

Review

Efficacy of mu-opioid agonists in the treatment of evoked neuropathic pain: Systematic review of randomized controlled trials

Elon Eisenberg^{a,*}, Ewan D. McNicol^{b,c}, Daniel B. Carr^{b,d,e}

^a Pain Relief Unit, Rambam Medical Center, Haifa Pain Research Group, the Technion-Israel Institute of Technology, P.O. Box 9602, Haifa 31096, Israel

^b Department of Anesthesia, New England Medical Center and Tufts University School of Medicine, Boston, MA, USA

^c Pharmacy Department, New England Medical Center and Tufts University School of Medicine, Boston, MA, USA

^d Division of Clinical Care Research, New England Medical Center and Tufts University School of Medicine, Boston, MA, USA

^e Javelin Pharmaceuticals Inc., Cambridge, MA, USA

Received 20 July 2005; accepted 21 October 2005

Available online 5 December 2005

Abstract

Several reviews of randomized controlled trials (RCTs) have shown the efficacy of mu-opioids in reducing spontaneous neuropathic pain (NP). However, relatively little is known about their specific efficacy for evoked pain, which is a significant problem for many patients with NP. The present systematic review assesses the efficacy of opioid agonists for the treatment of evoked NP based upon published RCTs. We searched articles in any language using the MEDLINE database (1966 to December 2004), the Cochrane Central Register of Controlled Trials (4th quarter, 2004) and the reference lists of retrieved papers, employing search terms for RCTs, opioids and NP. Only RCTs in which opioid agonists were given to treat NP of any etiology, and evoked pain was assessed were included. Data were extracted by two independent investigators. Nine articles met inclusion criteria and were classified as short-term (less than 24 h; $n = 7$) or intermediate-term trials (4 weeks; $n = 2$). Although the scarcity of retrieved data precluded formal meta-analysis of short-term trials, we found that the intensity of dynamic mechanical allodynia was significantly attenuated by opioids relative to placebo in all studies. In contrast, no consistent effects on the magnitude of static allodynia, the threshold for mechanical allodynia or the threshold or magnitude of heat allodynia were found. The threshold and magnitude of cold-induced allodynia generally responded positively to opioid treatments in patients with peripheral pain syndromes, but not central pain syndromes. Evoked pain was studied in only two intermediate-term trials, in both of which oxycodone was significantly superior to placebo. The results of the two trials were combinable for a meta-analysis that showed an overall 24 points difference in endpoint pain intensities between patients given opioids and those treated with placebo (95% CI -33 to -15 ; $p < 0.00001$). In conclusion: short-term studies show that opioids can reduce the intensity of dynamic mechanical allodynia and perhaps of cold allodynia in peripheral NP. Insufficient evidence precludes drawing conclusions regarding the effect of opioids on other forms of evoked NP. A meta-analysis of intermediate-term studies demonstrates the efficacy of opioids over placebo for evoked NP. These findings are clinically relevant because dynamic mechanical allodynia and cold allodynia are the most prevalent types of evoked pain in NP. © 2005 European Federation of Chapters of the International Association for the Study of Pain. Published by Elsevier Ltd. All rights reserved.

Keywords: Allodynia; Hyperalgesia; Quantitative sensory testing

* Corresponding author. Tel.: +972 4 854 2234; fax: +972 4 854 3505.
E-mail address: e_eisenberg@rambam.health.gov.il (E. Eisenberg).

1. Introduction

Neuropathic pain (NP) that results from traumatic, inflammatory, ischemic, metabolic and neoplastic insults to the peripheral or central nervous system is characterized by continuous or intermittent spontaneous pain and abnormal sensitivity of the painful site to a variety of noxious (hyperalgesia) or innocuous (allodynia) stimuli (Yarnitsky and Eisenberg, 1998). Evoked pain that results from light touch by garments, running water or even cold air can be extremely bothersome for many of these patients.

Pharmacotherapy of NP employs antidepressants or anticonvulsants, but even with the latest generations of these drugs, effective analgesia is achieved in fewer than half of this population (Sindrup and Jensen, 1999). The use of opioids for chronic pain in general and NP in particular has increased dramatically over the last decade. Yet, the belief that NP is opioid-resistant, as well as concerns over adverse effect profiles and potential for abuse often discourages the use of opioids for NP. Recent systematic reviews (Eisenberg et al., *in press*; Kalso et al., 2004; Katz and Benoit, 2005) of randomized controlled trials (RCTs) have shown the efficacy of opioids in reducing spontaneous NP. However, little is known about their efficacy for evoked pain. The present systematic review of published RCTs aimed to assess the efficacy of opioid agonists for the treatment of evoked NP. Since evoked pain in general and dynamic mechanical allodynia and cold allodynia in particular are prevalent in NP, this review is of clinical relevance.

2. Methods

2.1. Search

Full reports in any language were searched using the MEDLINE database (1966 to December 2004), the Cochrane Central Register of Controlled Trials (4th quarter, 2004) and the reference lists of reviews and retrieved articles. Authors were not contacted for original data, and abstracts or unpublished reports were not considered. Search terms for RCTs were combined with those for opioids and neuropathic pain (see [Appendix](#)).

2.2. Inclusion and exclusion criteria

Abstracts of all citations and retrieved studies were reviewed to see if they met the following inclusion criteria: (1) randomized, blinded and controlled trials; (2) opioid agonists (but not partial agonists or agonist-antagonists) were given to treat central or peripheral NP of any etiology; (3) one or more opioid agonists, or different doses of the same opioid agonist

were compared to placebo, each other, or another class of medications used for NP (e.g., antidepressants); (4) drugs were administered by any of the following routes: orally, rectally, transdermally, intravenously, intramuscularly or subcutaneously; (5) evoked NP was characterized with tools such as quantitative sensory testing (QST), von Frey filaments, measurement of area of hyperalgesia, and measurement of evoked-pain intensity with validated pain measurement tools such as the visual analogue scale (VAS).

We excluded studies in which: (1) patients with both neuropathic and other types of pain (e.g., nociceptive) were enrolled, and responses of the two groups of patients were pooled so that they could not be differentiated; (2) drugs other than opioid agonists were combined with opioids (e.g., codeine with acetaminophen); (3) opioids were administered epidurally, intrathecally or intracerebroventricularly; (4) tramadol was used as the active drug, because tramadol is not regarded as a pure opioid agonist and its efficacy for NP has been the subject of a recent systematic review (Duhmke et al., 2004).

2.3. Assessment of methodological quality

Studies that met inclusion criteria were graded for methodological quality using a scale reported by Jadad et al. (1996). Jadad (or “Oxford”) scores are based upon each paper’s description of randomization, blinding and withdrawals, and can range from 1 to 5, where higher scores indicate better methodological quality.

2.4. Data extraction

Information on study designs, methods, interventions and evoked-pain outcomes was extracted. In addition, diagnoses, patient inclusion and exclusion criteria, and numbers of patients enrolled and completing the study were extracted into a standardized table by two independent investigators. In many studies data were presented in graphical form only. In these cases, whenever possible, data were extracted by measurement of the photocopied and enlarged figures. Discrepancies in extracted data were resolved by discussion prior to including data in the analysis.

2.5. Statistical analysis

Statistical analysis of included trials was performed using The Cochrane Collaboration’s Review Manager software (RevMan) Version 4.2.7 for Windows, Oxford, England: The Cochrane Collaboration, 2004: CD-ROM and Internet. Whenever possible, results from the trials were combined using a fixed effects model to calculate

differences and 95% confidence intervals (CI) in post-intervention evoked-pain intensity. Heterogeneity between and within trials was evaluated using the Chi-square test (Clarke and Oxman, 2003). *P*-values less than 0.05 were considered significant. Unless otherwise stated, values presented are means \pm SD.

3. Results

3.1. Included studies

The literature search yielded 1995 citations of which 44 were selected for retrieval. Nine of the 44 trials met inclusion criteria and provided data on 178 opioid-treated patients in whom evoked NP was assessed. All nine trials used placebo as a control. A QUOROM flow diagram (Fig. 1) shows an overview of the study selection process. In seven trials opioids were administered mostly as brief intravenous infusions using a crossover design, and outcomes measured over less than 24 h (short-term trials). The number of patients in each of these studies was generally small (median 12; range 8–19). The test drug was alfentanil in four trials and morphine in three. The diagnosis was specified in all trials; two trials stud-

ied patients with post-herpetic neuralgia (PHN), two studied patients with central pain, two studied patients with post-traumatic neuralgia (PTN), and one studied patients with mixed neuropathies (Table 1). In the two other trials, oxycodone was administered orally over 4 weeks (intermediate-term trials), also using a crossover design, but to larger numbers (45 and 50) of patients. The diagnosis was diabetic neuropathy in one trial (Watson et al., 2003) and PHN in the other (Watson and Babul, 1998).

3.2. Study quality

The quality of the studies as judged by the Jadad score is presented in Table 1. The median overall score was 4 (range 3–5) indicating good methodological quality. The Jadad scores of the two intermediate-term studies scored higher (5 points each) than the short-term trials (median 4). Inadequate description of the randomization process (Attal et al., 2002; Eide et al., 1994; Leung et al., 2001; Max et al., 1995; Rowbotham et al., 1991) was the most common shortfall in the short-term trials. Other shortfalls included inadequate description of the double blinding process (Eide et al., 94; 95) and of dropouts (Jorum et al., 2003).

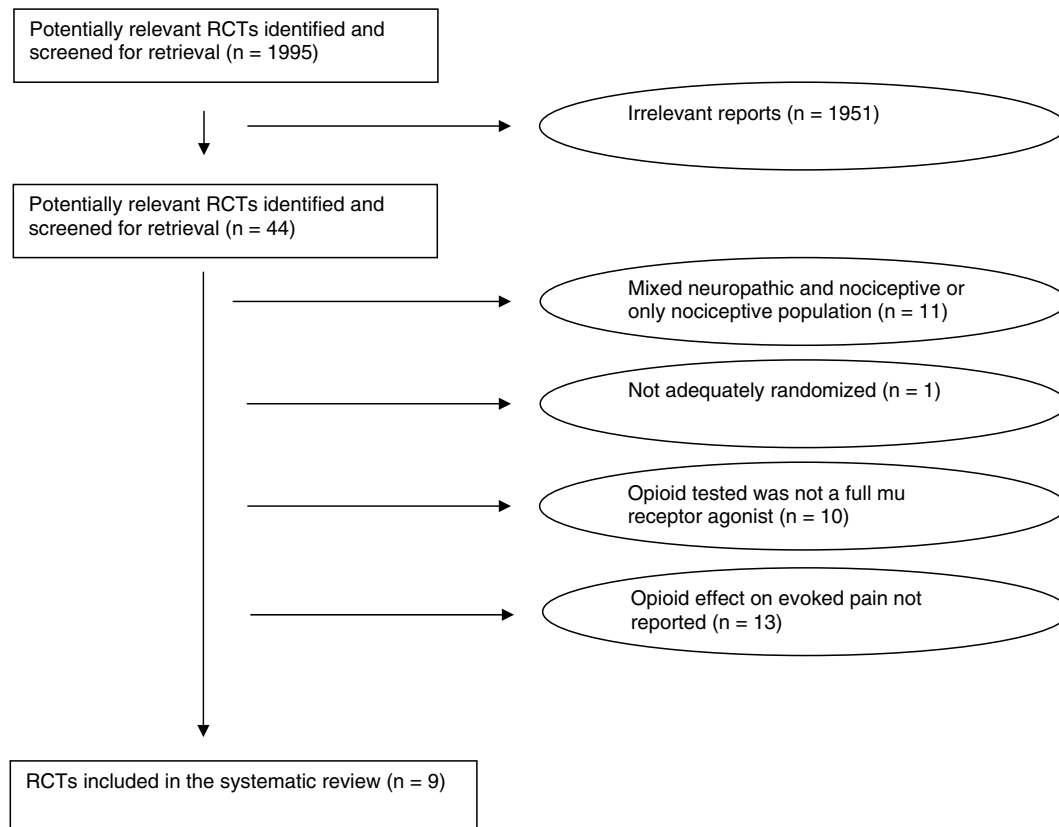


Fig. 1. A QUOROM flow diagram of included/excluded studies.

Table 1
Randomized controlled trials in the treatment of neuropathic pain: design, intervention and quality assessment

Study	Pain etiology (patient numbers)	Number of patients enrolled/evaluable	Design	Intervention, control, placebo ^a	Jadad quality score
<i>Short-term trials</i>					
Jorum 2003	PTN (11) PHN (1)	12/12	Crossover	Alfentanil: i.v. bolus of 7 µg/kg over 5 min + 0.6 µg/kg/min infusion over 20 min Ketamine: i.v. bolus of 60 µg/kg over 5 min + 6 µg/kg/min infusion over 20 min Placebo	+4
Attal 2002	Central: SC (9), post stroke pain (6)	15/15	Crossover	Morphine: 9–30 mg (mean 16 ± 6), individually titrated to AE, over 20 min Placebo	+4
Leung 2001	Mixed: RSD (6) PHN (4), SC (1), causalgia (1)	12/12	Crossover	Alfentanil: 20 min i.v. infusion aimed at achieving plasma levels of 25, 50 and 75 ng/ml Ketamine: 20 min i.v. infusion aimed at achieving plasma levels of 50, 100 and 150 ng/ml Active placebo (diphenhydramine)	+4
Max 1995	PTN	8/8	Crossover	Alfentanil: 1.5 µg/kg/min for 60 min; rate doubled as required at 60 and 90 min for a total of 2 h Ketamine: 0.75 mg/kg/hr for 60 min; rate doubled as required at 60 and 90 min for a total of 2 h Placebo	+4
Eide 1995	Central: SC	9/9	Crossover	Alfentanil: 7 µg/kg over 1 min + 0.6 µg/kg/min for 17–21 min Ketamine: 60 µg/kg over 1 min + 6 µg/kg/min for 17–21 min Placebo	+4
Eide 1994	PHN	8/8	Crossover	Morphine inf: 0.075 mg/kg over 10 min Ketamine inf: 0.15 mg/kg/ over 10 min Placebo	+3
Rowbotham 1991	PHN	19/19	Crossover	Morphine: 0.3 mg/kg (max 25 mg) over 1 h Lidocaine: 5 mg/kg (max 450 mg) over 1 h Placebo	+4
<i>Intermediate-term trials</i>					
Watson 1998	PHN	50/44	Crossover	Long-acting oxycodone: 10–30 mg twice daily (mean: 45 ± 17) for 4 weeks	+5
Watson 2003	Diabetic neuropathy	Active 45/35 Placebo 45/36	Crossover	Long-acting oxycodone: 10–40 mg twice daily (mean: 40.0 ± 18.5) for 4 weeks Active placebo [benztropine]: 0.25–1.0 mg twice daily (mean: 1.2 ± 0.6)	+5

PTN, post-traumatic neuralgia; PHN, post-herpetic neuralgia; SC, spinal cord; RSD, reflex sympathetic dystrophy; AE, adverse events; PCA, patient controlled analgesia.

^a All administered intravenously unless stated.

3.3. Efficacy: short-term trials

An overview of the results of the short-term RCTs is presented in Table 2.

3.3.1. Cold allodynia and hyperalgesia

The effect of opioids on cold allodynia was studied in four trials. Using QST in 12 patients (11 with PTN and 1 with PHN) and reduced baseline cold pain detection threshold (cold allodynia), Jorum et al. (2003) found

that alfentanil infusion, but not placebo, significantly increased the threshold for cold pain at the painful site. Alfentanil also significantly reduced the intensity of pain (VAS) from 4.5 to 1.4 (median values) at the threshold for cold detection. Leung et al. (2001) showed dose-dependent elevation of cold pain threshold by alfentanil in a group of 12 patients with mixed neuropathies. Notably, only two of the twelve patients in that study had reduced cold pain thresholds (cold allodynia) at baseline but the authors did not differentiate their

Table 2
Short-term randomized controlled trials of opioids in the treatment of evoked neuropathic pain: efficacy results

Study	Pain etiology (patient numbers)	Agent	Cold allodynia/hyperalgesia		Heat allodynia/hyperalgesia		Tactile allodynia/hyperalgesia		Area
			Threshold	VAS/area	Threshold	VAS	Threshold	VAS	
Jorum 2003	PTN (11) PHN (1)	Alfentanil vs. ketamine vs. placebo	O > P	VAS O > P	O > P	O = P	(D) O > P		
Attal 2002	Central: SC (9) post stroke pain (6)	Morphine vs. placebo	O = P (0/3)	VAS O = P (0/6)	O = P (0/1)	O = P (0/5)	(S) O = P (S) O = P	(D) O > P, (S) O = P	
Leung 2001	Mixed: RSD (6), PHN (4), SC (1), causalgia (1)	Alfentanil (3 plasma levels) vs. ketamine vs. placebo	O > P	Area O > P (2/2)	O = P		(S) O = P (D and S) O > P	(D) O > P, (S) O = P	
Max 1995	PTN (8)	Alfentanil vs. ketamine vs. placebo		VAS O > P (2/3)		O = P (0/2)	(D) O > P	(S) O > P 2/6, O = P 4/6	
Eide 1995	Central: SC (9)	Alfentanil vs. ketamine vs. placebo			O = P		(D and WU) O > P		
Eide 1994	PHN (8)	Morphine vs. ketamine vs. placebo			O = P		(D) O = P (WU) O = P		
Rowbotham 1991	PHN (19)	Morphine vs. lidocaine vs. placebo					O > P		

Numbers in brackets, number of patients; O > P, opioid superior to placebo; O = P, opioid not superior to placebo; D, dynamic allodynia (e.g., cotton wool or paintbrush strokes); PHN, post-herpetic neuralgia; PTN, post-traumatic neuralgia; RSD, reflex sympathetic dystrophy; S, static allodynia (e.g., von Frey filaments); SC, spinal cord; WU, 'wind-up' like pain; ?, questionable significance due to a small number of patients.

responses to alfentanil from those of the entire group. Further testing showed 67% and 87% reductions, respectively, in the area of cold allodynia following alfentanil treatment in these two patients. In a third trial (Max et al., 1995) alfentanil was administered to eight patients with PTN. The results of the study are somewhat difficult to understand due to the lack of a clear description of the testing procedure. However, the effect of alfentanil on cold hyperalgesia was tested in three patients. In two a dramatic effect was noted (88% and 100% reductions in VAS) and in the third little to no effect was found. A fourth trial (Attal et al., 2002) studied fifteen patients with central pain and yielded different results. Cold allodynia at baseline was present in three subjects and cold hyperalgesia in six. Intravenous morphine administration did not significantly reduce either symptom in any patient.

Due to heterogeneity between studies in the presentation of results, their data could not be quantitatively combined. However, these results suggest that in patients with peripheral nerve injuries, alfentanil: (1) elevates the threshold for cold pain detection regardless of the presence of baseline cold allodynia and (2) reduces the intensity and area of cold hyperalgesia. In contrast, morphine is less likely to have such benefits in patients with central NP.

3.3.2. Heat allodynia and hyperalgesia

The opioid effect on the heat pain detection threshold was tested in five studies that generally yielded negative results. Only one study showed that alfentanil significantly increased heat pain detection thresholds in 12 patients (11 with PTN and 1 with PHN) who had normal baseline heat pain thresholds (Jorum et al., 2003). In contrast, alfentanil had no effect on heat pain thresholds in another group of 12 patients with mixed neuropathies (Leung et al., 2001) whose baseline thresholds for heat pain were elevated (heat hypoalgesia) in comparison to previously published data from healthy volunteers. Similarly, morphine did not change heat pain thresholds in eight PHN patients with normal baseline heat pain thresholds (Eide et al., 1994). Two other studies that tested the effect of opioids on heat pain thresholds in patients with central pain yielded negative results. In one trial (Eide et al., 1995), alfentanil did not significantly change heat pain thresholds in nine patients with spinal cord injury, but the authors did not report whether the baseline thresholds were normal, reduced or elevated. In the other trial (Attal et al., 2002), only one subject had baseline heat allodynia, which remained unchanged after morphine treatment.

All three studies that evaluated the effect of opioids on the magnitude (VAS) of heat pain in patients with NP showed negative results. In one study (Jorum et al., 2003), however, pain intensity was tested at the threshold for detecting heat pain. Six of the 12 patients

in that study rated their baseline pain intensity as 0, thereby rendering baseline VAS for the entire group very low (median value of 3.45). Not surprisingly, no significant reduction in VAS following alfentanil treatment was found in that study. In the second trial, Max et al. (1995) reported little to no effect in two patients with heat hyperalgesia treated with alfentanil. In the third study (Attal et al., 2002), morphine did not attenuate heat hyperalgesia differently from placebo in the affected side in any of the five patients with central pain who presented with increased sensitivity to suprathreshold heat stimuli.

Quantitative analysis of the heat pain studies could not be performed due to a lack of uniformly presented, combinable data. Yet, with the exception of one study (Jorum et al., 2003), no trial suggested that opioids affect heat pain threshold or heat hyperalgesia in patients with either peripheral or central NP.

3.3.3. Mechanical allodynia and hyperalgesia

The effect of opioids on mechanical pain thresholds (tactile allodynia) was tested in three trials (Attal et al., 2002; Eide et al., 1994; Leung et al., 2001), all of which yielded negative results. Attal et al. (2002) found reduced baseline thresholds to punctuate stimuli produced by von Frey filaments in the affected side in seven of fifteen patients with central pain. Morphine was no better than placebo in modifying these thresholds for the group as a whole or for those with baseline mechanical allodynia. Similar results were reported by Leung et al. (2001) who found that alfentanil had no effect on mechanical pain detection thresholds in patients with mixed neuropathies. However, in contrast to those evaluated by Attal et al., the patients studied by Leung et al. had elevated baseline thresholds (hypoalgesia). Lastly, morphine had no effect on dynamic mechanical pain detection thresholds, which were elevated at baseline, in patients with PHN (Eide et al., 1994).

The effect of opioids on the magnitude of static hyperalgesia was tested in two trials. In one trial (Attal et al., 2002), morphine did not significantly reduce the VAS score compared with placebo in the eight of fifteen patients with central pain and pre-existing static mechanical hyperalgesia. In contrast (Leung et al., 2001), alfentanil significantly reduced pain intensity induced by von Frey testing in patients with mixed neuropathies (approximately $75 \pm 10\%$ reduction following alfentanil vs. $25 \pm 8\%$ following placebo; data extracted from a figure). Alfentanil's effect on the area of static hyperalgesia was also tested in two trials and had no effect on von Frey-induced allodynic area in patients with mixed neuropathies (Leung et al., 2001) or on the area on pinprick hyperalgesia in four of six patients with PTN (Max et al., 1995).

The effect of opioids on the intensity of dynamic allodynia was tested in all seven trials. Of ten patients with

central pain who had brush-induced allodynia, morphine attenuated its intensity by 50% in nine whereas placebo produced a 50% reduction only in three (Attal et al., 2002). Total pain relief was felt by four patients following morphine treatment and by two following placebo. The effect of morphine infusion averaged over all patients was significantly superior to placebo during the entire testing period (up to 2 h after conclusion of the infusion). The peak pain intensity difference between morphine and placebo was reported at 30 min. At that time, the VAS of the morphine and placebo treated groups were 11 ± 14 and 38 ± 9 , respectively (data extracted from figure). Notably, a significant correlation was found between the magnitude of baseline allodynia and morphine-induced decrease in allodynia. In another study of nine patients with central pain due to traumatic spinal cord injury, alfentanil produced 78% reduction in the magnitude of allodynia (median; data extracted from figure) whereas placebo had no effect (Eide et al., 1995). A similar reduction (70% vs. 0%) was found in the magnitude of wind-up-like pain, produced by repeatedly pricking the painful area with a von Frey filament (6.65 units) at a rate of 3 pricks per second for 30 s.

The other five trials tested the effects of opioids on dynamic allodynia in patients with peripheral NP syndromes. In one trial, the intensity and area of stroking-evoked allodynia was reduced by alfentanil in a concentration-dependent fashion (Leung et al., 2001). At the highest plasma concentration tested, VAS was reduced by $69 \pm 10\%$ with alfentanil treatment vs. $37 \pm 10\%$ with placebo, and the area was reduced by $68 \pm 12\%$ vs. $33 \pm 7\%$ accordingly. The effects of alfentanil on allodynia were significantly different from placebo in patients with PTN in two studies. In one (Max et al., 1995), mean peak relief (as assessed on a 0–100 VAS pain relief scale) produced by alfentanil was 57% (no standard deviations provided) vs. 21% by placebo. In the other (Jorum et al., 2003), the median endpoint evoked pain intensity following alfentanil treatment was 1.2 (on a 0–10 scale), and 6.2 following placebo (data extracted from figure). Two additional trials tested patients with PHN. In one, (Eide et al., 1994) the median reduction in allodynia after morphine was 40% (extracted from a figure), whereas after placebo allodynia was increased by 65%. In contrast, wind-up-like pain was aggravated (median increase, 60%) vs. no change after placebo. The differences between morphine and placebo were significant for both comparisons. In the other trial (Rowbotham et al., 1991), patients were asked to report if there was a change in their perception of the painful area, with special attention as to whether simple touching or mild pressure evoked pain. Eleven patients experienced either normalization of their aberrant sensation or loss of painful hypersensitivity following morphine infusion, vs. only one patient after placebo. Unfortunately, no numerical

data were provided and it is not clear whether static or dynamic stimuli were applied in this trial.

Although numerical data related to dynamic allodynia could be extracted from six trials (Table 3), the heterogeneity of their presentation precluded a formal meta-analysis. However, these studies uniformly found that opioids reduce the magnitude of dynamic mechanical allodynia. The effect of opioids on the magnitude of static mechanical allodynia seems equivocal, and there is no evidence that mechanical pain thresholds are elevated by opioids.

3.4. Efficacy: intermediate-term trials

The effect of opioids on evoked pain was studied in only two intermediate-term trials (Watson and Babul, 1998; Watson et al., 2003). In contrast to the short-term trials the assessment of evoked pain in both of these trials was based upon patients' self reports of "skin pain" rather than upon quantitative testing of specific sensations. In one trial (Watson et al., 2003) the authors noted that: "skin pain refers to pain elicited by non-painful stimulation of the skin" but did not specify the type of stimuli (e.g., heat, cold or mechanical). In the other trial (Watson and Babul, 1998) the authors also refer to "skin pain (allodynia)" and specify that 87% had mechanical evoked pain, 18% had cold evoked pain, and 18% warmth evoked pain. In both trials oxycodone was significantly superior to placebo in reducing evoked pain. The results of the two trials were combinable for a meta-analysis that showed that overall mean pain inten-

sity was 24 points lower in opioid treated patients than in those treated with placebo (95% CI -33 to -15 ; $p < 0.00001$; Fig. 2).

4. Discussion

The results of the present study are based primarily upon short-term trials that can be regarded as "feasibility trials". Due to their limited duration these short-term studies do not provide information regarding the intermediate- or long-term efficacy of opioids for evoked NP. Only two trials provided more clinically relevant information because they assessed the effects of opioid treatment for four weeks. Even a one-month study duration, however, falls short of what most clinicians would consider long-term therapy.

The short-term trials show a consistent opioid effect in reducing the intensity of dynamic mechanical allodynia. From a clinical standpoint, this seems to be exceedingly important information because rubbing garments, accidental light touch at a painful site or even blowing wind are common types of evoked-pain experienced by patients with NP, and likely contribute to the fear-avoidance behavior well-demonstrated in patients with chronic pain (Rogers et al., 2000). Furthermore, the opioid-induced reduction in the magnitude of this type of allodynia seems to be fairly robust in each of the short-term trials.

The effects of opioids on other forms of evoked pain were tested in smaller numbers of trials, and should

Table 3
Magnitude of opioids effect on evoked mechanical neuropathic pain

Study	Number		Effect on dynamic mechanical allodynia		
	Opioids	Placebo	Opioids	Placebo	Comments
<i>Short-term trials</i>					
Jorum 2003	12	12	1.2	6.2	Endpoint VAS (0–10), median
Attal 2002	15	15	38 ± 9	11 ± 14	Endpoint VAS (0–100), mean ± SD
Leung 2001	12	12	69 ± 10%	37 ± 10%	% Reduction, mean ± SD
Max 1995	8	8	57%	21%	% Reduction, no SD provided
Eide 1995	9	9	78%	0%	% Reduction, median
Eide 1994	8	8	60%	0%	% Reduction, median

Comparison: Intermediate-term Efficacy Studies: Treatment vs. Placebo
Outcome: Evoked pain intensity post intervention/placebo

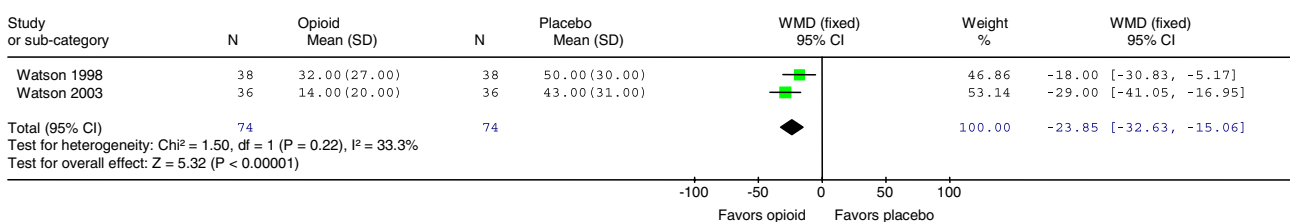


Fig. 2. Results of the meta-analysis of intermediate-term efficacy. Data presented as mean (95% CI) differences in post-treatment last measured skin pain (allodynia) intensity (VAS) between active treatment and placebo.

therefore be interpreted even more cautiously. Nonetheless, several observations deserve attention.

First, the response of cold-evoked pain to opioids depends on the type of the underlying pain syndrome: both the threshold and the magnitude of cold-evoked pain that accompanies peripheral syndromes are likely to be opioid responsive, whereas cold-evoked pain associated with central pain syndromes seems less responsive to opioids. In contrast, the available data, although limited, seems to show that heat-evoked-pain remains unchanged following opioid treatment in most patients with peripheral and central NP. More definitive confirmation of this difference would support the proposal that different mechanisms are involved in the pathogenesis of cold and heat-evoked-pain (Treede et al., 2004).

Another important finding of the present systematic review is that in contrast to the effect of opioids on dynamic mechanical allodynia, their efficacy in reducing static mechanical (punctate) allodynia is far less obvious. Only one trial showed a positive opioid effect on the intensity of static mechanical allodynia, whereas two trials that tested the effect of opioids on the threshold, one other trial that tested the effect on the intensity, and two trials that tested their effect on the area of punctate hyperalgesia were all negative. This possible discrepancy in opioid responsiveness between dynamic and static allodynia may support previous evidence suggesting that the underlying mechanisms of the two phenomena may differ (Treede and Magerl, 2000).

Whether or not opioids exert differential efficacy for central vs. peripheral NP is an unresolved question (Ballantyne and Mao, 2003; Canavero and Bonicalzi, 2003; DelleMijn, 1999; McQuay, 1997; Nicholson, 2004). A recent meta-analysis (Eisenberg et al., *in press*) found no consistent evidence to suggest that spontaneous central pain is less responsive to opioids than peripheral NP. Similarly, the present results for evoked central pain, although based upon two trials only, do not disclose a difference between the opioid responsiveness of central vs. peripheral dynamic mechanical allodynia. In contrast, the intensities of punctate hyperalgesia and cold allodynia were reduced by opioids in a small number of patients with peripheral NP, but not in patients with central pain. These differences, notably, are based upon the results of only one central pain study and cannot be regarded as conclusive. Nonetheless, from a practical, clinical standpoint, unless proven otherwise, there seems to be equal justification for the use of opioids for both spontaneous and mechanical evoked NP regardless of whether the origin is peripheral or central.

Although the results of the short-term trials could not be quantitatively merged, the meta-analysis of the two intermediate-term trials supports this finding by showing a 24-point difference in the final values for allodynia between the opioid and the placebo treated groups. This

difference is similar to that produced by opioids in spontaneous NP (Eisenberg et al., *in press*). This magnitude of effect seems clinically relevant, in that recent analyses of data from large randomized clinical trials showed that patients report a 15–20 point reduction from moderate baseline pain intensity, as meaningful (Farrar et al., 2000, 2001; Cepeda et al., 2003).

Several shortcomings of this systematic review should be emphasized. One is that included trials assessed outcomes using diverse scales and often presented them in ways that made raw data extraction inaccurate (e.g., presentation in figures only) or impossible. Therefore, results of most trials could not be included in our quantitative analysis. The problem of heterogeneity of outcome measures in the published literature on pain in general (Carr et al., 2004) and NP in particular (Stanton-Hicks et al., 2002) has been described, and has compelled systematic reviews of analgesic interventions to adopt a “best-available evidence” approach (Mailis and Furlan, 2003; McNicol et al., 2004). Unfortunately, the best available results of short-term trials published to date do not allow quantitative conclusions regarding the short-term efficacy of opioids for evoked NP, and in many cases preclude even qualitative conclusions.

Other shortcomings result from the relatively short duration of the intermediate-term studies, which were four weeks only, and from the fact that patients with central NP were not included in either of these studies. Therefore, we do not have any data on the efficacy of opioids in the treatment of evoked central NP for longer than a few hours or on the efficacy of opioids for any type of evoked NP over a period of months or longer. We also wish to reemphasize that the small numbers of patients included in most studies, the variability in study designs, the variety of opioids used and the dosages administered, in aggregate preclude firm conclusions.

In conclusion, the present review and meta-analysis suggest that in short-term studies opioids can reduce the intensity of dynamic mechanical allodynia and perhaps of cold allodynia in peripheral NP. Insufficient evidence precludes drawing conclusions regarding the effect of opioids on other forms of evoked NP. Meta-analysis of intermediate-term studies demonstrates efficacy of opioids over placebo for evoked NP. These findings are clinically relevant because dynamic mechanical allodynia and cold allodynia are the most prevalent types of evoked pain in NP. Furthermore, by examining the efficacy of opioids for evoked NP, this study takes an additional step towards characterizing the complexity of opioid responsiveness of NP. Further steps, including longer-term evaluation of larger numbers of patients with additional types of NP syndromes should be undertaken to elucidate the therapeutic role of opioids for NP.

Appendix. Search strategy

1. pain.sh.
2. neuralgia.sh.
3. pain, intractable.sh.
4. exp Complex Regional Pain Syndromes/
5. diabetic neuropathies.sh.
6. trigeminal neuralgia.sh.
7. exp somatosensory disorders/
8. (neuropathic adj2 pain).tw.
9. neuralgia.tw.
10. complex regional pain syndrome.tw.
11. reflex sympathetic dystrophy.tw.
12. causalgia.tw.
13. post-herpetic neuralgia.tw.
14. phantom limb pain.tw.
15. allodynia.tw.
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. Narcotics/
18. *"Analgesics, Opioid"/
19. (morphine or buprenorphine or codeine or dextromoramide or diphenoxylate or dipipanone or dextropropoxyphene or propoxyphene or diamorphine or dihydrocodeine or alfentanil or fentanyl or remifentanyl or meptazinol or methadone or nalbuphine or oxycodone or papaveretum or pentazocine or meperidine or pethidine or phenazocine or hydrocodone or hydromorphone or levorphanol or oxymorphone or butorphanol or dezocine or sufentanil or ketobemidone).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
20. 17 or 18 or 19
21. randomized controlled trial.pt.
22. meta-analysis.pt.
23. controlled-clinical-trial.pt.
24. clinical-trial.pt.
25. random:.ti, ab, sh.
26. (meta-anal: or metaanaly: or meta analy:).ti, ab, sh.
27. ((doubl: or singl:) and blind:).ti, ab, sh.
28. exp clinical trials/
29. crossover.ti, ab, sh.
30. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. Animals/
32. 16 and 30 and 20
33. 32 not 31

References

- Attal N, Guirimand F, Brasseur L, Gaude V, Chauvin M, Bouhassira D. Effects of IV morphine in central pain: a randomized placebo-controlled study. *Neurology* 2002;58:554–63.
- Ballantyne JC, Mao J. Opioid therapy for chronic pain. *New Engl J Med* 2003;349:1943–53.
- Canavero S, Bonicalzi V. Chronic neuropathic pain. *New Engl J Med* 2003;348:2688–9.

- Carr DB, Goudas LC, Balk EM, Bloch R, Ioannidis JP, Lau J. Evidence report on the treatment of pain in cancer patients. *J Natl Cancer Inst Monogr* 2004;32:23–31.
- Cepeda MS, Africano JM, Polo R, Alcalá R, Carr DB. What decline in pain intensity is meaningful to patients with acute pain? *Pain* 2003;105:151–7.
- Clarke M, Oxman AD, editors. Analysing and presenting results. In: *Cochrane reviewers' handbook 4.2* [updated November 2002]; section 8. Oxford: The Cochrane Library [database on disk and CDROM], The Cochrane Collaboration, Update Software; 2003, issue 1.
- Dellemijn P. Are opioids effective in relieving neuropathic pain? *Pain* 1999;80:453–62.
- Duhmke RM, Cornblath DD, Hollingshead JR. Tramadol for neuropathic pain. *Cochrane Database Syst Rev* 2004(2):CD003726.
- Eide PK, Jorum E, Stubhaug A, Bremnes J, Breivik H. Relief of post-herpetic neuralgia with the *N*-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. *Pain* 1994;58:347–54.
- Eide PK, Stubhaug A, Stenehjem AE. Central dysesthesia pain after traumatic spinal cord injury is dependent on *N*-methyl-D-aspartate receptor activation. *Neurosurgery* 1995;37:1080–7.
- Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of non-malignant origin: systematic review and meta-analysis of randomized controlled trials. *JAMA* [in press].
- Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. *Pain* 2000;88:287–94.
- Farrar JT, Young Jr JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94:149–58.
- 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.
- Jorum E, Warncke T, Stubhaug A. Cold allodynia and hyperalgesia in neuropathic pain: the effect of *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine—a double-blind, cross-over comparison with alfentanil and placebo. *Pain* 2003;101:229–35.
- Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain* 2004;112:372–80.
- Katz N, Benoit C. Opioids for neuropathic pain. *Curr Pain Headache Rep* 2005;9:153–60.
- Leung A, Wallace MS, Ridgeway B, Yaksh T. Concentration–effect relationship of intravenous alfentanil and ketamine on peripheral neurosensory thresholds, allodynia and hyperalgesia of neuropathic pain. *Pain* 2001;91:177–87.
- Mailis A, Furlan A. Sympathectomy for neuropathic pain. *Cochrane Database Syst Rev* 2003(2):CD002918.
- Max MB, Byas-Smith MG, Gracely RH, Bennett GJ. Intravenous infusion of the NMDA antagonist, ketamine, in chronic posttraumatic pain with allodynia: a double-blind comparison to alfentanil and placebo. *Clin Neuropharmacol* 1995;18:360–8.
- McQuay HJ. Opioid use in chronic pain. *Acta Anaesthesiol Scand* 1997;41:175–83.
- McNicol E, Strassels S, Goudas L, Lau J, Carr D. Nonsteroidal anti-inflammatory drugs, alone or combined with opioids, for cancer pain: a systematic review. *J Clin Oncol* 2004;22:1975–92.
- Nicholson BD. Evaluation and treatment of central pain syndromes. *Neurology*. 2004;62(5 Suppl. 2):S30–6.
- Rogers WH, Wittink HM, Ashburn MA, Cynn D, Carr DB. Using the "TOPS", an outcomes instrument for multidisciplinary outpatient pain treatment. *Pain Med* 2000;1:55–67.
- Rowbotham MC, Reisner-Keller LA, Fields HL. Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia. *Neurology* 1991;41:1024–8.

- Sindrup HJ, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* 1999;83:389–400.
- Stanton-Hicks MD, Burton AW, Bruehl SP, Carr DB, Harden RN, Hassenbusch SJ, et al. An updated interdisciplinary clinical pathway for CRPS: report of an expert panel. *Pain Pract* 2002;2: 1–16.
- Treede RD, Magerl W. Multiple mechanisms of secondary hyperalgesia. In: Sandkuhler J, Bromm B, Gebhart GF, editors. *Nervous system plasticity and chronic pain, progress in brain Research*, vol. 129. Elsevier: Amsterdam; 2000. p. 331–41.
- Treede RD, Handwerker HO, Baumgartner U, Meyer RA, Magerl W. Hyperalgesia and allodynia: taxonomy, assessment and mechanisms. In: Brune K, Handwerker HO, editors. *Hyperalgesia: molecular mechanisms and clinical implications, progress in pain research and management*, vol. 30. Seattle: IASP Press; 2004. p. 3–15.
- Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. *Neurology* 1998;50: 1837–41.
- Watson CP, Moulin D, Watt-Watson J, Gordon A, Eisenhoffer J. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. *Pain* 2003;105:71–8.
- Yarnitsky D, Eisenberg E. Neuropathic pain: between positive and negative ends. *Pain Forum* 1998;7:241–2.