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Analgesic tolerance without demonstrable opioid-induced hyperalgesia: A double-blinded, randomized, placebo-controlled trial of sustained-release morphine for treatment of chronic nonradicular low-back pain

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ABSTRACT

Although often successful in acute settings, long-term use of opioid pain medications may be accompanied by waning levels of analgesic response not readily attributable to advancing underlying disease, necessitating dose escalation to attain pain relief. Analgesic tolerance, and more recently opioid-induced hyperalgesia, have been invoked to explain such declines in opioid effectiveness over time. Because both phenomena result in inadequate analgesia, they are difficult to distinguish in a clinical setting. Patients with otherwise uncomplicated low-back pain were titrated to comfort or dose-limiting side effects in a prospective, randomized, double-blind, placebo-controlled clinical trial using sustained-release morphine or weight-matched placebo capsules for 1 month. A total of 103 patients completed the study, with an average end titration dose of 78 mg morphine/d. After 1 month, the morphine-treated patients developed tolerance to the analgesic effects of remifentanil, but did not develop opioid-induced hyperalgesia. On average, these patients experienced a 42% reduction in analgesic potency. The morphine-treated patients experienced clinically relevant improvements in pain relief, as shown by a 44% reduction in average visual analogue scale pain levels and a 31% improvement in functional ability. The differences in visual analogue scale pain levels ($P = .003$) and self-reported disability ($P = .03$) between both treatment groups were statistically significant. After 1 month of oral morphine therapy, patients with chronic low-back pain developed tolerance but not opioid-induced hyperalgesia. Improvements in pain and functional ability were observed.

1. Introduction

Approximately one quarter of U.S. adults reported experiencing back pain during the preceding 3 months [15]. Low-back pain accounts for 25% of work absence in developed countries [25]. In the last 20 years, opioid prescriptions have increased substantially for the treatment of chronic noncancer pain conditions such as low-back pain [7]. Currently, opioids are among the most common medications prescribed by physicians in the USA [31]. Despite this dramatic increase, their use remains controversial within the medical and scientific communities [18,35]. Issues of tolerance and opioid-induced hyperalgesia have further fueled the controversy [8].

A common clinical observation in patients receiving opioid medication is the need to escalate opioid dose over time to maintain adequate analgesia [8,10]. This is commonly attributed to the development of tolerance to the analgesic effects of opioids. However, some evidence suggests that dose escalation could also be due to a separate pharmacologic phenomenon called opioid-induced hyperalgesia [8]. This state is characterized by a paradoxical response in which a patient receiving opioids for pain becomes more sensitive to certain painful stimuli. It is not possible to distinguish between tolerance and opioid-induced hyperalgesia solely based on the clinical observation of the need for dose escalation. Furthermore, although treatment of opioid tolerance usually involves dose escalation, opioid-induced hyperalgesia is treated by dose reduction and initiating alternative analgesic strategies. The prevalence and relevance of these 2 distinct phenomena on the efficacy of chronic opioid therapy for the treatment of chronic painful conditions remain inadequately investigated.

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There is a dearth of high-quality clinical evidence demonstrating analgesic efficacy and the rate of complications associated with chronic opioid use for the treatment of chronic nonradicular low-back pain [13,19,35]. Therefore, we designed a large-scale, double-blind, randomized, placebo-controlled clinical trial to quantitatively measure the development of analgesic tolerance and/or opioid-induced hyperalgesia associated with 1 month of chronic opioid therapy among low-back pain patients who were either opioid naïve or low-dose opioid users. This marks the first large-scale, comprehensive study to directly and quantitatively measure the development of opioid-induced hyperalgesia and opioid analgesic tolerance through changes in pain sensitivity and opioid potency.

2. Methods

2.1. Participants

Adults with moderate to severe chronic nonmalignant low-back pain were recruited by fliers, e-mail, and radio advertisements in the San Francisco Bay area. Eligible patients were between ages 18 and 70 years; diagnosed with chronic nonmalignant, nonradicular low-back pain of at least 6 months duration with a minimum average visual analogue scale (VAS) pain level of 40 (0 = no pain, 100 = worst pain imaginable); and eligible for chronic opioid therapy. Participants were not currently taking opioid pain medication in excess of 30 mg oral morphine equivalents per day, which we defined as low-dose opioid therapy. Patients currently on low-dose opioid therapy were allowed to continue with their normal drug routine; however, they were instructed to refrain from taking their daily pain medication at least 10 hours before any pain testing sessions.

Volunteers completed a questionnaire online or over the telephone as an initial screening procedure. Eligible candidates were subsequently invited for a screening intake examination performed by the principal investigator (L.C.). The intake examinnation consisted of medical history-taking, physical examination, administration of neuropsychological testing (Beck Inventory [5] and Roland-Morris Disability Index [30]), and a pregnancy test, if the subject were female. Additionally, patients were asked about any previous therapy or treatment options pursued before enrollment in our study. Eligible patients must have tried 1 or more therapies, including nonsteroidal anti-inflammatory drugs or low-dose opioids. The screening questionnaire is available in Table 1.

Exclusion criteria included history of substance abuse or severe psychiatric disease, use of medications for neuropathic pain, pain outside the lower back, and neurological conditions interfering with experimental pain testing. Additionally, no patients enrolled in this study were using anticonvulsant or antidepressant drugs; had a history of coronary artery disease or heart attacks; currently had pain outside the region of the low back or had clinically significant health concerns of other sorts, e.g., cancer or liver, renal, or pulmonary conditions, cognitive impairment, major depression, antisocial or borderline personality disorder, sleep apnea, allergy to study medications, or pregnancy.

2.2. Study design

This prospective, randomized, double-blind, placebo-controlled clinical trial was approved by the Stanford University Institutional Review Board and took place at Stanford University from October 2005 through October 2008. This study was registered at ClinicalTrials.gov, number NCT00246532. Patients gave written informed consent and were randomly assigned to receive either sustained-acting morphine (15 mg MS-Contin; Purdue Pharma, Stamford, CT) or weight-matched placebo capsules. Study drugs were over encapsulated in an opaque blinding capsule (DBCaps; Capsugel, Peapack, NJ) to ensure adequate blinding of the study medications.

2.2.1. Study session 1 (S1)

This study session was designed to assess baseline pain sensitivity in the absence of opioid analgesics and to establish a baseline opioid-dose analgesic response relationship before chronic morphine exposure. Patients were instructed to abstain from eating or drinking 8 hours before S1 and to take their last dose of usual pain medication at least 10 hours before S1 (if using pain medications before enrollment in the study).

2.2.2. Initial surveys

At the beginning of the study session, patients completed a series of questionnaires designed to evaluate their mental and physical status before beginning the study procedures. First, patients were asked to rate least, average, and worst daily chronic low-back pain as experienced during the preceding 2 weeks on a 100-mm VAS (0 = no pain; 100 = worst pain imaginable). The Roland-Morris Disability Scale [30] was administered to measure self-rated disability in patients with chronic low-back pain. The scale yields a score between 0 and 24; higher scores indicate more pronounced disability. The Beck Depression Inventory [5] was administered to measure self-rated mental depression. The test yields a single score between 0 to 63; higher scores indicate more severe depression. A questionnaire was given to determine changes in pain sensitivity over the previous 2 weeks.

The presence and degree of opioid withdrawal was also assessed. An Objective Opioid Withdrawal Scale (OOWS) [23] survey was completed by a research assistant trained in evaluation of opioid withdrawal. The OOWS survey evaluates 13 observable physical signs of opioid withdrawal (e.g., piloerection, lacrimation, and yawning). Each item is either rated present (score = 1) or absent (score = 0) over the course of 10 minutes. Finally, the participants completed a Subjective Opioid Withdrawal Scale (SOWS) [23] survey, which evaluates 15 self-reported physical symptoms associated with opioid withdrawal (e.g., perspiration, anxiety, and restlessness). Each item is rated on a 5-point scale (0 = not at all, 4 = extremely), and yields a single score between 0 and 60, with higher scores indicating more pronounced opioid withdrawal.

2.2.3. Pain testing procedures

Patients were trained in cold pressor and heat pain testing. They completed at least 2 training pain assessments, and a test-retest variability of <20% was required before beginning formal pain testing. During each study session, pain sensitivity was first assessed using the cold pressor test and an experimental phasic heat pain model in the absence of any opioid.

Next, a target-controlled infusion with the μ-opioid agonist remifentanil was initiated. A computer-controlled infusion pump (Harvard Apparatus, South Natick, MA) was used to quickly achieve and maintain 3 different random plasma target concentrations consisting of 0 ng/mL and one of the following randomly assigned pairings: 1 ng/mL and 2 ng/mL, or 2 ng/mL and 4 ng/mL. STANPUMP was the software used to drive the pump (S. L. Shafer; available at http://www.anesthesia.stanford.edu). The computer-controlled infusion algorithm has been validated previously [17]. The patient and the clinician performing the testing were blinded to the infusion paradigm. A blinding curtain was drawn as an additional precaution. A sham infusion was run during the 0 ng/mL target to simulate the sound generated by the other 2 Harvard infusion pumps during other infusion periods. An unblinded third investigator was solely responsible for monitoring the patient's wellbeing and controlling the infusions. Each target infusion was maintained for 15 minutes before starting experimental pain testing to allow drug equilibration between plasma and effect site. The

Table 1
Screening questionnaire.

* = Required
1. Please enter your first name.*
2. Please enter your last name.*
3. Please enter your street address (information is confidential).*
4. Please enter your city.*
5. Please enter your state.*
6. Please enter your zip code.*
7. Please enter your email address*
8. Please enter your preferred contact telephone number (information is confidential and will not be shared). Please include your area code.*
9. Please enter a cell phone or alternate contact telephone number (information is confidential and will not be shared). Please include your area code.
10. Where did you hear about our study?*
Word of mouth
Previous study participant told you about the study
Newspaper Advertisement
Google (or online ad)
Saw a flyer at Stanford hospital
Saw a flyer at another hospital
Saw a flyer at a pharmacy
Other (Please Specify)
11. How old are you (years)?*
12. Have you had back pain usually every day for at least the past 6 months?*
Yes
No
13. What is the LEAST amount of back pain you have each day over the last 2 weeks. (0 = no pain to 10 = the worst pain you could imagine).*
14. What is the MOST SEVERE amount of back pain you have each day over the last 2 weeks. (0 = no pain to 10 = the worst pain you could imagine).*
15. What is the AVERAGE amount of back pain you have each day over the last 2 weeks. (0 = no pain to 10 = the worst pain you could imagine).*
16. Are you currently taking prescription pain medicine (e.g. Vicodin, Percocet, Darvocet, Morphine or others)?*
17. Are you currently taking any of the following anticonvulsant or antidepressant drugs?*
I take Gabapentin
I take a Amitriptyline
I take Nortriptyline
I take Desipramine
I take Doxepin
I take Imipramine
I take Trimipramine
No, I do not take any of the following antidepressant or anticonvulsant drugs.
18. Please answer YES if any of the following are true: 1) you have a history of substance abuse, 2) you have peripheral neuropathy (malfunction of the nerves in your arms or legs), 3) you are planning to become pregnant in the next 3 months. Are any of these items TRUE for you?*
Yes
No
19. Do you have a history of heart problems such as coronary artery disease or heart attack?*
Yes
No
20. Even if I am not eligible for this study, I agree to allow the information on this page to be used for research purposes and to be contacted in the future if I later become eligible for other back pain research studies.*
21. I prefer to be contacted by: *
Phone
Email
Postal Mail

opioid-dose analgesic response relationship was determined by repeating quantitative sensory testing of cold pressor and heat pain at each remifentanil target concentration.

During each infusion, the following outcomes were assessed: (1) vital signs, (2) quantitative sensory testing (cold pressor and heat pain test), and (3) associated opioid effects (sedation, euphoria, itchiness, nausea) as assessed on an 11-point scale (0 = not at all, 10 = extremely). Noninvasive blood pressure, arterial oxygen saturation (SaO_2) as measured by pulse oximetry, and 5-lead electrocardiogram were continuously recorded throughout the duration of the study; oxygen was administered via nasal cannula during the remifentanil infusions only; and antinausea medication (metoclopramide) was available by request.

2.2.4. Heat pain test

A thermal sensory analyzer (TSA 2001; Medoc Advanced Medical Systems, Durham, NC) was used to administer heat stimuli via a 3.1-cm^2 thermode in contact with skin of the volar left forearm as described previously [4]. The adaptation temperature of the probe was set at 35°C. The thermode temperature was raised from the adaptation temperature at a rate of 1°C/s until the patient activated the button of a handheld device or the maximum temperature of 52°C was reached. The patient was instructed to activate the button of a handheld device to indicate that the perception of heat had changed to that of pain. This assessment of phasic heat pain threshold was repeated an additional 4 times, and the median temperature inducing pain was recorded. Phasic heat pain tolerance was measured using a similar procedure except that the patient was instructed to activate the button of a handheld device when the pain had become intolerable. The interstimulus interval was 30 seconds. The maximum thermode temperature was limited to 52°C to prevent tissue damage.

2.2.5. Cold pressor test

Immediately after the heat pain test, patients were asked to immerse their right hand up to the wrist into a 0.5°C to 1°C ice water bath continuously recirculated by a submerged pump (Micro-Jet; Aquarium Systems, Mentor, OH) within a 12-L container. Patients were asked to indicate when they first detected pain and to remove their hand when the pain could no longer be tolerated. The time to pain detection (threshold) and to withdrawal of the hand (tolerance) was recorded [9].

2.2.6. End of study and study drug titration

After the final cycle of pain testing, participants completed a survey assessing the perceived difficulty of the study session. Next, patients received an intensive 20-minute educational session instructing them on how to begin study drug titration. Medication diaries were also given at this time to ease the titration process and monitor compliance. Study drug titration proceeded as follows: starting at an oral dose of 1 capsule (15 mg oral morphine or a weight-matched placebo pill) twice per day, followed every 2 days by a dose increase of 1 capsule per day, if tolerated, until (1) adequate analgesia (as determined by the subjects) had been achieved, (2) side effects (severe sedation, nausea or vomiting, constipation, sleep disturbances) limited further titration, or (3) a total of 8 capsules (120 mg/d of oral morphine if on active treatment) had been reached. Patients were contacted by telephone daily for the first 10 days of titration or until adequate and stable dosing was achieved. Patients were contacted at least once per week throughout the duration of the study to ensure strict adherence to the opioid titration protocol, to detect and treat side effects to ensure patient wellbeing, and to adjust study drug dosage in response to patients' self-reported levels of pain relief.

2.2.7. Study session 2 (S2)

This study session was designed to reassess pain sensitivity and opioid dose–analgesic response relationship after 1 month of study drug therapy. All procedures and surveys were identical to those performed and administered during S1. After the final cycle of pain testing, participants completed a survey assessing the perceived difficulty of the study session and guessing the identity of their study drug medication (morphine vs placebo). Next, patients received an intensive 20-minute educational session instructing them on how to taper off of the study drug. Remaining pills were counted and recorded. An individualized tapering plan was designed based on the pill count. Patients were tapered off of their treatment to 0 capsules per day over a 10-day period with a dose decrease of 1 capsule every 2 days. Patients were contacted by telephone daily to monitor side effects and patient health until the patient reached 0 capsules per day.

2.2.8. Follow-up

Patients were asked to complete an online follow-up survey approximately 1 year after study participation. This survey asked about current pain levels and medication use.

2.2.9. Morphine and morphine metabolite assay

Patients abstained from taking both their normal pain medication, if applicable, and the study drug at least 10 hours before a study session. Five milliliters of venous ethylenediaminetetraacetic acid blood was collected, centrifuged, and plasma stored at 20°C until further processing. Trough plasma concentrations of morphine, morphine-3-glucuronide, and morphine-6-glucuronide were measured using a validated semi-automated liquid chromatographic tandem mass spectrometric assay (LC-MS/MS assay) for the simultaneous quantification of morphine and its active metabolites morphine 3β -glucuronide (M3G) and morphine 6β-glucuronide (M6G) in human plasma. The only manual step was the addition of the protein precipitation solution that contained the corresponding deuterated internal standards for the 3 analytes. The assay had the following performance characteristics: range of reliable response of 0.25 to 1000 ng/mL ($r^2 > 0.99$) for morphine and M3G and of 2.5 to 1000 ng/mL for M6G. Interday accuracies and precisions for morphine (all at 5 ng/mL) were 107% and 9.3%, for M3G were 111% and 1.8%, and for M6G were 95.7% and 4.9%, respectively. There was no carry-over, ion suppression or matrix interferences. The bioanalytics were carried out by Clinical Research and Development (Department of Anesthesiology, University of Colorado, Denver).

2.3. Data analysis

We estimated that we would need to enroll 50 patients in each group for the study to have 80% power to detect a difference between the morphine group and the placebo group of a 30% change in baseline pain sensitivity indicative of opioid-induced hyperalgesia, our primary outcome measure.

2.3.1. Measurement of hyperalgesia

Hyperalgesia was inferred from a reduction of the experimental pain threshold and pain tolerance when comparing measurements (in the absence of remifentanil) taken before and 1 month after starting sustained-acting oral morphine therapy or placebo medication. Within-group comparisons of the degree of change in pain sensitivity from baseline measurements were computed as a paired *t* test of cold pressor time (seconds) or heat pain threshold (°C) within each treatment group. Between-group comparison of the change in pain sensitivity between morphine and placebo treatments was computed using a Student *t* test of 2 independent means of the change score of the outcome measure of interest. Change score was computed by taking the difference in outcome measure before and after 1 month of treatment.

2.3.2. Measurement of opioid tolerance

To measure the development of tolerance to analgesic opioid effects, each patient's remifentanil target concentration vs analgesic effect relationship was determined before and 1 month after starting sustained-acting oral morphine therapy or placebo medication. A change score of each outcome measure before and after 1 month of treatment was computed for each patient at each remifentanil target concentration. Regression analysis was used to fit a curve describing the change in remifentanil dose–analgesic response relationship after treatment. The parameter used to infer tolerance was the slope of the linear regression line, where the null hypothesis (H_0) = β = 0.

2.3.3. Tests of statistical significance

Statistical analysis was performed using SAS for Windows version 9.1 (SAS Institute, Cary, NC). Normality of distribution of outcome measures was determined by Q-Q plot and the Kolmogorov-Smirnov test. Continuous normally distributed variables were compared using paired *t* test and Student *t* test of 2 independent means for matched and independent sample comparisons. Discrete outcome measures were analyzed using χ^2 or Fisher exact test. Skewed variables were analyzed using nonparametric techniques, including Mann-Whitney *U* test for independent samples and Wilcoxon signed-rank test for matched samples. Regression analysis was performed using general linear models methods with SAS proc GLM. Post-hoc power analysis for opioid-induced hyperalgesia was computed using Student *t* test of 2 independent samples, assuming α = .05. A value of $P \leqslant .05$ was considered statistically significant. Data are expressed as the mean and the standard deviation. All data were analyzed by the principal investigator (L.C.).

3. Results

3.1. Patient population

A total of 683 patients were assessed for eligibility; 544 were excluded. Of the 139 randomized patients, 69 were allocated to the morphine group and 70 were allocated to the placebo group. See the Appendix for the CONSORT diagram [26]. Patients in both groups were similar with respect to sex, age, weight, height, body mass index, and race (Table 2). Patients in both groups reported similar baseline average VAS pain scores (49.5 ± 14.7 for morphine; 50.2 ± 14.8 for placebo; $P = .77$; Table 2). All patients enrolled were

diagnosed with chronic nonmalignant, nonradicular low-back pain; either opioid-naïve or using pre-existing low-dose opioid therapy (<30 morphine equivalent mg/d); between the ages of 18 and 70 years; and eligible for opioid therapy as determined by the treating physician.

A total of 103 patients completed the study. Primary reasons given by patients who withdrew from the study were significantly different between groups ($P = .03$). The complete list of discontinuation reasons are given in Table 3. Patients explored an average of 3 therapies before enrolling, with no significant difference between groups ($P = .41$). All therapies explored are listed in Table 4.

Among all patients allocated to treatment groups, 12 patients from each treatment group were already taking low-dose opioids at daily dosages of 10.2 ± 7.9 morphine equivalent mg/d in the morphine group and 9.5 ± 6.1 morphine equivalent mg/d in the placebo group (Table 2). Treatment groups did not differ with respect to pre-existing opioid dose ($P = .80$; Table 2) or type of opioid used ($P = .46$; Table 2). The majority (83%) of patients allocated to treatment groups in this study were not currently using opioids at the time of enrollment in our study. The prevalence of pre-existing low-dose opioid use at the time of enrollment did not differ between treatment groups ($P = 1$). The patients reported similar baseline Beck Depression Inventory scores (6.19 ± 5.9 for morphine and 7.12 ± 5.1 for placebo; $P = .32$; Table 2) and baseline Roland-Morris Disability Index scores (7.07 ± 4.7 for morphine and 7.57 ± 4.6 for placebo; $P = .54$; Table 2).

3.2. Primary outcome measures

3.2.1. Opioid-induced hyperalgesia

After 1 month of study medication treatment, the degree of opioid-induced hyperalgesia as measured by changes in baseline pain sensitivity was negligible in both groups, and there was no significant difference between groups.

Table 3
Primary reasons for discontinuation.

Reason for discontinuation	Morphine	Placebo
Pain testing too painful	3	1
Unable to complete test due to anxiety	1	2
Study drug titration failure*	10	1
Nausea during testing	0	5
Lightheadedness and sweating during remifentanil infusion	0	1
Stopped taking meds on own	0	2
Crying during reminfentanil infusion	1	0
Heart attack	1	0
Didn't want to complete titration diaries	1	0
Didn't want to come back for session 2	1	2

* The patient developed side effects or other problems, and opioid therapy was discontinued.

Table 4
Alternate therapies previously explored by patients.

Previous Explored Therapies	Number of Patients
NSAIDS	117
Physical Therapy	71
Opioid Therapy	68
Chiropractic Treatment	61
Acupuncture	34
Pool Therapy	26
Steroid Injections	18
Massage Therapy	10
RF Ablation and Electrostimulation	5

When tested at the second session, patients did not demonstrate significant changes in cold pain tolerance ($P = .15$ for placebo; $P = .87$ morphine) or heat pain tolerance ($P = .50$ placebo; $P = .08$ morphine). Percent changes in heat pain tolerance and threshold were calculated using a degrees Celsius temperature

Table 2
Demographic and baseline characteristics of the patients.

Characteristic	Morphine Group (N = 69)	Placebo Group (N = 70)	P Value
Sex (no.)			
Male	44	34	.14
Female	25	36	
Age (yr)			.39
Mean	44 ± 14.2	46 ± 13.5	
Weight (kg)	83.30 ± 18.8	84.28 ± 18.4	.76
Height (m)	1.71 ± 0.10	1.70 ± 0.10	.51
Body Mass Index	28.03 ± 5.1	29.07 ± 5.7	.38
Race (no.)			
Caucasian	46	45	
African-American	3	11	.13
Asian	9	7	
Hispanic	11	7	
Baseline Average Pain*	49.5 ± 14.7	50.2 ± 14.8	.77
Pre-existing Opioid Therapy (no.)	12	12	1
Average Pre-existing Opioid Dose Among All Patients (morphine equivalents mg/day)	1.78 ± 5.04	1.63 ± 4.33	.85
Average Opioid Dose Among Pre-existing Opioid Users Only (morphine equivalents mg/day)	10.2 ± 7.9 (n = 12)	9.5 ± 6.1 (n = 12)	.8
Pre-existing Opioid Treatment (no.)			
Vicodin	7	6	
Percocet	2	1	.46
Darvocet	0	3	
Tylenol No. 3	2	1	
Norco	1	1	
Baseline Beck Depression Inventory†	6.19 ± 5.9	7.12 ± 5.1	.32
Baseline Roland-Morris Disability Index‡	7.07 ± 4.7	7.57 ± 4.6	.54

Note: Values are mean ± SD. *P* values for comparisons of gender, ethnicity, and concomitant medications were determined by χ^2 test. *P* values for age, weight, height, body mass index, baseline average pain, average low-dose opioid therapy, baseline Beck Depression Inventory, and baseline Roland-Morris Disability Index were computed using Student *t* test of 2 independent means.

* 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.

† Beck Depression Inventory [23] is a single score between 0 to 63: 0 to 13 = normal, 14 to 19 = mild depression, 20 to 28 = moderate depression, and 29 to 63 = severe depression.

‡ Roland-Morris Disability Index [1] yields a score between 0 and 24; 0 = no disability and 24 = severe disability.

Table 5
Primary outcome measure opioid-induced hyperalgesia (normalized–paired analyses).

Outcome	Morphine (N = 48)	*P* Value	Placebo (N = 55)	*P* Value	Group Effect *P* Value
%Δ in Cold Pressor Tolerance at Remi = 0	2.33 ± 94.7	.87	−6.0 ± 30.5	.15	.56
%Δ in Cold Pressor Threshold at Remi = 0	−13.2 ± 31.3	**.005**	−7.9 ± 34.2	.09	.42
%Δ in Heat Pain Tolerance at Remi = 0	0.58 ± 2.3	.08	0.25 ± 2.8	.5	.52
%Δ in Heat Pain Threshold at Remi = 0 (%)	1.8 ± 6.1	**.05**	2.1 ± 5.4	**.006**	.79

Remi = remifentanil.

rating. Percent changes in cold pain tolerance and threshold were calculated using difference in time (seconds). Differences between changes in cold pressor tolerance ($P = .56$) or heat pain tolerance ($P = .52$) were not statistically significant between groups.

Although patients in each treatment group had significant changes in pain threshold from baseline, there were no significant differences in the changes between the 2 groups. Patients assigned to the placebo group demonstrated an 8% decrease in cold pressor threshold ($P = .09$) between sessions and a 2% increase in heat pain threshold ($P = .006$) after 1 month (Table 5). Patients assigned to the morphine group demonstrated a 13% decrease ($P = .005$) in cold pressor threshold and a 2% increase in heat pain threshold ($P = .05$) from baseline. The differences between changes in cold pressor threshold ($P = .42$) and heat pain threshold ($P = .79$) were not statistically significant between groups.

3.2.2. Analgesic tolerance

We detected a significant degree of opioid analgesic tolerance in patients exposed to chronic morphine therapy compared with control subjects after 1 month of study drug therapy. The placebo group did not demonstrate significant changes after 1 month of study drug, as evidenced by an extremely small $\beta_{remifentanil}$ of −0.6 ($P = .82$), where null hypothesis (H_0) = $\beta_{remifentanil} = 0$ (Fig. 1). In contrast, patients taking oral morphine therapy demonstrated a significant decrease in their responsiveness to remifentanil, with a $\beta_{remifentanil}$ of −11.9 ($P < .001$). Furthermore, patients on the morphine therapy in the 4 ng/mL target plasma concentration remifentanil group experienced a 42.7% decrease in analgesic potency, compared with a 2.6% increase in placebo patients ($P = .005$). If we take $\beta_{remifentanil}$ as a measure of analgesic tolerance, where $\beta_{remifentanil} = 0$ indicates no analgesic tolerance, then patients in the morphine group were significantly more tolerant to the analgesic effects of remifentanil than placebo patients, as measured by cold pressor tolerance, after 1 month of oral morphine therapy. We also reanalyzed the analgesic tolerance data excluding patients with opioid use at the time of study enrollment. Results of this subgroup analysis were consistent with results reported for all patients.

3.3. Secondary outcome measures

3.3.1. Roland-Morris Disability Index

The degree of self-reported disability decreased significantly in the morphine group over time, whereas there was no significant change from baseline in the placebo group. After the 1-month study drug treatment regimen, patients in the morphine group could not perform 2.02 ± 3.06 tasks out of 24 on average, which represented a 31% improvement from baseline disability levels—a highly significant difference ($P < .001$; Table 6). The placebo group experienced a small, 6% improvement in ability, which was not significant compared with baseline ($P = .37$; Table 6). When comparing the changes between the 2 treatment groups, the morphine group had a significantly greater reduction in disability when compared with placebo ($P = .04$; Table 6).

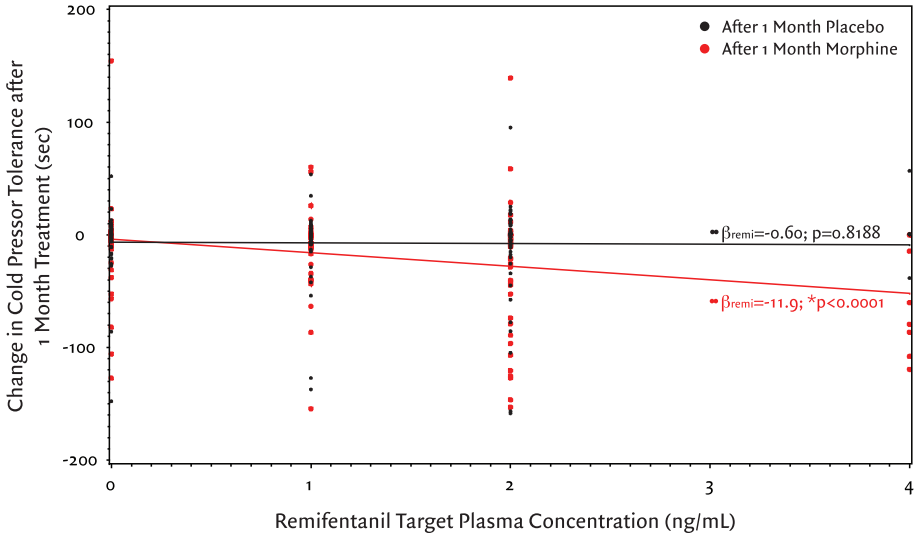

Fig. 1. Analgesic tolerance but no opioid-induced hyperalgesia after 1 month of oral morphine therapy. This randomized, double-blind, placebo-controlled study examined changes in opioid responsiveness over time in opioid-naïve chronic pain patients before and after 1 month of oral morphine (N = 48) vs placebo therapy (N = 55). The mean dose of oral morphine was 78 mg/d. There was no significant difference in the y-intercept after oral morphine therapy ($P = .63$) or placebo ($P = .11$), indicating the absence of opioid-induced hyperalgesia. The remifentanil dose–analgesic response relationship did change very significantly in the morphine group (−11.9β, $P < .001$), whereas this change did not occur in the placebo group (−0.60β, $P = .82$). The difference between the 2 regression coefficients was −11.33, which represents a significant decrease for this parameter in the morphine users compared with the placebo group ($P < .01$).

Table 6
Secondary outcome measures.

Outcome	Morphine (N = 48)	*P* Value*	Placebo (N = 55)	*P* Value*	Group Effect *P* Value†
Δ Least VAS Pain‡	15.2 ± 15.9	**<.001**	8.5 ± 16.5	**<.001**	**.04**
Δ Average VAS Pain‡	21.1 ± 15.9	**<.001**	12.5 ± 19.2	**<.001**	**.02**
Δ Worst VAS Pain‡	26.7 ± 19.3	**<.001**	16.3 ± 22.4	**<.001**	**.01**
Δ Roland-Morris Disability Index§	2.02 ± 3.06	**<.001**	0.51 ± 4.14	.37	.04
% Δ Beck Depression Inventory¶	-13 ± 87.6	.32	5.8 ± 101.4	.67	.32

Note: Values are mean ± SD.
VAS = visual analogue scale.
* *P* value computed as a 1-way *t* test of percent change in outcome measure from baseline measurement (Δ) where the null hypothesis (H_0) = Δ = 0.
† *P* value computed as a Student *t* test of 2 independent samples of percent change in outcome measure from baseline measurement (Δ) where null hypothesis (H_0) = $\Delta_{morphine} = \Delta_{placebo}$.
‡ 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. Δ VAS pain scores = $VAS_T = _0 - VAS_T = 1$ month.
§ Roland-Morris Disability Index yields a score between 0 and 24; higher scores indicate more pronounced disability. Δ Roland-Morris Disability Index = $RMD_T = _0 - RMD_T = 1$ month.
¶ Beck Depression Inventory is a single score between 0 to 63; higher scores indicate more severe depression. Δ Beck Depression Inventory = $Beck_T = _0 - Beck_T = 1$ month.

Table 7
OOWS survey results.

	Placebo	Morphine	Group Effect *P* Value*
Session 1	0.09 ± 0.35	0.1 ± 0.37	.85
Session 2	0.05 ± 0.3	0.13 ± 0.33	.26
Δ	0.04 ± 0.47	-0.02 ± 0.43	
P Value†	.57	.74	

Note: The OOWS survey evaluates 13 observable physical signs of opioid withdrawal (e.g., piloerection, lacrimation, and yawning). Each item is either rated present (score = 1) or absent (score = 0) over the course of 10 minutes, and yields a single score between 0 to 13; higher scores indicate more pronounced opioid withdrawal. Values are mean ± SD.
* *P* value computed as a *t* test of 2 independent means between the morphine and placebo groups.
† *P* value computed as a within-group paired *t* test between session 1 and session 2.

3.3.2. Beck depression inventory

No significant changes after 1 month of study drug therapy were observed in psychological state and mood as measured by the Beck Depression Inventory within the morphine group (*P* = .32) or the placebo group (*P* = .67; Table 6). Additionally, the differences in change from baseline depression scores between the 2 treatment groups were not significant (*P* = .32; Table 6).

3.3.3. OOWS and SOWS

Patients did not show any clinically significant signs of withdrawal during study sessions. This was not significantly different between S1 and S2, neither for the morphine group (*P* = .74) nor for the placebo group (*P* = .57; Table 7). In addition, the differences between groups were not significantly different at baseline (*P* = .85) or after 1 month of study drug administration (*P* = .26; Table 7).

There were no clinically significant changes after 1 month of study drug therapy observed in the SOWS score within the morphine group (*P* = .48; Table 8) or the placebo group. There was a small 1.5-point reduction in SOWS (out of a total of 60 possible points) at the 1-month time point in the placebo group, but this was not clinically significant, although it reached statistical significance (*P* = .002; Table 8). In addition, the differences between groups were not significantly different at baseline (*P* = .36) or after 1 month of study drug (*P* = .47; Table 8).

Table 8
SOWS survey results.

	Placebo	Morphine	Group Effect *P* Value*
Session 1	4.78 ± 3.20	4.28 ± 3.16	.36
Session 2	3.25 ± 3.24	3.78 ± 4.09	.47
Δ	1.54 ± 3.45	0.43 ± 1.64	
P Value†	.002	.48	

Note: The SOWS survey evaluates 15 self-reported physical symptoms associated with opioid withdrawal (e.g., perspiration, anxiety, and restlessness). Each item is rated on a 5-point scale (0 = not at all, 4 = extremely), and yields a single score between 0 and 60, with higher scores indicating more pronounced opioid withdrawal. Values are mean ± SD.
* *P* value computed as a *t* test of 2 independent means between the morphine and placebo groups.
† *P* value computed as a within-group paired *t* test between session 1 and session 2.

3.3.4. Pain intensity

The intensity of pain as reported by least, average, and worst VAS pain levels over the preceding 2 weeks decreased in both treatment groups; however, there was a greater VAS_{Ave} reduction in the morphine group (44%, *P* < .001; Table 6) than the placebo group (23%, *P* < .001; Table 6). Although both treatment groups demonstrated improved pain relief at the end of the 1-month therapy, the morphine group had significantly greater pain relief when compared with that of the placebo group (*P* = .02; Table 6). Similarly, this effect was observed for both VAS_{Least} pain scores and VAS_{Worst} pain scores. Both treatment groups had significant reductions in VAS_{Least} and VAS_{Worst} pain at the end of the 1-month treatment course (Table 6). However, the degree of pain relief was significantly larger in the morphine group when compared with that of the placebo group for both VAS_{Least} pain (*P* = .04) and VAS_{Worst} pain (*P* = .01; Table 6).

3.3.5. Opioid titration

The mean number of pills used during the study numbered 140.8 ± 57.4 for the morphine group and 191.1 ± 33.8 for the placebo group, and this difference was significant between groups (*P* < .001; Table 9). After approximately 1 month of treatment, the average daily dose for the morphine group was 5.22 ± 2.5 pills per day (78.3 ± 37.5 mg morphine/d) and for the placebo group was 7.76 ± 0.98 pills per day (*P* < .001).

The average length of treatment days was not significantly different between the 2 groups (31.52 ± 3.1 for morphine; 30.89 ± 2.2 for placebo; *P* = .24). The reasons for selecting the final dose of study drug medication at the end of titration differed between groups. Distributions of reasons for selecting this final daily dose were significantly different between treatment groups (*P* < .001). Weight, age, gender, and baseline average VAS pain scores were examined as covariates in our statistical model and were not found to be significant predictors of total number of study drug pills used throughout the study.

Table 9
Study drug treatment.

Outcome	Morphine (N = 48)	Placebo (N = 55)	Group Effect *P* Value
Total Pills Used After 1 Month (no.)	140.8 ± 57.4	191.1 ± 33.8	**<.001**
Dose of Study Drug Achieved at S2 (no. capsules/day)	5.22 ± 2.5	7.76 ± 0.98	**<.001**
Dose of Morphine Achieved at S2 (mg/day)*	78.3 ± 37.5	N/A	N/A
Average Daily Dose Morphine During Treatment (mg/day)†	67.87 ± 28.8	N/A	N/A
Average Length of Treatment (days)	31.52 ± 3.1	30.89 ± 2.2	.24
Reason for Achieving Final End Titration Dose (number of patients and % of patients)‡			
Pain Well-controlled	13 (27%)	5 (9%)	
Dose Escalation Limited by :			
Pruritis	1 (2%)	0	
Nausea	4 (8%)	0	**<.001**
Constipation	5 (10%)	1 (2%)	
Sedation	8 (17%)	1 (2%)	
Dry Mouth	0	1 (2%)	
Reached Maximum Study Dose	15 (31%)	47 (85%)	
Anxiety	1 (2%)	0	
Erectile Dysfunction	1 (2%)	0	

Note: Values are mean ± SD. *P* values for comparisons of gender, ethnicity, and concomitant medications were determined by χ^2 test. *P* values for Total pills used, Dose of study drug achieved at S2, and Average length of treatment were computed using Student *t* test of 2 independent means.
N/A = not applicable.
* Dose of morphine achieved at S2 is the number of capsules reached at end titration multiplied by the oral morphine dose per capsule (15 mg).
† Average daily dose of morphine during treatment was computed by multiplying the total number of pills used after 1 month by the oral morphine dose (15 mg). That number was then divided by the average length of treatment to yield the average daily morphine dose during treatment.
‡ At S2, patients were asked to pick a reason from the list given above for the achievement of their final end titration dose.

Table 10
Follow-up survey results.

Treatment Group	Number of Respondents	Average VAS Pain	Number of Patients Currently Using Opioids	% Patients Currently Using Opioids	% Patients Currently Not Using Opioids	Group Effect *P* Value
Placebo	20	4.1	8	40%	60%	*P* = .034
Morphine	28	3.4	3	11%	89%	
Total	48	3.75	11	23%	77%	

Table 11
Plasma morphine and morphine metabolite concentrations.

		Morphine	Morphine-3-glucuronide (ng/mL)	Morphine-6-glucuronide (ng/mL)
Placebo	Session 1	0 (0)	0.50 (2.39)	4.09 (29.94)
	Session 2	0 (0)	0.42 (1.93)	0 (0)
Morphine	Session 1	0.03 (0.21)	2.67 (17.13)	1.18 (8.29)
	Session 2	2.79 (2.73)	151.8 (149.1)	47.94 (56.61)

Note: Values are mean ± SD.

3.3.6. Follow-up survey

Patients were surveyed a minimum of 1 year after study participation; 48 patients responded to the survey request; 11% of patients from the morphine group and 40% of patients from the placebo group were currently using prescription opioid medications for pain management. Patients who received morphine were significantly less likely than those who received placebo to be using opioid pain medications after study completion, despite the persistence of their low-back pain (*P* = .034; Table 10). Our data show that in 89% of cases, morphine patients chose not to continue with long-term use of opioid pain medications after the study.

3.3.7. Morphine plasma concentrations

Patients assigned to the placebo group had a plasma morphine concentration of 0 ng/mL at baseline and 1 month after initiating study drug administration (Table 11). Patients assigned to the morphine group had a plasma morphine concentration of 0.03 ng/mL at baseline and a concentration of 2.79 ng/mL after 1 month of study drug administration (Table 11).

4. Discussion

Although often successful in acute settings, long-term use of opioids may be accompanied by waning levels of analgesic response not readily attributable to advancing underlying disease, necessitating dose escalation to manage pain. Analgesic tolerance and opioid-induced hyperalgesia have been invoked to explain such declines in opioid effectiveness over time. Because both phenomena result in inadequate analgesia, they are difficult to distinguish in a clinical setting. Moreover, analgesic tolerance requires dose escalation, whereas opioid-induced hyperalgesia requires dose reduction and alternative analgesic strategies. Although in clinical practice chronic pain patients stand to gain the most from chronic opioid therapy, neither tolerance nor opioid-induced hyperalgesia have been carefully evaluated in this patient population [8].

Our results suggest that opioid-naïve, chronic low-back pain patients maintained on oral morphine therapy for 1 month developed analgesic tolerance to opioids but did not develop opioid-induced hyperalgesia. Patients exposed to morphine at an average dose of

78 mg/d experienced a statistically significant tolerance to the analgesic effects of remifentanil, as measured by the cold pressor test, when compared with placebo patients. These results are in agreement with those of a small pilot study in which 6 patients developed tolerance after 1 month of oral morphine therapy at an average dose of 75 mg/d [9].

We also analyzed analgesic tolerance data by excluding patients with low-dose opioid use at the time of study enrollment. Results of this subgroup analysis were consistent with results obtained in all study subjects. Because we did not assess the duration of opioid exposure in patients on low-dose opioid therapy before study enrollment, potentially confounding effects of opioid therapy duration could not be evaluated.

Although the development of analgesic tolerance was observed in our study, our chronic pain patients did not develop opioid-induced hyperalgesia, based on insignificant changes in their tolerance of cold pain and heat pain taken at baseline and after 1 month of oral morphine therapy. The morphine patients did demonstrate significant changes in both cold pressor and heat pain threshold; however, these results were not statistically significant between groups. Thus, we conclude that opioid-induced hyperalgesia was not observed in this study. It should be recognized that cold pressor testing has been the pain test most commonly used to detect opioid-induced hyperalgesia in human studies [36].

Our results from this large trial are not in complete agreement with findings from our previous pilot study [9]. In that small clinical trial, morphine patients' cold pressor pain threshold decreased by 16% and cold pressor pain tolerance by 24% after 1 month of oral opioid therapy [9]. The most likely explanations for the 2 studies' discordant results are the preliminary study's small sample size and the lack of blinding or placebo control.

This study marks the first time that opioid-induced hyperalgesia has been prospectively studied in a large-scale, double-blind, clinical trial. Within the context of our studied dose and treatment duration, we did not observe this phenomenon in our patients because they did not experience an increased sensitivity to pain as measured by quantitative sensory testing. These results are consistent with existing literature in chronic pain patients [23,29], but inconsistent with studies involving former opioid addicts on methadone maintenance therapy [11,16], patients exposed perioperatively to opioids [6,21], healthy human volunteers undergoing acute perioperative opioid exposure [3,12], and extensive animal data [2]. These other studies are generally limited by one or more of the following factors: they are retrospective and cross-sectional; opioid addicts may demonstrate increased sensitivity to pain even before initiating drug use [11]; the opioid doses being tested are not clinically relevant for chronic pain patients; or the human laboratory models may only measure secondary hyperalgesia at the site of a pre-existing lesion and may not be clinically relevant for chronic pain patients. Therefore, it is still possible that opioid-induced hyperalgesia exists, just not in the patient cohort and dose regimen we studied.

Our observations do not necessarily discount numerous anecdotal case reports in which opioid-induced hyperalgesia was apparently observed in isolated patients receiving large doses of opioids [14,24,27,32–34,37]. In this study of limited duration (1 month), tolerance rather than hyperalgesia emerged as the more readily identified adaptation. Although opioid-induced hyperalgesia occurring after longer exposure or higher drug doses cannot be ruled out, tolerance might be the more significant problem associated with moderate doses of opioids. Opioid rotation or combination therapies may be beneficial to prevent the development of analgesic tolerance [20]. The development of opioid-induced hyperalgesia may not be a significant clinical concern for doctors prescribing moderate opioid doses for limited periods for chronic noncancer pain.

Although development of opioid-induced hyperalgesia and tolerance were the primary outcome measures of this study, the efficacy of sustained-release morphine for the treatment of chronic low-back pain is also of substantial interest. The morphine group experienced a significant 44% reduction in VAS pain scores after 1 month of oral morphine therapy. These results are similar to other studies examining the use of opioids for the treatment of chronic low-back pain [28]. The placebo group demonstrated a 23% improvement in VAS pain scores after 1 month of study drug treatment. Although these results may be somewhat surprising, a strong placebo effect has been documented in other studies [22,28].

Interestingly, although both groups in our study reported decreased pain scores, only the morphine group experienced improvements in self-reported disability as measured with the Roland-Morris Disability Index. The morphine patients reported a 31% decrease from baseline disability levels, which represents a 5-fold difference from placebo patients, who did not experience significant improvements. In sum, although both groups of patients felt better after 1 month of study drug treatment, only the patients using morphine actually experienced improvements in ability to perform daily tasks such as walking up stairs, getting dressed, or standing for long periods of time. The disparity we observed between improvements in pain vs functionality has been noted in other studies assessing the efficacy of opioids in the treatment of chronic low-back pain [13].

Our finding of a much lower rate of eventual opioid use in patients assigned to the morphine treatment group rather than the placebo group was surprising, but potentially quite relevant. It is not clear what mechanism may account for this observation. However, it should be noted that patients receiving opioids had significant side effect rates. Although pain reduction was observed, perhaps the aversive effects of morphine more than counterbalanced desirable opioid effects. Based on this observation, it may be a useful clinical maneuver to perform drug test titrations coupled with a dose de-escalation trial to allow patients to fully judge the value of opioid therapy for treating their pain. Our data suggest that a trial of opioids concluding with taper from the drugs could provide a useful treatment response screening technique.

Our study provides the first high-quality prospective evidence for the development of tolerance and absence of opioid-induced hyperalgesia after 1 month of chronic opioid therapy. This study is not meant to discount the abundance of data from animals and case studies documenting isolated cases of severe opioid-induced hyperalgesia [8]. Clinicians may still suspect expression of opioid-induced hyperalgesia when opioid treatment becomes entirely ineffective and pain becomes increased and widespread, even in the absence of disease progression [1]. However, our results suggest that tolerance might be a more salient concern in the clinical arena, especially early in the course of chronic treatment. In summary, chronic nonradicular low-back pain patients maintained on sustained-release morphine for 1 month developed analgesic tolerance but did not develop opioid-induced hyperalgesia, and they experienced significant improvements in both pain and disability ratings.

Conflict of interest statement

The authors have no conflict of interest in this study.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2012.02.028.

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