 trial.[17] The duration of treatment varied from seconds (ie, a single intramuscular injection) to 8 hours but was less than 1 hour in 10 trials. The tested drug was morphine in 7 trials, alfentanil in 4 trials, and fentanyl, meperidine, or codeine in 1 trial each. Placebo was used as a control in 12 trials. The diagnosis was specified in all trials: 3 trials studied patients with PHN only,[21,23,26] 2 studied patients with posttraumatic neuralgia,[13,19] 5 studied patients with mixed neuropathies,[16,18,22,24,25] 2 studied patients with central pain,[14,20] 1 studied patients with secondary (eg, posttraumatic) trigeminal neuropathy,[17] and 1 enrolled patients with postamputation stump and phantom pain.[15] Considerable variation between studies in dosages, durations of treatment, and methods of pain assessment allowed only limited quantitative synthesis of data.

Figure 2. Flow Diagram of Included and Excluded Studies



RCT indicates randomized controlled trial.

Change in spontaneous pain intensity was the primary outcome measure in all 14 trials (Table 1). Mixed results were found with respect to the analgesic efficacy of opioids for neuropathic pain in general and for specific conditions (ie, PHN, posttraumatic neuralgia, and central pain). Six trials showed greater efficacy of the tested opioid than of placebo.[13,15,16,18,20,23] In contrast, 5 trials observed equivalent efficacy for opioids and placebo.[14,19,21,25,26] Partial efficacy, meaning that some patients responded to the opioid treatment while others did not, was reported in 2 trials.[17,22] Another trial reported reduction in the affective but not in the sensory component of pain.[24]

Table 1. Short-term RCTs of Treatment of Neuropathic Pain: Design, Quality Assessment, and Effects of Opioids vs Placebo on Spontaneous Pain

Source	No. of Patients Enrolled/ Evaluable	Pain Etiology (No. of Patients)	Interventions[a]	Jadad Quality Score	Initial Pain Intensity[b,c]	Final Pain Intensity[b,c]	Relief[b,c]	Reduction, %[d]
Jorum et al,[13] 2003	12/12	PTN (11), PHN (1)	Alfentanil: 7 μg/kg over 5 min + 0.6 μg/kg per min over 20 min Ketamine: 60 μg/kg over 5 min + 6 μg/kg per min over 20 min Placebo	4	Median (IQR): 3.8 (2.3-5.5) vs 4.4 (3.0-5.3)[e]	Median (IQR): 2.2 (0.3-3.0) vs 4.3 (2.1-5.6)[f]		
Attal et al,[14] 2002	15/15	Central spinal cord (9), poststroke (6)	Morphine: 9-30 mg (mean, 18 [SD, 6]), individually titrated to adverse events over 20 min Placebo	4	62 (17) vs 69 (17)	33 (23) vs 62 (19)		
Wu et al,[15] 2002	32/31	Stump (22), phantom (20)[g]	Morphine: 0.05-mg/kg bolus + 0.2 mg/kg over 40 min Lidocaine: 1.0-mg/kg bolus + 4.0 mg/kg over 40 min Active control (diphenhydramine): 10 mg bolus + 40 mg over 40 min	5	Stump: 52 (19) vs 55 (22) Phantom: 46 (18) vs 44 (18)	Stump: 33 (16) vs 50 (25) Phantom: 30 (22) vs 46 (22)		Stump: 45 (35) vs 6 (16) Phantom: 48 (38) vs 3 (10)
Leung et al,[16] 2001	12/12	Mixed: RSD (6), PHN (4), spinal cord (1), causalgia (1)	Alfentanil: 20-min infusion to achieve plasma levels of 25, 50, and 75 ng/mL Ketamine: 20-min infusion to achieve plasma levels of 50, 100, and 150 ng/mL Placebo	4				62 (11) vs 36 (12)[f]
Rabben et al,[17] 1999	30/26	Trigeminal neuropathic pain	Meperidine: 1.0 mg/kg IM Ketamine: 0.4 mg/kg IM + midazolam, 0.05 mg/kg IM	4		Nonresponders 84% (23%) vs 87% (20%) Long-term effects 48% (34%) vs 9% (7%) Short-term effects: 77% (22%) vs 37% (34%)[h]		
Delorme and Vanneste,[18] 1997	53/24	Mixed, peripheral (50), central (3)	Fentanyl: 5 μg/kg per min for max 5 h Diazepam: 0.2 μg/kg per min for max 5 h Placebo	5				50 (95% CI, 36-63) vs 12 (95% CI, 4-20)
Max et al,[19] 1995	8/8	PTN	Alfentanil: 1.5 μg/kg per min for 60 min; rate doubled as required at 60 and 80 min for a total of 2 h Ketamine: 0.75 mg/kg per h for 20 min; rate doubled as required at 60 and 90 min for a total of 2 h Placebo	4				45 (35) vs 22 (27)
Eide et al,[20] 1995	9/9	Central (spinal cord)	Alfentanil: 7 μg/kg over 5 min + 0.6 μg/kg per min for 17-21 min Ketamine: 60 μg/kg over 5 min + 6 μg/kg per min for 17-21 min Placebo	4				Median (IQR): 20 (4-50) vs 0 (0-8)
Eide et al,[21] 1994	8/8	PHN	Morphine infusion: 0.075 mg/kg over 10 min Ketamine infusion: 0.15 mg/kg over 10 min Placebo	3				Median (IQR): 7 (0-50) vs 0 (0-38)
Jadad et al,[22] 1992	7/6[i]	Mixed: central (1), peripheral (6)	Morphine (low vs high dose): PCA up to 30 mg/h for up to 8 h, or up to 90 mg/h for up to 8 h	3				53 (41) vs 51 (32)[f]
Rowbotham et al,[23] 1991	12/10	PHN	Morphine: 0.3 mg/kg (max 25 mg) over 1 h Lidocaine: 5 mg/kg (max 450 mg) over 1 h Placebo	4	47 (29) vs 52 (31)	33 (33) vs 44 (29)	45 (36) vs 22 (33)	
Kupers et al,[24] 1991	14/14	Mixed: central (5), peripheral (8)	Morphine: 0.3 mg/kg in 5 divided bolus doses every 10 min Placebo	4	62 (13) vs 58 (20) (central) 45 (14) vs 45 (20) (peripheral)	43 (13) vs 58 (25) (central) 28 (14) vs 40 (28) (peripheral)		
Arner and Meyerson[25] 1988	8/8	Mixed deafferentation[k]	Morphine: 15 mg over 15 min Placebo	3				
Max et al,[26] 1988	40/39	PHN	Codeine: 120-mg single oral dose Clonidine: 0.2-mg single oral dose Ibuprofen: 800-mg single oral dose Placebo	3			2.9 (0.8) vs 2.2 (0.6)	

Abbreviations: CI, confidence interval; IM, intramuscularly; IQR, interquartile range; PCA, patient-controlled analgesia; PHN, postherpetic neuralgia; PTN, posttraumatic neuralgia; RCT, randomized controlled trial; RSD, reflex-sympathetic dystrophy.

[a]Administered intravenously unless otherwise specified; bold font indicates drugs for which efficacy is compared in table.

[b]Measured on a scale from 0 to 100 unless otherwise specified, with 0 = no pain and 100 = worst imaginable pain.

[c]Data are reported as mean (SD) unless otherwise specified.

[d]Measured on a scale from 0 to 10 in which 0 = no pain and 10 = unbearable pain.

[e]Numbers do not add to 32 because some patients had both stump and phantom pain.

[f]Values are maximal reductions.

[g]Values are percentage of initial pain at best time point (maximal response). Three different subgroups of response were defined, short-term effect = less than 2 hours; long-term effect = 0-24 hours.

[h]Six additional patients with nociceptive pain were included in this study.

[i]Presented as percentage of maximal total pain relief.

[j]Results refer to the "affective" component of pain.

[k]Deafferentation pain is defined as neuropathic pain associated with extensive sensory loss (ie, anesthesia dolorosa).

[l]Relief was measured on a scale from 0 to 4, with 0 = no relief and 4 = complete relief.

Table 2. Intermediate-term Studies, Design, Quality Assessment, and Outcome of Treatment[a]

Source	Pain Etiology	Trial Design/ Duration	Intervention (No. of Patients Enrolled/ Completed)	Oral Dose	Jadad Quality Score	Outcomes[b]			
						End Point Intensity	Relief	Allodynia	Disability/Other
Watson and Babul,[1] 1998	PHN	Crossover, 4 wk	Long-acting oxycodone (50/44) Placebo (50/44)	10-30 mg twice per day (mean, 45 [SD, 17])	5	Daily VAS: 35 (25) vs 54 (25) Daily CPS: 1.7 (0.7) vs 2.3 (0.7) (0-4 scale)[c]	Daily CPRS: 2.9 (1.1) vs 1.9 (1.0)[d]	Weekly VAS: 32 (27) vs 50 (30) Weekly CPS: 1.6 (1.0) vs 2.0 (1.1)	CDS: 0.3 (0.6) vs 0.7 (1.0) (0-3 scale) Effectiveness rating: 1.8 (1.1) vs 0.7 (1.0) (0-3 scale) POMS and BDI: no difference
Huse et al,[16] 2001	Phantom limb	Crossover, 4 wk	Long-acting morphine (12/12) Placebo (12/12)	70-300 mg/d	3	VAS: 3.3 (1.6) vs 4.0 (1.2) (0-10 scale) 50% reduction in VAS: 42% vs 8%		Electrical pain threshold: 4.0 (1.8) mA vs 4.0 (1.5) mA	No correlation between reduction in VAS and PRSS, BSS, or WHYMPI; d2-test: 101 (19) vs 105 (18)
Harke et al,[17] 2001	Mixed peripheral	Parallel, 8 d	Long-acting morphine (21/20) Placebo (17/15) Carbamazepine (27/19) Placebo (21/19)	30 mg 3 times per day 200 mg 3 times per day	2	No significant differences between morphine and placebo Carbamazepine reduced pain intensity and increased time without spinal cord stimulation vs placebo			
Raja et al,[18] 2002	PHN	Crossover, 8 wk	Morphine or methadone (76/56) Nortriptyline or desipramine (76/70) Placebo (76/75)	Morphine, 15-240 mg/d, or methadone, 5-60 mg/d (mean, 91 [SD, 49.3] and 15 [SD, 2.0]) Nortriptyline or desipramine, 10-160 mg/d (means, 89 [SD, 27.4] and 63 [SD, 3.6])	5	VAS, opioid, 4.4 (2.4), TCA, 5.1 (2.3), placebo, 6.0 (2.0) (0-10 scale)	Opioid, 38.2 (32.2); TCA, 31.9 (30.4), placebo, 11.2 (19.6)[e]		Cognitive function slightly worsened with TCA; sleep improved from baseline with opioids and TCA; all other MPI unchanged
Gimbel et al,[19] 2003	Diabetic neuropathy	Parallel, 6 wk	Long-acting oxycodone (82/63) Placebo (77/52)	10-60 mg twice per day (mean, 37 [SD, 21])	5	VAS: 41 (27) vs 63 (26)			Oxycodone superior to placebo in satisfaction with medication, sleep quality, and 9 of 14 BPI parameters, median time to achieve mild pain: 6 vs 17 d; % days with mild pain: 47 (39) vs 29 (37); no difference in RMH, SIP, SF-36
Watson et al,[20] 2003	Diabetic neuropathy	Crossover, 4 wk	Long-acting oxycodone (45/35) Active placebo (benztropine) (45/36)	Oxycodone, 10-40 mg twice per day (mean, 40.0 [SD, 18.5]) Benztropine, 0.25-1.0 mg twice per day (mean, 1.2 [SD, 0.6])	5	Daily VAS: 26.3 (24.7) vs 46.7 (26.9) Daily CPS: 1.3 (0.9) vs 1.9 (0.9)	CPRS: 1.8 (1.4) vs 2.7 (1.2)[f]	"Skin pain": 14.3 (20.4) vs 43.2 (31.3)	Oxycodone superior to placebo for overall PSQ, PDI, SF-36; NNT for moderate relief, 2.6
Morley et al,[21] 2003	Mixed neuropathic	Crossover, 20 d	Low dose methadone or placebo (18/18) High-dose methadone or placebo (17/11)	5 mg twice per day alternating with placebo on odd and rest on even days 10 mg twice per day alternating with placebo on odd days and rest on even days	5	VAS maximal: 69 (17) vs 74 (13) (NS) VAS average: 60 (20) vs 64 (19) (NS) VAS maximal: 64 (23) vs 74 (16) VAS average: 57 (26) vs 64 (22)	23 (19) vs 15 (16) (NS) 32 (27) vs 23 (21)		
Rowbotham et al,[22] 2003	Mixed neuropathic	Parallel, 8 wk	High-dose levorphanol (43/29) Low dose levorphanol (30/30)	0.75 mg 3 times per day (mean, 2.7 mg/d) vs 0.15 mg 3 times per day (mean, 0.9 mg/d)	5	VAS: high-dose, 42 (25) (−36%) vs low-dose, 53 (25) (−21%)	CPRS: no significant difference		POMS unchanged; SDMT and MPI improved in both groups

Abbreviations: BDI, Beck Depression Inventory; BPI, Brief Pain Inventory; BSS, Brief Stress Scale; d2-test, test for attention performance; CDS, Categorical Disability Scale; CPRS Categorical Pain Relief Scale; CPS, Categorical Pain Scale; MPI, Multidimensional Pain Inventory; NNT, number needed to treat; NS, nonsignificant; PDI, Pain Disability Index; PHN, postherpetic neuralgia; POMS, Profile and Mood Status Questionnaire; PRSS, Pain-Related Self-Treatment Scale; PSQ, Pain and Sleep Questionnaire; RMH, Rand Mental Health Inventory; SDMT, Symbol-Digit Modalities Test; SF-36, Short Form-36; SIP, Sickness Impact Profile, TCA, tricyclic antidepressant; VAS, visual analog scale; WHYMPI, West Haven-Yale Multidimensional Pain Inventory.

[a]Results compare the first listed intervention with the others in each trial.

[b]Data are reported as mean (SD) unless otherwise specified, measured on a scale from 0 to 100 unless otherwise specified, with 0 = no pain and 100 = worst imaginable pain; all results are significant at $P<.05$ unless specified as nonsignificant.

[c]Pain measured on a scale from 0 to 4, with 0 = no pain and 4 = unbearable pain.

[d]Measured on a scale from 0 to 5, with 0 = pain worse and 5 = complete relief.

[e]Relief measured as percentage of reduction from baseline.

[f]Relief measured on a scale from 0 to 5, with 0 = complete relief and 5 = pain worse.

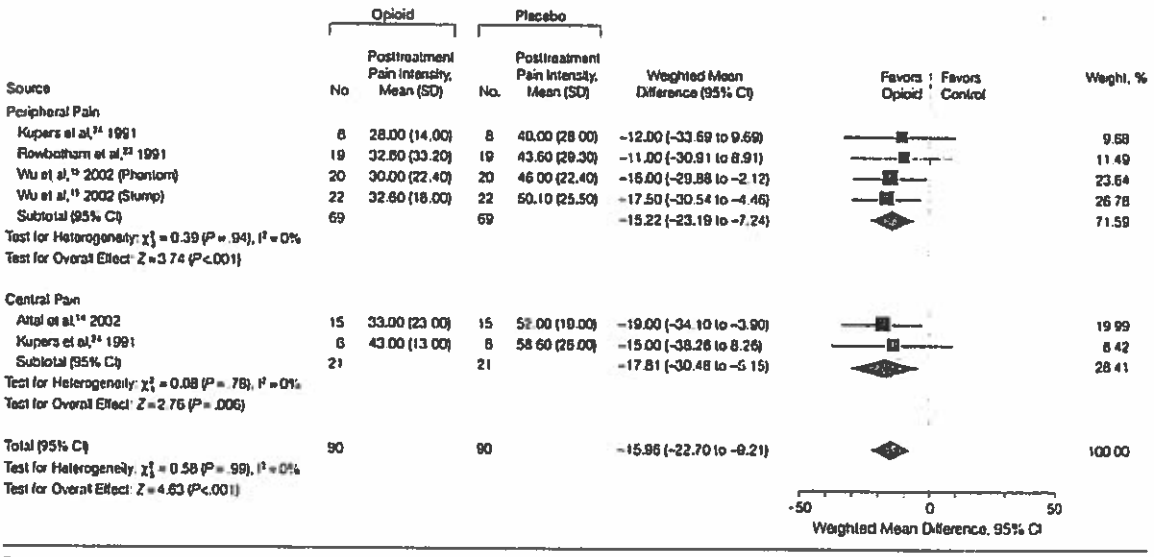
Data from 4 articles (comprising 6 trials) with a total of 90 patients were combinable for a meta-analysis,[14,15,23,24] since they reported means and standard deviations for pain intensity after active drug or placebo. The χ^2 test for heterogeneity was 0.58 ($P = .99$), indicating a high degree of homogeneity between and within studies. Opioid treatment was superior to placebo in all trials but reached statistical significance in only 3 trials (FIGURE 3). The overall mean difference in the last measured pain intensity for active treatment vs placebo was −16 (on a 0-100 VAS) (95% CI, −23 to −9, $P<.001$). Data from 2 trials in a total of 21 patients with central pain and from 4 trials in 69 patients with peripheral neuropathic pain were combinable for a further meta-analysis. For peripheral pain, the final pain intensity following opioid administration was 15 points lower than that after placebo (95% CI, −23 to −7; $P<.001$), whereas for central pain, the difference was 18 points (95% CI, −30 to −5; $P = .006$) (Figure 3). When categorized according to etiology (eg, posttraumatic neuralgia,[13,19] PHN[21,23,26]), the results were equivocal. One within-study comparison[22] and 2 other between-study comparisons (Jorum et al[19] vs Max et al[19] and Eide et al[21] vs Rowbotham et al[23]) of high vs low opioid doses did not show an association between the opioid dose administered and analgesic efficacy.

Intermediate-term Studies

Eight trials provided data on 403 opioid-treated patients (Table 2). The number of patients per treatment group ranged from 12 to 82 and the duration of treatment varied from 8 days to 8 weeks (median, 28 days). Five trials had a crossover design and 3 had a parallel design. Four drugs were tested: morphine and oxycodone, each in 3 trials; methadone in 1 article comprising 2 trials; and levorphanol in 1 trial. Placebo was used as a control in all but 1 trial.[34] In 2 trials, additional study groups in which patients were administered nonopioid active drugs were included for comparison: carbamazepine in 1 trial[29] and the tricyclic antidepressants nortriptyline and desipramine in 1 trial.[30] Two trials compared different dosages of an opioid: 1 compared 2 different dosages of methadone[33] and 1 compared 2 different dosages of levorphanol.[31] Five trials enrolled patients with 1 specific pain syndrome: diabetic neuropathy,[11,32] PHN,[27,30] and phantom pain.[25] The other 3 studies enrolled patients with neuropathic pain of diverse etiologies.

All trials reported that opioids were efficacious in reducing spontaneous neuropathic pain by demonstrating either superiority over placebo or a dose-dependent analgesic response. Six of the 8 studies provided data suitable for pooling based on data on pain intensity after active drug and placebo treatments. The χ^2 test did not suggest that the data were heterogeneous ($\chi^2=6.34$; $P=.27$). The meta-analysis included 263 opioid- and 258 placebo-treated patients and found overall mean pain intensity to be 14 points lower in opioid-treated patients than in those treated with placebo (95% CI, −18 to −10; $P<.001$; FIGURE 4). A post hoc subanalysis of the highest-quality trials was performed, excluding 1 study[18] with a Jadad score of 3. The new esti-

Figure 3. Results of the Meta-analysis of Short-term Trial Efficacy



Data are presented as mean (95% confidence interval [CI]) differences in last measured posttreatment pain intensity (on a visual analog scale from 0-100) between active treatment and placebo (fixed-effects model). Size of the data markers corresponds to the weight of the study in the meta-analysis

mate of the difference between VAS values in the opioid and placebo groups for the remaining 5 studies was −15 (95% CI, −19 to −11).

Dose-dependent analgesic effect was found in 2 studies[33,34] that included patients with mixed neuropathies. In 1 study,[33] low and high doses of methadone were each compared separately with placebo, and the higher dose produced a larger effect than the lower dose. In the other study,[34] a direct comparison showed that a high dose of levorphanol produced a significantly larger analgesic effect than the lower dose. The use of different outcome measures in the 2 studies precluded the performance of dose-response meta-analysis. Evoked pain was measured in only 2 studies.[27,32] In both trials, oxycodone was significantly superior to placebo in reducing allodynia, categorized as "skin pain."

Six of the 8 trials measured the effects of opioids on secondary outcome parameters, such as disability, sleep, cognition, and depression. However, because of the use of 20 different measurement tools, these trials' data could not be quantitatively combined. These findings are summarized in Table 2. Both the physical and mental health components of the Short Form-36 were improved by oxycodone treatment to a greater degree than placebo in patients with diabetic neuropathy in one study[32] but not in another.[31] In patients with PHN, neither the Multidimensional Pain Inventory[30] nor the Categorical Disability Scale[27] showed improvement with oxycodone treatment. Thus, no consistent reduction in disability was found. Depression, measured by the Beck Depression Inventory and by the Profile of Mood States Questionnaire (POMS), failed to improve with oxycodone treatment in patients with PHN.[27] Similarly, no improvement was noted in the POMS scores of patients with mixed neuropathies treated with 2 different dosages of levorphanol[34] nor in the RAND Mental Health Inventory completed by patients with diabetic neuropathy following oxycodone treatment.[31]

Adverse Events and Withdrawals Due to Adverse Events

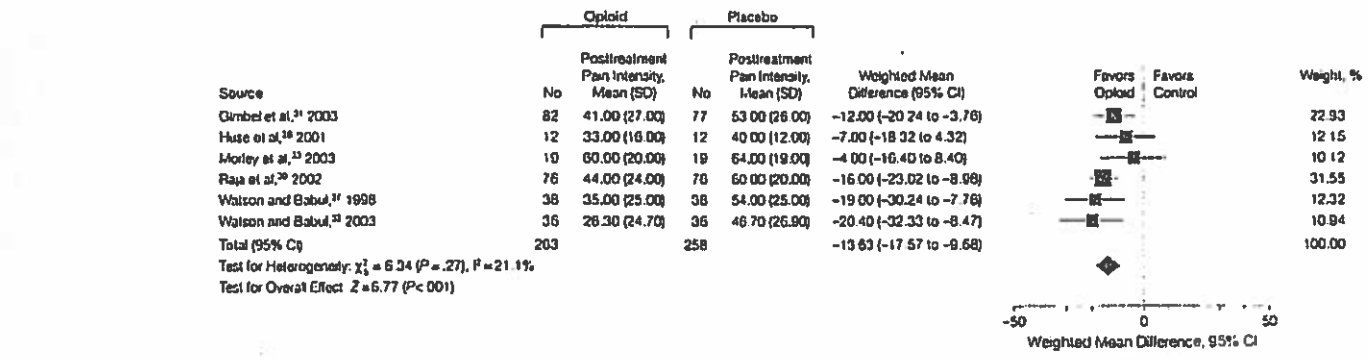
Although data on the prevalence of common opioid-related adverse effects were extracted from all studies, the majority of information was obtained from 5 intermediate-term placebo-controlled trials[29-33] and a lesser amount from 2 additional studies.[27,34] Another study[28] reported adverse events on a VAS scale, precluding determination of the numbers of affected patients (TABLE 3). Whenever possible, we calculated number needed to harm[38] (NNH) for each of the common opioid adverse effects. To avoid the possibility that NNH might have been biased due to selective dropout of patients experiencing adverse effects, we included only studies in which the adverse event that led to the patient's withdrawal was specified. The most common adverse effect was nausea (NNH, 3.6; 95% CI, 2.9-4.8), followed by constipation (NNH, 4.6; 95% CI, 3.4-7.1), drowsiness (NNH, 5.3; 95% CI, 3.7-8.3), vomiting (NNH, 6.2; 95% CI, 4.6-11.1), and dizziness (NNH, 6.7; 95% CI, 4.8-10.0). Data on cognitive impairment as well as on other adverse effects were insufficient to allow calculation of NNH.

When opioid therapy is initiated, there is always a possibility that patients will abandon treatment because of adverse events. Of the 8 intermediate-term RCTs reviewed, 4 trials provided combinable information regarding the number of dropouts due to adverse events.[31-34] In total, 33 (13.5%) of 244 patients in these 4 studies withdrew because of adverse events during opioid therapy vs 12 (7.6%) of 158 patients receiving placebo.

COMMENT

The results of this study can be divided into 2 categories according to the duration of included trials. Short-term trials yielded mixed results with respect to the analgesic efficacy of opioids. Intermediate-term trials demon-

Figure 4. Results of the Meta-analysis of Intermediate-term Trial Efficacy



Data are presented as mean (95% confidence interval [CI]) differences in posttreatment pain intensity (on a visual analog scale from 0-100) between active treatment and placebo (fixed effects model). Size of the data markers corresponds to the weight of the study in the meta-analysis

strated consistent opioid analgesic efficacy in reducing spontaneous neuropathic pain that was statistically significant when their results were pooled. These larger trials are more clinically relevant than the shorter ones because they assess the benefits and risks associated with opioid treatments for weeks to months.

This study included trials that assessed outcomes using diverse scales and often presented them in ways that made accurate extraction of raw data impossible. Because of this, results of many of the studies, and, in particular, the short-term studies, could not be included in our quantitative analyses. The problem of heterogeneity of outcomes in the published literature on pain,[39] including neuropathic pain,[40] has been described and has compelled systematic reviews of analgesic interventions to adopt a "best available evidence" approach.[41,42] Any conclusions from our meta-analyses of short-term trials should be interpreted with caution because they are based on only 4 of 14 studies (and only 90 of 267 treated patients), all of which showed positive results.

In contrast with the short-term trials, the meta-analysis of intermediate-term studies was based on most of the available trials and included the majority of treated patients. Furthermore, the 2 studies not included in the meta-analysis because of noncombinable data also found benefit from opioids over placebo. Hence, we conclude that intermediate-term opioid treatment has a beneficial effect over placebo for spontaneous neuropathic pain for up to 8 weeks of treatment and that the magnitude of this opioid effect is a nearly 14-point difference in pain intensity at study end compared with placebo. A 14-point difference out of 100 points can be compared with that achieved by other commonly used treatments for neuropathic pain. For example, the equivalent pain intensity at study end with gabapentin treatment would be 12 points lower than placebo (39 vs 51) in patients with painful diabetic neuropathy.[43] To achieve this effect, 67% of the patients in the gabapentin study required the maximal daily dose (3600 mg), whereas in the opioid studies a larger effect was achieved by a low to moderate dose of opioid. The dose-dependent analgesic effect shown in 2 of the opioid studies[33,34] suggests that higher doses of opioids may have the potential to produce a greater magnitude of pain reduction in patients with neuropathic pain. Yet, for the most part, patients in the trials received opioids within a relatively narrow range of fixed doses. Our meta-analysis suggests that a goal of future studies in this area should be to evaluate true efficacy of opioids for neuropathic pain by means of trials with wider dose ranges rather than fixed-dose studies.

A challenging question is whether an average decline of 14 points on a scale of 0 to 100 is meaningful for patients. The mean initial pain intensity was recorded from the patients in 4 of the intermediate-term trials and ranged from 46 to 69. This 14-point difference therefore corresponds to a 20% to 30% greater reduction of neuropathic pain with opioids than with placebo. Analysis of data from large randomized clinical trials has shown that 30% reduction in pain intensity may be the threshold for patients to describe a reduction in chronic pain as meaningful.[44-46]

Correlations between the response to a brief exposure to local anesthetics and *N*-methyl-D-aspartate receptor antagonists and long-term response to their oral analogues have been reported.[47-49] The difference in outcomes between short-term and intermediate-term opioid studies does not support a similar use of short-term opioid administra-

Table 3. Adverse Events in RCTs of Opioid Treatment of Neuropathic Pain

Source	Intervention (No. of Patients Enrolled/Completed)	Nausea/ Vomiting	Constipation	Drowsiness/ Somnolence	Dizziness	Altered Cognition	Withdrawals for Adverse Events
Watson and Babul,[27] 1998	Long-acting oxycodone (50/44)	4/NR	5	3	NR	NR	NR
	Placebo (50/44)	NR/NR	NR	NR	NR	NR	NR
Huse et al,[29] 2001	Long-acting morphine (12/12)	NR	NR	NR	NR	Worsened[a]	NR
	Placebo (12/12)	NR	NR	NR	NR	Improved	NR
Harke et al,[29] 2001	Long-acting morphine (21/20)	7/5	2	NR	4	NR	NR
	Placebo (17/15)	1/1	0	NR	0	NR	NR
Raja et al,[33] 2002	Morphine or methadone (76/56)	30/NR	23	23	14	Normal[a]	7
	Placebo (76/75)	5/NR	8	11	5	Normal	NR
Gimbel et al,[31] 2003	Long-acting oxycodone (82/63)	30/17	35	33	26	NR	7
	Placebo (77/52)	6/2	11	1	8	NR	4
Watson et al,[32] 2003	Long-acting oxycodone (45/35)	16/5	13	9	7	NR	7
	Active placebo (benztropine) (45/36)	8/2	4	11	3	NR	1
Morley et al,[33] 2003	Low-dose methadone or	7/4	2	2	6	1	1
	Placebo (19/18)	4/1	1	2	0	0	0
	High-dose methadone or	8/1	3	3	3	0	3
	Placebo (17/11)	4/1	1	2	1	1	3
Rowbotham et al,[34] 2003	High-dose levorphanol (43/29)	NR	NR	NR	2	Improved[a]	12
	Low-dose levorphanol (38/30)	NR	NR	NR	0	Improved	3

Abbreviations: NR, not reported; PHN, postherpetic neuralgia; RCT, randomized controlled trial.
[a] Number of patients not reported.

tion as a predictive tool to decide whether to initiate intermediate-term opioid therapy.

The debate regarding the differential efficacy of opioids for central vs peripheral pain[1-8] has not been resolved by our study. Results of the included studies varied considerably and the meta-analyses could not include all relevant studies. Despite limited data, the meta-analyses showed similar opioid responsiveness for pain of central and peripheral etiologies.

This study also included a quantitative analysis of common opioid-related adverse effects.[30] Although the analysis is based on a relatively large number of patients with neuropathic pain, patients enrolled in clinical trials may not be representative of the broader patient population seen in clinical practice. Enrolled patients have met inclusion criteria, and their willingness to enter a clinical trial suggests that they may have a higher adherence profile compared with unselected patients.

Two other limitations of this systematic review result from the design of the included studies. First, the duration of studies was at most 8 weeks. Therefore, we do not have data on the efficacy or adverse event rate of opioids in the treatment of neuropathic pain over months to years. Second, the available RCTs do not clearly address the issues of addiction and abuse. The absence of any report of addictive behavior or abuse in any of intermediate-term trials may have several explanations. It is possible that the prevalence of these behaviors is indeed low.[31] Alternatively, the duration of treatment in these studies may have been too short to allow such behaviors to develop. Furthermore, although not mentioned specifically as an exclusion criterion, it is reasonably likely that recruitment of patients with apparent abuse or addiction potential[32] into such studies would often be avoided. The need to further assess the risk of abuse and addiction continues to be important.

Finally, the management of any form of chronic pain requires not only reduction in pain intensity but also improved quality of life in dimensions such as sleep, mood, work, social, and recreational capacities.[33] Unfortunately, because of the use of a large number of measurement tools in the included trials, these results could not be quantitatively combined and no consistent improvement in quality of life could be demonstrated. Our meta-analysis takes an initial and necessary first step of showing efficacy for spontaneous pain during opioid treatment for up to 2 months. Further RCTs assessing longer-term efficacy, safety (including addiction potential), and improved quality of life should be undertaken before the value of opioids for management of neuropathic pain is finally established.

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Author Contributions: Dr Eisenberg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis
Study concept and design: Eisenberg, Carr.
Acquisition of data: Eisenberg, McNicol.
Analysis and interpretation of data: Eisenberg, McNicol, Carr.
Drafting of the manuscript: Eisenberg, McNicol.
Critical revision of the manuscript for important intellectual content: Eisenberg, McNicol, Carr.
Statistical analysis: Eisenberg, McNicol.
Administrative, technical, or material support: Eisenberg, Carr.
Study supervision: Eisenberg.
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The time to read is any time: no apparatus, no appointment of time and place, is necessary.
—John Aikin (1747-1822)