

ORIGINAL ARTICLE

Oral Opioid Therapy for Chronic Peripheral and Central Neuropathic Pain

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ABSTRACT

BACKGROUND

Although opioids are commonly used to treat chronic neuropathic pain, there are limited data to guide their use. Few controlled trials have been performed, and many types of neuropathic pain remain unstudied.

METHODS

Adults with neuropathic pain that was refractory to treatment were randomly assigned to receive either high-strength (0.75-mg) or low-strength (0.15-mg) capsules of the potent μ -opioid agonist levorphanol for eight weeks under double-blind conditions. Intake was titrated by the patient to a maximum of 21 capsules of either strength per day. Outcome measures included the intensity of pain as recorded in a diary, the degree of pain relief, quality of life, psychological and cognitive function, the number of capsules taken daily, and blood levorphanol levels.

RESULTS

Among the 81 patients exposed to the study drug, high-strength levorphanol capsules reduced pain by 36 percent, as compared with a 21 percent reduction in pain in the low-strength group ($P=0.02$). On average, patients in the high-strength group took 11.9 capsules per day (8.9 mg per day) and patients in the low-strength group took close to the 21 allowed (18.3 capsules per day; 2.7 mg per day). Affective distress and interference with functioning were reduced, and sleep was improved, but there were no differences between the high-strength group and the low-strength group in terms of these variables. Noncompletion of the study was primarily due to side effects of the opioid. Patients with central pain after stroke were the least likely to report benefit.

CONCLUSIONS

The reduction in the intensity of neuropathic pain was significantly greater during treatment with higher doses of opioids than with lower doses. Higher doses produced more side effects without significant additional benefit in terms of other outcome measures.

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OPIOIDS, ALTHOUGH FREQUENTLY PRESCRIBED, remain a controversial treatment for chronic neuropathic pain.¹⁻⁷ Studies in animals and some studies in humans have suggested that chronic neuropathic pain may respond poorly to opioid therapy,^{2,3,8} but placebo-controlled studies of brief intravenous infusions have demonstrated analgesia.^{9,10} Oral controlled-release opioids have been reported to be superior to placebo for postherpetic neuralgia, but the responsiveness to opioids of many types of neuropathic pain, including the pain syndromes that follow central nervous system injuries and are considered to be especially difficult to manage, have not been evaluated in a blinded, prospective manner.^{5,6,11-13}

There are important issues with respect to the design of such trials. First, it is difficult to use a placebo control group, since the patients receiving placebo will have unrelieved chronic pain. In trials in which opioids are active treatments, their side effects can easily reveal the treatment-group assignment to which patients are initially blinded. "Active placebo" agents, such as lorazepam or benztropine, may improve blinding but may produce serious adverse effects, especially in the elderly. Therefore, we took advantage of the dose-dependent nature of opioid analgesia to test efficacy by comparing two different doses under randomized, double-blind conditions in an eight-week study involving patients with neuropathic pain of central or peripheral origin.¹⁴ Within preset limits for capsule intake, patients titrated their own doses to attain the optimal balance between pain relief and side effects. The potent μ -opioid agonist levorphanol was chosen for its six-to-eight-hour duration of analgesic action, relatively simple pharmacokinetics, and receptor selectivity.¹⁴⁻¹⁷

METHODS

STUDY DESIGN

Patients were randomly assigned to receive either low-strength (0.15-mg) or high-strength (0.75-mg) levorphanol capsules. As shown in Figure 1, after a one-week period for the collection of base-line data, patients received levorphanol therapy for eight weeks, after which the doses were tapered over a period of one to four weeks. Within the limits of safety and tolerability, patients could titrate their doses up to 21 capsules per day (7 capsules three times a day) by the end of the fourth week of treatment. Maximal allowable doses were therefore 3.15 mg per day in

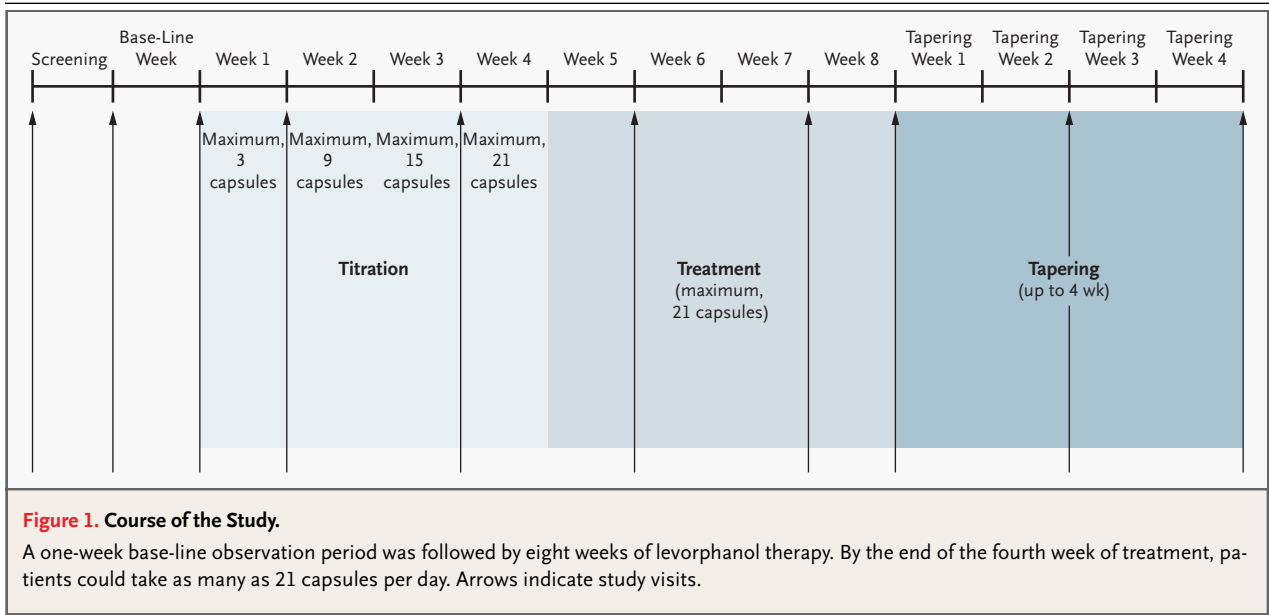
the low-strength group and 15.75 mg per day in the high-strength group. The study was approved by the institutional review board at the University of California, San Francisco, and the California Research Advisory Panel. Written informed consent was obtained from all patients.

STUDY PATIENTS

Adults with neuropathic pain due to confirmed peripheral neuropathy or focal nerve injury, postherpetic neuralgia, spinal cord injury with incomplete myelopathy, central pain following a stroke or focal brain lesion, or clinically definite multiple sclerosis were recruited by advertisements and referrals from physicians. Criteria for exclusion included previous opioid therapy exceeding 360 mg of codeine per day or the equivalent; allergy to levorphanol; another pain problem of equal or greater severity; cognitive impairment; ongoing major depression with a risk of suicide; antisocial or borderline personality disorder; unstable health; clinically significant liver, renal, or pulmonary disease; sleep apnea; active treatment for cancer; immunosuppression due to drugs or disease; current drug or alcohol abuse; and history of opioid abuse. Procedures for screening visits included medical history taking, physical examination, evaluation by a psychologist (including neuropsychological testing and the Structured Clinical Interview of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition),¹⁸ routine hematologic and chemical analyses, and testing of urine for drugs of abuse.

OUTCOME MEASURES

Patients used a daily diary to score their pain daily on a visual-analogue scale labeled "no pain" at 0 mm and "worst pain imaginable" at 100 mm. Each evening, patients rated the average intensity of their pain during the preceding 24 hours.¹⁹ Each patient used a categorized pain-relief scale to score the pain relief achieved since beginning study treatment; on this scale, 0 indicated "worse" pain, 1 "no pain relief," 2 "slight" pain relief, 3 "moderate" pain relief, 4 "a lot" of pain relief, and 5 "complete" pain relief.¹⁹ In addition, patients completed several other assessments at the beginning of the study and thereafter as noted below. These assessments included the Profile of Mood States, which includes 65 items rated from 0 to 4 and scored in terms of total mood disturbance²⁰; the Multidimensional Pain Inventory, a 61-item inventory entailing 13 empirically derived scales and assessing the effect of pain on



quality of life, perceived social support, and ability to engage in daily activities²¹; the Symbol-Digit Modalities Test, which assesses attention or concentration and immediate recall through verbal matching of meaningless geometric designs with a number key²²; and the Opiate-Agonist Effects Scale and Opiate Withdrawal Scale, 16-item and 21-item questionnaires on which patients rate symptoms related to agonist and antagonist activity on a 0-to-4 scale.²³

STUDY VISITS AND TREATMENT

After the screening visit, study visits took place at the start of the base-line week; the beginning of the first, second, fourth, sixth, and eighth weeks of treatment; at the initiation of the tapering of the dose of the study drug; in the middle of the tapering period; and at the end of the study (Fig. 1). Patients kept a daily diary to record their intake of study capsules, their use of concomitant medications, and their daily pain on the visual-analogue scale described above. Patients were contacted by telephone every 7 to 14 days so that investigators could monitor compliance and safety. After complete discontinuation of previous opioid use (if any) for at least one week, the base-line evaluation took place, including repeated urine testing for opioids. Procedures at subsequent study visits included measurement of vital signs, physical examination, review of the daily diary, counting of levorphanol capsules, and the completion of the assessments described above. Pa-

tients began taking the study drug at the visit at the beginning of week 1 if their average daily pain according to the diary scale exceeded 25 mm during the base-line week. They continued to receive all other medical treatments and stable nonopioid therapies for pain, but were not allowed to begin any new treatments for pain.

Randomization was stratified according to sex, age (≤ 70 years or > 70 years), and diagnosis (peripheral neuropathy or focal nerve injury, postherpetic neuralgia, central pain following stroke or focal brain lesion, spinal cord injury, or multiple sclerosis). Low-strength capsules and high-strength capsules were identical in appearance and were packaged in patient-specific bottles. Maximal total daily intake was 3 capsules during week 1 of treatment, 9 capsules during week 2, 15 capsules during week 3, and 21 capsules from week 4 through the end of week 8. The minimal dose was one capsule per day. Throughout the study, patients were encouraged to find the optimal balance between pain reduction and side effects within the limits of the protocol. The visit at the beginning of week 8 also included screening of urine for opioids, an interview with a psychologist, and measurement of the blood levorphanol level.²⁴ On completion of eight weeks of treatment or at the time of withdrawal from the study, patients tapered their dose of levorphanol to zero over a period of one to four weeks.

STATISTICAL ANALYSIS

Base-line demographic variables were compared by Fisher's exact test or an unpaired t-test. The primary outcome measure was the change in the weekly averages of the daily ratings of pain on the visual-analogue scale from the base-line week through the eighth week of treatment before the tapering of the dose of the study drug. The primary outcome meas-

ure of the mean pain ratings for the two treatment groups was tested with the use of a repeated-measures, mixed-effects model for longitudinal data.²⁵ This procedure allowed the use of all data collected from all patients exposed to the study drug without the exclusion of patients from the analysis or the imputation of missing data. As a secondary analysis, we reestimated the model using the base-line scores on the visual-analogue scale as an additional covariate.

Secondary measures analyzed in the group of all patients exposed to the study drug included the category of pain relief (analyzed by unpaired t-test), maximal weekly capsule intake (by unpaired t-test), and change from base line to the last week of treatment for the Profile of Mood States, Symbol-Digit Modalities Test, Opiate-Agonist Effects Scale, and Opiate Withdrawal Scale (all by analysis of covariance). Results on the Multidimensional Pain Inventory were analyzed (by analysis of covariance) only for patients who completed the study (patients who continued therapy with the study drug through week 8). P values of less than 0.05 were considered to indicate statistical significance. No interim analyses were scheduled or performed.

RESULTS**STUDY PATIENTS**

A total of 100 patients were recruited, but 19 did not undergo randomization and did not receive study medication (14 withdrew consent, 1 had pain scores below the minimal level, and 4 were excluded after the psychological evaluation). Of 81 patients who received levorphanol, the 43 randomly assigned to high-strength capsules and the 38 assigned to low-strength capsules were similar with respect to sex, age, race, cause of pain, average daily pain at base line, and duration of pain (Table 1). Twenty-three patients had pain originating in the central nervous system (central pain following stroke or focal brain lesion, spinal cord injury, or multiple sclerosis), and 58 had pain originating in the peripheral nervous system (peripheral neuropathy, focal nerve injury, or postherpetic neuralgia).

In all patients, one or more previous trials of non-opioid medications had failed to relieve the pain. Thirty-seven patients (46 percent) had previously tried low-dose opioids, and in 16 of these patients, the doses of previously used opioids had to be tapered before study entry. There was a trend toward previous use of low-dose opioids in the low-strength

Table 1. Demographic and Base-Line Characteristics of the Patients.*

Characteristic	High-Strength Group (N=43)	Low-Strength Group (N=38)	P Value
Sex (no.)			0.66
Male	20	20	
Female	23	18	
Age (yr)			0.63
Median	65	64	
Range	37–91	32–87	
Race (no.)			0.34
White	37	34	
Other	6	4	
Cause of pain (no.)			0.99
Central nervous system	12	11	
Multiple sclerosis	4	4	
Spinal cord injury	3	2	
Central pain after stroke or focal brain lesion	5	5	
Peripheral nervous system	31	27	
Postherpetic neuralgia	15	11	
Peripheral neuropathy or focal peripheral-nerve injury	16	16	
Intensity of pain at base line†	65.4±18.2	69.3±17.0	0.33
Duration of pain (mo)			0.48
Mean	86	75	
Range	11–387	12–244	
Previous opioid treatment (no.)‡	15	22	0.06
Concomitant medications (no.)§	21	28	0.03
Antidepressants	11	13	0.47
Nonsteroidal antiinflammatory drugs	12	12	0.81
Anticonvulsants	3	8	0.10

* Plus-minus values are means ±SD. P values for comparisons of sex, race, cause of pain, previous opioid treatment, and concomitant medications were determined by Fisher's exact test; P values for comparisons of age, intensity of pain at base line, and duration of pain were determined by unpaired t-tests.

† Intensity of pain was as reported by patients on a visual-analogue scale labeled "no pain" at 0 mm and "worst pain imaginable" at 100 mm.

‡ Data are the numbers of patients who had undergone two or more trials of low-dose-low-potency opioids or patients in whom treatment with opioids had to be stopped before entry in the trial.

§ Concomitant medications include all potentially analgesic medications that patients continued to receive in stable doses during the study.

Figure 2. Time Course of Intensity of Pain as Measured on the Visual-Analogue Scale (Panel A), of Categorical Ratings of Pain Relief (Panel B), and of Capsule Intake per Day (Panel C).

Each week of entries in the diary of pain intensity was averaged. Categorical ratings of pain relief (Panel B) were collected at study visits from weeks 2 through 8. A rating of 0 indicates that pain was “worse,” 1 “no pain relief,” 2 “slight” pain relief, 3 “moderate” pain relief, 4 “a lot” of pain relief, and 5 “complete” pain relief. Pain relief was not significantly greater with the use of high-strength capsules.

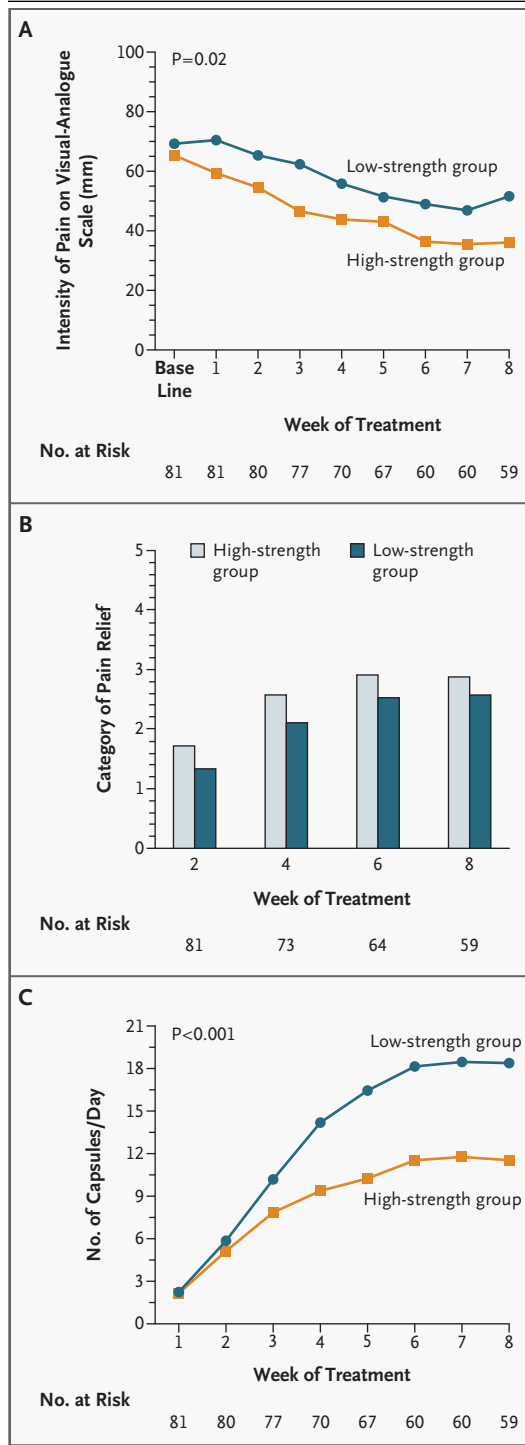
group (P for trend=0.06). Thirty-two patients did not use concomitant medications, and 23 used more than one type of concomitant medications. The most common types of concomitant medications were antidepressants (in 24 patients), nonsteroidal antiinflammatory drugs (in 24 patients), and anticonvulsants (in 11 patients). Although patients in the low-strength group were more likely to use concomitant medications for control of pain ($P=0.03$), the proportion using each specific type of concomitant medication was similar in the two groups.

PRIMARY OUTCOME MEASURE

The intensity of pain as judged by the ratings on the visual-analogue scale during the base-line week was moderately severe in both groups (mean [±SD] in the high-strength group, 65.4±18.2 mm; mean in the low-strength group, 69.3±17.0 mm; $P=0.33$). The degree of reduction of pain was significantly greater in the high-strength group (a 36 percent reduction to 42.1±26.5 mm) than in the low-strength group (a 21 percent reduction to 53.4±24.7 mm, $P=0.02$) (Fig. 2A). The addition of the base-line visual-analogue score as a covariate in statistical models did not alter this result.

SECONDARY OUTCOME MEASURES

Figure 2B shows the time course of categorized ratings of pain relief. Differences between the treatment groups were greatest at the week 2 visit ($P=0.07$) but then declined steadily ($P=0.31$ for the difference at week 8). Among all patients exposed to the study drug in the high-strength group, 47 percent reported pain relief that was moderate or better at the end of treatment. Among those who completed the study taking high-strength capsules, there was a 48 percent reduction in pain, and the proportion reporting pain relief that was moderate



or better was 66 percent. Among all patients who completed the study, the ratio of the mean blood levorphanol level in the high-strength group at week 8 (4.8 ng per milliliter) to the mean level in the low-strength group (1.4 ng per milliliter) closely mirrored the ratio of the actual levels of levorphanol intake.

A total of 59 patients completed eight weeks of levorphanol therapy — 67 percent in the high-strength group and 79 percent in the low-strength group (P=0.32). Patients in the high-strength group took significantly fewer capsules each day (11.9±5.5 vs. 18.3±4.3 capsules per day, P<0.001) (Fig. 2C). Patients assigned to high-strength capsules took a mean dose of 8.9 mg per day, and patients assigned to low-strength capsules took a mean dose of 2.7 mg per day. As shown in Figure 3, there was a broad range of capsule intake in each group, but there was minimal overlap in actual levorphanol intake, since all but six patients in the high-strength group exceeded 3.15 mg per day.

There was no significant change in total mood disturbance (according to the Profile of Mood States) during the study in either treatment group. Cognitive impairment was not apparent, and scores on the Symbol–Digit Modalities Test actually improved in both treatment groups. Although results on the Multidimensional Pain Inventory among patients who completed the study (Table 2) showed significant reductions over the course of the trial in the severity of pain, interference in functioning, and affective distress, as well as a significant improvement in the ability to “get enough sleep,” there were no significant differences between the two treatment groups in terms of any of the scales in the inventory.

The intensity of pain decreased during treatment in every subgroup defined according to the cause of pain (Table 3). The advantage of high-strength capsules over low-strength capsules was most apparent in the subgroups with postherpetic neuralgia, spinal cord injury, and multiple sclerosis. The degree of

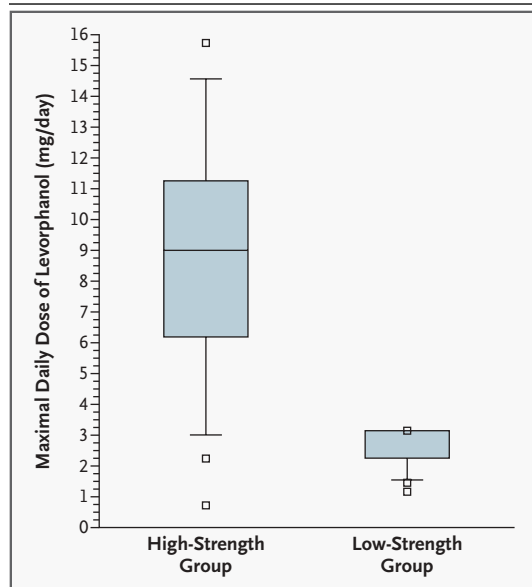


Figure 3. Box Plot of Maximal Daily Dose in All Patients Exposed to the Study Drug.

The lower and upper bars represent the 10th and 90th percentiles, respectively; the lower and upper ends of the box represent the 25th and 75th percentiles, respectively; the line in the box represents the median; and the open squares represent outliers. A total of 23 patients in the low-strength group reached the maximal dose of 3.15 mg per day. The doses of only six patients in the high-strength group overlapped with the range of doses in the low-strength group; these patients took 3 mg of levorphanol per day or less.

Table 2. Results on the Multidimensional Pain Inventory among the 59 Patients Who Completed the Study.*

Scale	Base-Line Week	Week 8
Severity of pain	47.8	35.7†
Interference in functioning	43.5	37.6†
Control of life	51.5	52.2
Affective distress	43.2	39.6‡
Support	47.5	45.5
Punishing responses	51.2	51.3
Solicitous responses	47.3	46.1
Distracting responses	47.8	47.3
Household chores	53.6	54.2
Outdoor work	53.5	55.3
Activities away from home	54.5	53.5
Social activities	50.1	48.9
General activities	54.1	54.1
Ability to get enough sleep	3.5	2.5†

* The Multidimensional Pain Inventory is a 61-item inventory entailing 13 empirically derived scales and assessing the effect of pain on quality of life, perceived social support, and ability to engage in daily activities.

† P<0.001 by analysis of covariance.

‡ P=0.009 by analysis of covariance.

pain reduction during treatment with levorphanol did not vary significantly according to whether patients had previously used opioids or according to whether they used concomitant nonopioid medications. Older age and longer duration of pain were not associated with smaller reductions in pain. Reductions in pain during levorphanol therapy were reversed during the period of tapering of the doses, when patients remained unaware of their treatment-group assignment. By the last seven days of the tapering period, the intensity of pain had returned to 96 percent of the base-line levels. Those who completed the study took an average of 17 days to stop taking levorphanol completely.

WITHDRAWAL FROM THE STUDY AND ADVERSE EVENTS

No base-line measure significantly predicted which patients would withdraw from the study, but 7 of 10 patients with central pain due to a stroke or focal brain lesion did not complete the study. Reasons for

withdrawal from the study included physical or psychological adverse events in 15 patients (12 in the high-strength group and 3 in the low-strength group, P=0.06), treatment failure in 3 patients, lack of adherence to the protocol in 1 patient, and other reasons in 3 patients. According to their self-ratings while they were still taking the study drug, those who later withdrew from the study were less talkative (P=0.001), more restless (P=0.007), and more depressed (P=0.005) than patients who went on to complete the study. At the time of withdrawal from the study, these patients were taking fewer capsules than those who went on to complete the study and had a mean reduction in pain of only 10 percent.

No serious or unexpected drug-related adverse events occurred. One death due to long-standing cardiovascular disease occurred in the low-strength group. Opioid-agonist effects measured on the subscales entitled “Dry Mouth,” “Itchy Skin,” “Sweating,” “Sleepy,” “Noise,” “Carefree,” and “Drunk-en” increased during treatment in both treatment

Table 3. Change in the Intensity of Diary-Recorded Pain as Measured on the Visual-Analogue Scale, According to Diagnosis.*

Group	No. of Patients	Base-Line Week	Last Week before Tapering Began	Percent Reduction from Base Line		
				All Patients	High-Strength Group	Low-Strength Group
<i>mm on visual-analogue scale</i>						
All patients exposed to study drug	81					
Central nervous system						
Central pain after stroke or focal brain lesion	10	67.0	60.1	11	16	6
Spinal cord injury	5	62.6	50.1	23	30	13
Multiple sclerosis	8	60.5	40.3	27	63	-9
Peripheral nervous system						
Postherpetic neuralgia	26	63.1	48.4	25	33	14
Peripheral neuropathy or focal peripheral-nerve injury	32	73.0	44.0	40	39	40
Patients who completed the study	59					
Central nervous system						
Central pain after stroke or focal brain lesion	3	61.9	49.5	20	23	14
Spinal cord injury	4	71.0	57.4	22	31	13
Multiple sclerosis	8	60.5	40.3	27	63	-9
Peripheral nervous system						
Postherpetic neuralgia	18	63.6	48.1	26	42	10
Peripheral neuropathy or focal peripheral-nerve injury	26	74.0	37.6	50	55	46

* The visual-analogue scale was labeled “no pain” at 0 mm and “worst pain imaginable” at 100 mm.

groups. As compared with patients in the low-strength group, those in the high-strength group reported significantly greater effects with regard to “Itchy Skin,” “Sweating,” and “Skin Clammy.” Some adverse effects were reported only by patients in the high-strength group, including anger, irritability, or mood or personality change in six patients, generalized weakness or confusion in five patients, and dizziness or loss of equilibrium in two patients. One patient had suicidal ideation because of worsening pain during the tapering period, and her primary physician decided to continue levorphanol therapy.

DISCUSSION

This double-blind dose–response study demonstrates that the reduction in neuropathic pain achieved with higher doses of the potent opioid levorphanol (through the use of a higher-strength preparation) was significantly greater than the reduction achieved with lower doses (pain reduction, 36 percent vs. 21 percent). Patients randomly assigned to low-strength levorphanol capsules took close to the maximal number of capsules allowed. However, the mean opioid intake in the low-strength group, 2.7 mg per day, is far from a placebo level. In patients receiving repeated doses, 3 mg of levorphanol is equivalent to as much as 45 to 90 mg of oral morphine or 30 to 45 mg of oral oxycodone — the latter being a dose that has been shown in a placebo-controlled study to relieve postherpetic neuralgia.¹²

We chose a dose–response design over a placebo-controlled study for several reasons. Opioids are already an approved therapy for pain, and enrolled patients had severe daily pain originating in the central or peripheral nervous system despite having access to nonopioid medications for pain control. The distinctive side effects of opioids make it difficult to maintain blinding with the use of an inactive placebo, and “active” placebos carry their own risks of adverse effects. Without a placebo control group, the reductions in pain cannot be attributed to the effects of the opioids. The significant differences in pain reduction between the study groups and the return to the base-line levels of pain after the discontinuation of opioid treatment strongly suggest that higher-dose opioids effectively reduce the intensity of chronic neuropathic pain. As compared with a placebo-controlled study, a dose–response study is less able to show differences between treatment

groups in complex measures that may be less responsive to opioid therapy, such as mood and quality of life. In our study, the advantage of high-strength capsules was limited to improved pain reduction.

High rates of withdrawal from the study, mostly because of side effects, have been reported before in studies of opioids for neuropathic pain. In a placebo-controlled crossover trial of oxycodone for postherpetic neuralgia, 24 percent of patients did not complete the trial.¹² Recently, Raja and colleagues compared controlled-release morphine with the tricyclic antidepressant nortriptyline and a placebo in patients with postherpetic neuralgia.¹³ Although pain reduction with morphine was superior to that with placebo, and there was a trend toward superiority to that with nortriptyline, patients in that study were much more likely to withdraw during the opioid-therapy phase. In our study, patients were encouraged to find the optimal balance between pain reduction and adverse effects and could remain in the study by taking as little as one capsule per day. A long titration period and a strict upper limit for capsule intake were used to protect the patients, many of whom were elderly or partially disabled or had not previously taken opioids. Despite these measures, 27 percent of patients withdrew. Furthermore, anger, irritability, and personality changes were reported only by patients in the high-strength group, and more patients in this group withdrew from the study. On the basis of our findings, it is clear that not all patients will benefit from opioids, and some will have worsening of mood and function without relief of pain.

The belief that tolerance to opioid analgesics quickly eliminates any initial analgesic benefit remains widespread.^{26–28} Retrospective and open-label prospective studies have not adequately addressed the important issue of tolerance.^{29–33} Moulin and colleagues compared controlled-release morphine with placebo in 61 patients with musculoskeletal pain.³⁴ Pain reduction of about 25 percent occurred during the initial three-week titration period but was largely lost during the subsequent six-week period of administration of stable doses. In our study, daily capsule intake and ratings of intensity of pain were stable during the last two weeks of therapy, suggesting that there was no tolerance in the form of a loss of analgesic efficacy that might be reflected in a rapid escalation of doses. There was no addictive behavior observed. In fact, only four patients in the high-strength group ever reached

the maximal capsule intake allowed. However, prospective, controlled studies assessing the stability of pain control and dose requirements over periods of many months to years are needed.

The magnitude of the reduction in neuropathic pain achieved with high-strength levorphanol capsules is similar to that reported in placebo-controlled studies of tricyclic antidepressants and the anticonvulsant gabapentin. A placebo-controlled trial of eight weeks of treatment with gabapentin in 229 patients with postherpetic neuralgia reported a 33 percent reduction in the intensity of pain and moderate or better pain relief in 50 percent of patients.³⁵ In our study, which included patients with central pain, the intensity of pain decreased by 36 percent during therapy with high-strength levorphanol, and moderate or better pain relief was achieved in 47 percent of patients. Our results showing a 48 percent reduction in pain and moderate or better pain relief in 66 percent of patients in the high-strength group who completed the study are almost identical to results reported in four con-

trolled trials of tricyclic antidepressants for peripheral neuropathy and postherpetic neuralgia in which only the data from patients who completed the study were analyzed.^{18,36-38} In summary, higher doses of the opioid levorphanol are more effective than low doses in reducing the intensity of chronic neuropathic pain originating in the central or peripheral nervous system, but in many patients, pain relief is not achieved or there are intolerable side effects.

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