

Adding Ultralow-Dose Naltrexone to Oxycodone Enhances and Prolongs Analgesia: A Randomized, Controlled Trial of Oxytrex

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Abstract: Oxytrex is a novel drug that combines oxycodone with ultralow-dose naltrexone, an opioid antagonist. Ultralow-dose opioid antagonists have been demonstrated to enhance and prolong opiate analgesia and alleviate opioid tolerance and withdrawal in rodents. This 3-week, Phase II clinical trial assessed safety and analgesic efficacy of Oxytrex in patients with moderate to severe pain from osteoarthritis. Patients with a pain score ≥ 5 received placebo, oxycodone 4 times a day (qid), Oxytrex qid, or Oxytrex twice a day (bid). All active treatment groups received the same total daily dose and dose escalation of oxycodone starting at 10 and ending at 40 mg/day. Importantly, the Oxytrex bid group received a lower daily dose of naltrexone than Oxytrex qid (0.002 vs 0.004 mg/day). Oxytrex bid produced a 39% reduction in pain intensity, which was significantly greater than that of placebo ($P < .001$), oxycodone qid ($P = .006$), and Oxytrex qid ($P = .003$). Oxytrex bid was also superior to placebo in quality of analgesia ($P = .002$), duration of pain control each day ($P = .05$), patients' global assessments ($P = .04$), and the Western Ontario and MacMaster Universities Osteoarthritis Index total score ($P = .03$). The incidence of side effects was comparable between active treatments. In this Phase II dose-ranging study, Oxytrex bid demonstrated greater pain relief with a more convenient dosing schedule compared to oxycodone qid.

Perspective: Preclinical data have shown ultralow-dose opioid antagonists to enhance and prolong opioid analgesia while reducing analgesic tolerance and physical dependence. Recent molecular pharmacology data show a mechanism of action to be the prevention of aberrant G protein coupling by opioid receptors that underlies opioid tolerance and dependence.

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Key words: Oxytrex, analgesia, osteoarthritis, oxycodone, naltrexone, opiate.

Osteoarthritis is a progressive disease caused by a breakdown of cartilage in the joints, most commonly the knees and hips. Osteoarthritis currently affects more than 20 million people in the US and is expected to grow dramatically.¹⁹ Anti-inflammatory drugs provide an effective initial treatment. Advanced osteoarthritis is characterized by chronic pain, restricted movement, and functional limitations.¹⁷ Patients with advanced osteoarthritis with moderate to severe chronic pain can require more aggressive drug therapy and are often prescribed opiates. Oxycodone, for example, effectively treats severe pain due to osteoarthritis of the knee or hip.^{18,23} Despite widespread clinical use, opiates are associated with side effects that include nausea, vomiting, pruri-

tus, insomnia, constipation, sedation, and impaired physical function. In addition, long-term opioid treatment can cause opioid tolerance and physical dependence, characterized by withdrawal effects.

Oxytrex (oxycodone + ultralow-dose naltrexone) is being developed as an alternative to oxycodone to treat moderate to severe chronic pain. Oxytrex is intended to improve the therapeutic index of oxycodone by increasing pain relief without increasing side effects. Preclinical data have demonstrated enhanced and prolonged opiate analgesia and the alleviation of opioid tolerance by ultralow-dose opioid antagonists.^{7,20,25,26} Clinical experience with opioid antagonists combined with opiates is limited to case reports and a few small clinical studies.^{2,3,9,10,12} In one case study, a diabetic polyneuropathy patient, who previously had no pain relief from a variety of treatments, reported profound analgesia when 2 μ g/day of naltrexone was added to methadone.⁹ The first controlled clinical study demonstrated an opioid-sparing effect and a reduction in side effects by a continuous infusion of naloxone at 0.25 μ g/kg/h added to morphine administered by patient-controlled analgesia (PCA).¹⁰ In a subsequent study, patients receiving a single 15- or 25- μ g injection of nalmeferene before morphine PCA reported decreased severity of pain 24 hours later and had

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a decreased need for antiemetics and antipruritics.¹² Cepeda et al² were unable to replicate these effects by using a higher dose of naloxone mixed with morphine for PCA. A more recent study by Cepeda et al³ demonstrated a decrease in side effects but no opioid-sparing effect and no enhancement of analgesia.

The present Phase II clinical trial evaluated the safety and efficacy of Oxytrex in 360 patients with moderate to severe chronic pain caused by osteoarthritis of the knee or hip. This 3-week dose escalation study was randomized, double-blinded, active- and placebo-controlled, and conducted at 37 centers. All active treatment groups received the same total daily dose and dose escalation of immediate-release oxycodone starting at 10 mg/day and ending at 40 mg/day, which is a typical daily dose for osteoarthritis patients taking oxycodone. As the oxycodone dose increased, the ratio of naltrexone to oxycodone decreased, because the naltrexone dose was fixed. Because preclinical data have shown ultralow-dose opioid antagonists to markedly prolong the analgesic effect of opiates, we hypothesized that a twice a day (bid) dose regimen of Oxytrex might provide around-the-clock analgesia. The oxycodone active control was administered 4 times a day (qid) because immediate-release oxycodone is only approved for qid dosing, and the half-life does not support less frequent dosing.^{14,21,22} On the basis of unpublished preclinical dose-response data for ultralow-dose naltrexone combined with oxycodone, Oxytrex was formulated to contain 0.001 mg naltrexone. Therefore, the Oxytrex bid group received a total daily naltrexone dose of 0.002 mg/day, whereas the Oxytrex qid group received 0.004 mg/day. These 2 Oxytrex dose regimens also allowed comparison of these 2 different total daily doses of naltrexone.

Materials and Methods

Subjects

Inclusion criteria were as follows: men and women ≥ 18 and ≤ 70 years of age; women who were postmenopausal, physically incapable of childbearing, or practicing an acceptable method of birth control; ambulatory; moderate to severe pain in 1 or more hip or knee joints caused by osteoarthritis for at least 3 months before screening; moderate to severe pain in the hip or knee while taking 1 or more oral analgesic medications in the previous month; a pain intensity score ≥ 5 on an 11-point numeric scale; a mean daily diary overall pain intensity ≥ 5 during the last 2 days of the 4- to 7-day washout period and a confirmatory pain intensity level ≥ 5 measured at the clinic before randomization; able to understand and cooperate with study procedures; and, no pain medications other than study drug during the 3-week treatment period, except for aspirin up to 325 mg/day for cardiovascular prophylaxis.

Patients were excluded for a daily opioid dose equivalent to >20 mg oxycodone for 2 or more days within the previous 4 weeks; administration of an opioid within 72 hours; body weight >300 lb or <100 lb; major surgery within 3 months or planned surgery during the study

period; oral or parenteral corticosteroid therapy within 1 month; intra-articular injection of hyaluronic acid within 9 months; epidural or intrathecal infusion of any analgesic medication within 1 month; female patients who were pregnant or breast-feeding; history of severe hepatic or renal impairment; acute hepatitis; known allergy or significant reaction to any of the study medications; severe impairment of pulmonary function, hypercarbia, hypoxia, significant chronic obstructive airways disease or cor pulmonale, acute or severe bronchial asthma, sleep apnea syndrome or respiratory depression; paralytic ileus, acute abdomen (serious abdominal pain requiring emergency surgery) or delayed gastric emptying; chronic biliary tract disease, chronic pancreatitis, or inflammatory bowel disorders; untreated myxedema, untreated hypothyroidism, elevated intracranial pressure, severe anemia, adrenocortical insufficiency, hypotension or hypovolemia; monoamine oxidase inhibitors, tricyclic antidepressant drugs, serotonin reuptake inhibitors, glucosamine/chondroitin, or St. John's Wort within 4 weeks before receiving study medication (a constant dose for longer than 4 weeks was acceptable); high doses of sedatives, hypnotics, or tranquilizers; phenothiazines or other agents that compromise vasomotor tone; history of alcohol or drug abuse; previous administration of Oxytrex; participation in another investigational drug trial or therapeutic trial within 30 days of the screening visit; and analgesic medication (other than acetaminophen, up to five 500-mg caplets per day) during the 4- to 7-day washout period before randomization. This study was approved by Institutional Review Board of each site, and informed consent was obtained from all study participants.

Treatment Procedures

This study was a randomized, double-blind, placebo- and active-controlled dose escalation trial. Qualifying patients were randomly assigned and stratified by sex to 1 of 4 treatments for 3 weeks (Table 1).

Active treatment groups received the same daily dose of oxycodone, administered either in bid or qid dose regimens, and this oxycodone was immediate-release in all 3 groups. To maintain blinding, each patient took study medication 4 times a day according to the schedule shown in Table 2. Besides the dosing regimen, Oxytrex bid differed from Oxytrex qid by the total daily dose of naltrexone. Each active dose contained 0.001 mg naltrexone, so that the Oxytrex bid group received 0.002 mg/day, and the Oxytrex qid group received 0.004 mg/day. All study medications were identical in appearance, and patients, site personnel, and study monitors were blinded to treatment assignments.

Patients visited the clinic on the first day of weeks 2 and 3, at the end of week 3, and 1 week after the final dose as a post-treatment follow-up. To ensure patient safety, patients were also contacted by telephone on the third and fourth days of week 1, the first day of weeks 3 and 4, and each day for the first 4 days after cessation of treatment.

Efficacy and Functional Assessments

The primary efficacy measure used was the 11-point numeric diary Pain Intensity Scale. Patients were asked to record a numeric score at bedtime each day for the overall pain intensity during the past 24 hours (0, no pain, and 10, severe pain).

Other efficacy assessments, conducted weekly, included (1) quality of analgesia: patients rated pain relief as poor, fair, good, very good, or excellent; (2) pain control, designed to measure both duration and extent of pain control: patients indicated that pain was controlled for a few hours or less each day, several hours each day, most of each day, or throughout each day; and (3) global assessment of study drug: patients gave an overall rating as poor, fair, good, very good, or excellent, taking into consideration the quality of pain relief, side effects, activity level, mood, and sense of well-being in this evaluation.

In addition, responses to the SF-12 Health Survey¹¹ and the Western Ontario and MacMaster Universities (WOMAC) Osteoarthritis Index¹ were collected weekly to assess functional changes during the study.

Safety Assessments

Adverse experiences spontaneously reported by patients or observed by the investigators were recorded at each visit. Clinical evaluations and selected laboratory assessments were performed at baseline and subsequent patient visits. Before dose escalations at the beginning of weeks 2 and 3, opioid toxicity was assessed to assure that each patient was not experiencing serious toxicity.

Statistical Analysis

The primary efficacy variable was the percent change in baseline pain intensity scores. Baseline scores were the mean of the last 2 days of washout, and weekly scores were the mean of the last 2 days of each week of treatment. Both actual values and percent changes from baseline to the end of each week were analyzed by analysis of variance (ANOVA) by using treatment and gender as factors. Pairwise treatment comparisons were performed by using contrasts within the ANOVA framework.

The primary analysis used the last observation carried forward (LOCF) imputation methods for handling missing pain intensity values. When a pain intensity value was missing, such as in the case of early termination from

the study, the missing value was replaced with the last available observed value. To validate the use of the LOCF imputation procedure, 2 additional imputation procedures were evaluated for the analysis of the pain intensity scores. These included (1) replacing a missing value by the mean of the non-missing values for patients in the same treatment group with the same previous non-missing value and (2) replacing a missing value by the mean of the non-missing values for all patients with the same previous non-missing value. An additional post hoc analysis performed for the study was a nonparametric (ranks-based) analysis of pain intensity by week. These analyses were performed after the study data were unblinded.

Results

Disposition of Patients

The study profile is summarized in Fig 1. Of the 362 patients randomized to treatment, 119 patients (32.2%) did not complete the study, and most of these discontinuations (60.5%) occurred during the first week of treatment. The primary reason for discontinuation of study drug in the active treatment groups was adverse events (17% to 31%), predominantly common opioid-related side effects. Inadequate pain relief was the second most frequent reason for discontinuation in the active treatment groups (2.0% to 8.7%) and the primary reason for discontinuation in the placebo group (13.7%). The 1-week post-treatment visit was planned for all patients, including those who terminated study drug early. The percentage of patients who completed this visit was similar across all treatment groups (78.6% to 88.2%).

Randomization produced similar treatment groups with respect to mean age, weight, height, and race distributions. Ages ranged from 21 to 70 years old with a mean of 54.3 years, and the race distribution was 80.8% white, 13.3% black, 4.4% Hispanic, and 0.8% Asian. Stratification ensured equivalent sex distributions, and 69.2% were female.

Although most patients were not previously on opioids, 6.7% were on hydrocodone/acetaminophen, 0.6% were on oxycodone, and 1.9% were on oxycodone/acetaminophen, all fairly evenly distributed across groups. No notable differences were observed in these few patients with prior opioid exposure, and these percentages

Table 1. Treatments

TREATMENT GROUP	WEEK 1		WEEK 2	WEEK 3
	DAYS 1-3	DAYS 4-8	DAYS 1-8	DAYS 1-8
Placebo qid (51 patients)	Placebo qid	Placebo qid	Placebo qid	Placebo qid
Oxycodone qid (102 patients)	Oxycodone 2.5 mg qid	Oxycodone 5 mg qid	Oxycodone 7.5 mg qid	Oxycodone 10 mg qid
Oxytrex qid (104 patients)	Oxycodone 2.5 mg + NTX 0.001 mg qid	Oxycodone 5 mg + NTX 0.001 mg qid	Oxycodone 7.5 mg + NTX 0.001 mg qid	Oxycodone 10 mg + NTX 0.001 mg qid
Oxytrex bid (103 patients)	Oxycodone 5 mg + NTX 0.001 mg bid	Oxycodone 10 mg + NTX 0.001 mg bid	Oxycodone 15 mg + NTX 0.001 mg bid	Oxycodone 20 mg + NTX 0.001 mg bid

Abbreviations: qid, 4 times a day; NTX, naltrexone; bid, twice a day.

Table 2. Daily Dosing Schedule

TREATMENT GROUP	ON WAKING	NOON	AFTERNOON	BEDTIME
Placebo	Placebo	Placebo	Placebo	Placebo
Oxycodone qid	Oxycodone	Oxycodone	Oxycodone	Oxycodone
Oxytrex qid	Oxytrex	Oxytrex	Oxytrex	Oxytrex
Oxytrex bid	Oxytrex	Placebo	Oxytrex	Placebo

Abbreviations: qid, 4 times a day; bid, twice a day.

were too small for tolerance to influence treatment effects. In addition, because each of the 37 sites enrolled less than 10% of the total patient population, this study did not allow meaningful analysis by site. The results of the primary efficacy variable were reviewed by site by using descriptive statistics, and this analysis by site showed results consistent with the overall analysis.

Pain Intensity

Oxytrex bid achieved statistical significance over the other 3 treatment groups in the primary outcome measure of percent change in pain intensity. By week 3, the Oxytrex bid group achieved a 39% reduction in pain intensity from baseline, and this reduction was signifi-

cantly greater than that of placebo (21.5%, $P < .001$), oxycodone qid (24.6%, $P = .006$), and Oxytrex qid (26%, $P = .003$).

The analysis of actual values of pain intensity scores showed that the Oxytrex bid group reported significantly lower pain intensity than all other groups at all time points with the exception of the pairwise comparison to oxycodone at week 1 (Table 3). In this dose escalation study, pain scores decreased over time in all groups. Notably, the differences in pain scores between Oxytrex bid and the other groups were most pronounced at week 3.

Although there was no interaction of the factors treatment and gender, a subgroup analysis of percent reduc-

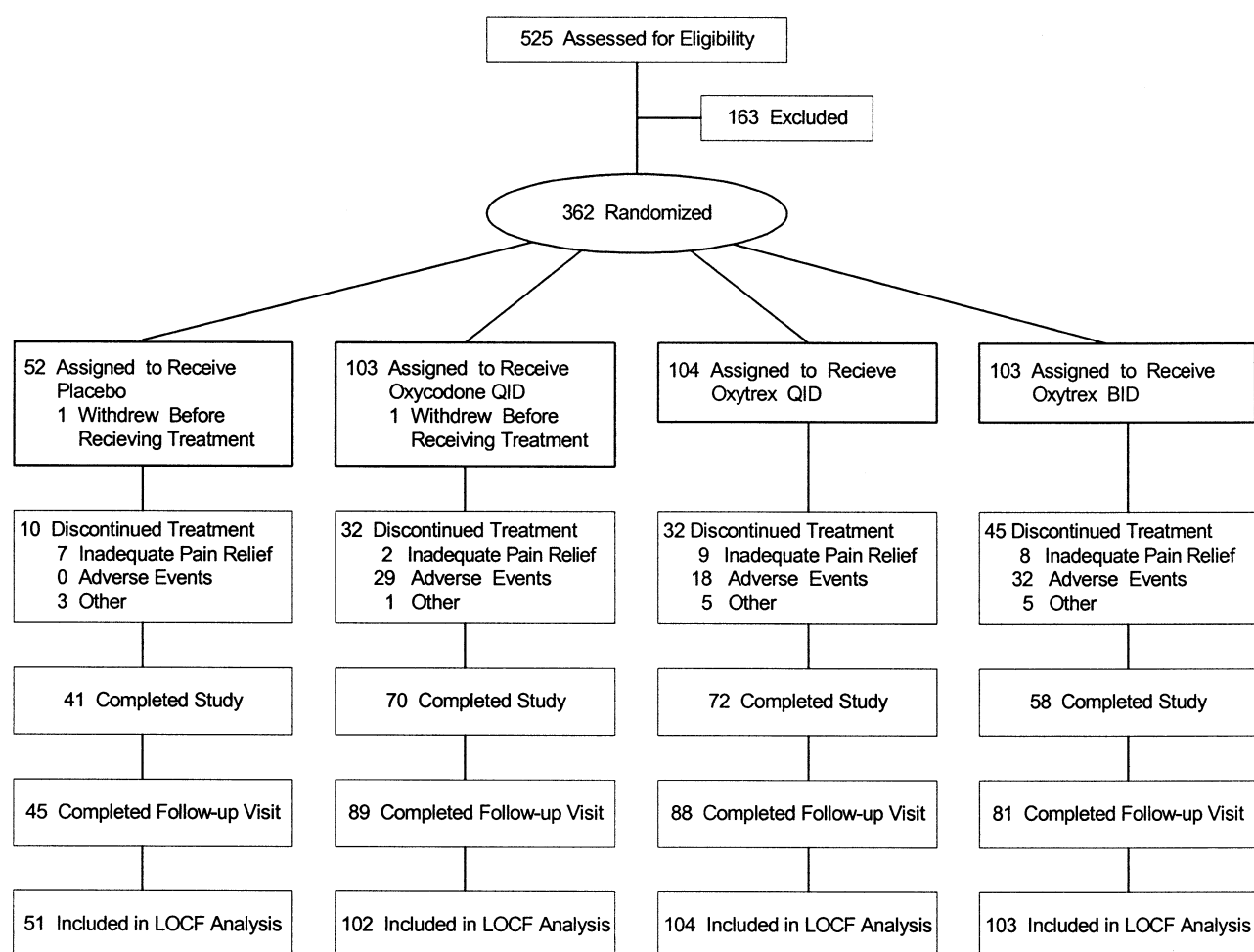


Figure 1. Study flow diagram.

Table 3. Pain Intensity Scores (Mean $\pm$ Standard Deviation)

	PLACEBO	OXYCODONE QID	OXYTREX QID	OXYTREX BID
Baseline	7.7 $\pm$ 1.3	7.4 $\pm$ 1.3	7.7 $\pm$ 1.4	7.6 $\pm$ 1.4
Week 1	6.5 $\pm$ 2.1	6.1 $\pm$ 2.2	6.3 $\pm$ 2.1	5.5 $\pm$ 2.1*
Week 2	6.2 $\pm$ 2.5	5.8 $\pm$ 2.3	6.0 $\pm$ 2.2	5.0 $\pm$ 2.2†
Week 3	6.1 $\pm$ 2.8	5.6 $\pm$ 2.3	5.7 $\pm$ 2.4	4.5 $\pm$ 2.4‡

Abbreviations: qid, 4 times a day; bid, twice a day.

* $P = .01$ vs. placebo.

† $P = .002$ vs placebo and $P = .05$ vs oxycodone.

‡ $P < .0001$ vs placebo and $P = .009$ vs oxycodone.

tion in pain intensity by gender revealed a greater treatment effect in men than in women ($P = .01$ in men vs $P = .056$ in women) (Fig 2). In men, Oxytrex bid was significantly more effective than placebo ($P = .002$), whereas oxycodone showed a trend toward greater pain reduction than placebo ($P = .06$). The difference between Oxytrex bid and oxycodone in men was not statistically significant possibly because of the small number of men in this study. Women did exhibit significantly greater pain reduction from Oxytrex bid than from oxycodone ($P = .007$). However, the larger placebo effect in women resulted in only a slight trend toward greater efficacy of Oxytrex bid compared to placebo ($P = .10$).

As described in Methods, 2 additional imputation methods were used to validate the LOCF procedure for the analysis of pain intensity scores. The results from these analyses were essentially the same as above and confirmed the statistically significant reductions in pain intensity for the Oxytrex bid group. By using the mean among patients in the same treatment group with the same previous non-missing value, the Oxytrex bid group achieved a 42.3% reduction in pain intensity, and this reduction was significantly greater than that of placebo (22.9%, $P < .001$), oxycodone qid (24.1%, $P < .001$), and Oxytrex qid (27.5%, $P < .001$). By using the mean among

all patients with the same previous non-missing value, the Oxytrex bid group achieved a 38.3% reduction in pain intensity that was significantly greater than that of placebo (23.2%, $P < .001$), oxycodone qid (26.5%, $P = .01$), and Oxytrex qid (29.1%, $P = .01$).

Global Assessment

At week 3, the percentages of patients whose global assessments were either excellent or very good were 16.0% for placebo, 19.6% for oxycodone, 22.5% for Oxytrex qid, and 30.4% for Oxytrex bid. Both Oxytrex bid and Oxytrex qid were significantly better than those for placebo in the week 3 global assessment ($P = .04$ and $.05$, respectively). There were no significant group differences at week 1 or week 2.

Quality of Analgesia

At week 3, the percentages of patients assessing quality of analgesia as either excellent or very good were 12.0% for placebo, 19.6% for both oxycodone and Oxytrex qid, and 33.3% for Oxytrex bid. All active treatments were significantly better than placebo on this measure at week 3 ($P = .05$ for oxycodone qid, $P = .03$ for Oxytrex qid, and $P = .002$ for Oxytrex bid). There were no significant group differences at weeks 1 or 2.

Pain Control Assessment

In the week 3 assessments of pain control throughout the day, the percentages of patients reporting that their pain was controlled throughout each day or most of each day were 26.0% for placebo, 34.3% for oxycodone, 37.3% for Oxytrex qid, and 43.2% for Oxytrex bid (Fig 3). Oxytrex bid was the only group significantly better than placebo at week 3 ($P = .05$). Although oxycodone was significantly better than placebo at week 1 ($P = .05$), this treatment was not different from placebo at the later time points.

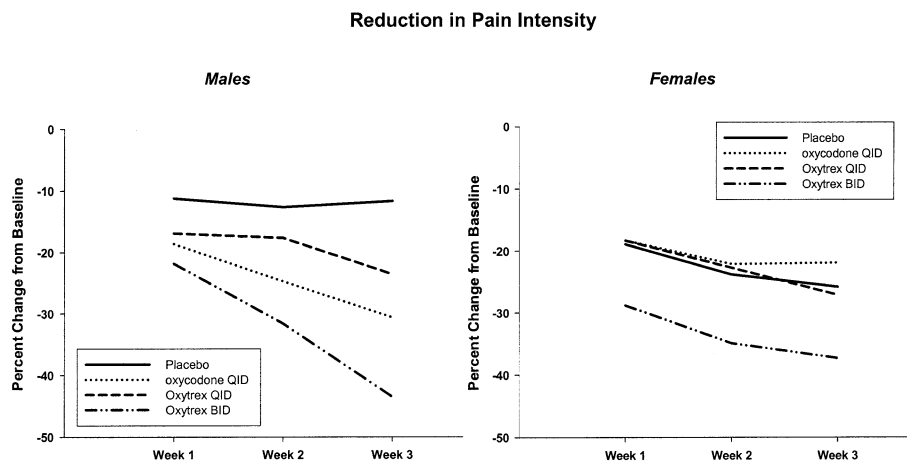


Figure 2. Reduction in pain intensity in men and women. Oxytrex bid provided the greatest reduction in pain intensity scores in both men and women. At week 3, Oxytrex bid was significantly better than placebo in men and significantly better than oxycodone in women.

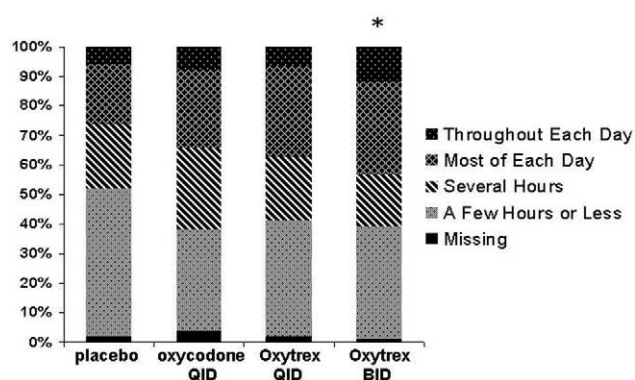


Figure 3. Duration of pain control each day. Oxytrex bid was significantly better than placebo in the assessment of duration of pain control at week 3, indicated by percentages of patients in each level of assessment for each treatment.

WOMAC Index

On the WOMAC osteoarthritis index, the Oxytrex bid group showed greater improvements in each subscale than the other treatment groups, although the differences between Oxytrex bid and oxycodone were not significant. Oxytrex bid was consistently better than placebo at weeks 2 and 3. These week 2 and week 3 differences were seen on the pain subscale ($P = .02$ and $.03$, respectively), as well as the stiffness subscale ($P = .02$ and $.04$), the physical function subscale ($P = .04$ and $.05$), and the WOMAC total score ($P = .02$ and $.04$). By com-

parison, oxycodone was significantly better than placebo on the pain subscale, the physical function scale, and the WOMAC total score, but at week 1 only ($P = .03$, $.03$, and $.04$, respectively).

Adverse Events

No overall trend was observed between the adverse event profiles of active treatment groups, and most adverse events were considered opioid related. The most frequent adverse events were gastrointestinal disorders and nervous system disorders. The most common specific side effects and their ranges in active treatment groups were nausea (24% to 39%), constipation (19% to 22%), and dizziness (26% to 32%). Any adverse event experienced by at least 5% of patients in any treatment group through the follow-up period is listed in Table 4.

Discussion

In this 360-patient, multicenter clinical trial in osteoarthritis, Oxytrex (oxycodone + ultralow-dose naltrexone) administered bid was significantly better than all 3 other treatment groups in percent reduction of pain intensity and actual pain intensity scores by weeks 2 and 3. Despite less frequent dosing, Oxytrex bid was the only treatment with pain control throughout the day significantly better than placebo by week 3. In addition, Oxytrex bid outperformed oxycodone and Oxytrex qid in comparisons to placebo by week 3 on all other measures: global assess-

Table 4. Adverse Events

SYSTEM ORGAN CLASS ADVERSE EVENT	NUMBER (%) OF PATIENTS			
	PLACEBO (N = 51)	OXYCODONE QID (N = 102)	PTI-801 QID (N = 104)	PTI-801 BID (N = 103)
Gastrointestinal disorders	12 (23.5)	54 (52.9)	57 (54.8)	62 (60.2)
Abdominal pain upper	2 (3.9)	4 (3.9)	4 (3.8)	7 (6.8)
Constipation	4 (7.8)	19 (18.6)	23 (22.1)	18 (17.5)
Diarrhea	4 (7.8)	9 (8.8)	14 (13.5)	10 (9.7)
Dry mouth	0 (0.0)	9 (8.8)	9 (8.7)	15 (14.6)
Nausea	6 (11.8)	37 (36.3)	25 (24.0)	40 (38.8)
Vomiting	3 (5.9)	15 (14.7)	5 (4.8)	12 (11.7)
Nervous system disorders	14 (27.5)	49 (48.0)	54 (51.9)	54 (52.4)
Dizziness	0 (0.0)	26 (25.5)	27 (26.0)	33 (32.0)
Headache	12 (23.5)	24 (23.5)	18 (17.3)	18 (17.5)
Somnolence	3 (5.9)	21 (20.6)	23 (22.1)	19 (18.4)
Skin and subcutaneous tissue disorders	3 (5.9)	18 (17.6)	13 (12.5)	22 (21.4)
Pruritus	2 (3.9)	12 (11.8)	7 (6.7)	19 (18.4)
Sweating increased	1 (2.0)	6 (5.9)	7 (6.7)	4 (3.9)
General disorders and administration site conditions	4 (7.8)	9 (8.8)	16 (15.4)	11 (10.7)
Fatigue	4 (7.8)	8 (7.8)	13 (12.5)	7 (6.8)
Weakness	0 (0.0)	1 (1.0)	6 (5.8)	4 (3.9)
Psychiatric disorders	2 (3.9)	9 (8.8)	8 (7.7)	4 (3.9)
Insomnia	2 (3.9)	9 (8.8)	8 (7.7)	4 (3.9)
Musculoskeletal and connective tissue disorders	6 (11.8)	5 (4.9)	3 (2.9)	2 (1.9)
Arthralgia	3 (5.9)	2 (2.0)	3 (2.9)	2 (1.9)
Joint stiffness	4 (7.8)	3 (2.9)	0 (0.0)	0 (0.0)

Abbreviations: qid, 4 times a day; bid, twice a day.

ment, quality of analgesia, and the WOMAC total score and subscales of pain, stiffness, and physical function.

In this 3-week study, oxycodone alone was rarely significantly different from placebo, in contrast to the significant effects seen with this dose combined with ultralow-dose naltrexone in the Oxytrex bid group. The lack of a consistent statistical difference between oxycodone and placebo suggests that this dose of oxycodone alone might be insufficient for the level of pain in the patients in this study. Other osteoarthritis clinical studies have reported a lack of effect of oxycodone at similar or lower daily doses in patients with similar or lower initial pain scores. In one prior clinical trial, a total daily oxycodone dose of 40 mg, but not 20 mg, produced a significant difference from placebo in patients with moderate to severe pain.²³ In another clinical trial, a total daily oxycodone dose of 40 mg was not significantly different from placebo in patients with osteoarthritis pain equivalent to at least a 4 on the 0 to 10 numeric scale used here.¹⁵

Because all active treatment groups received the same escalating daily dose of oxycodone, the Oxytrex bid group differed from the oxycodone qid group by the dosing regimen and by the addition of ultralow-dose naltrexone. The duration of action and short half-life of immediate-release oxycodone, reported as 2.6 to 5.5 hours,^{14,20,21} do not suggest that a bid dose regimen would produce greater analgesia than a qid regimen, even with higher doses. In addition, pharmacokinetic analyses on plasma samples from approximately half of each active treatment group did not reveal any differences in concentrations of oxycodone or metabolites (data not shown), indicating that the increased efficacy of Oxytrex bid was not due to a change in oxycodone pharmacokinetic parameters as a result of the dose regimen or the addition of naltrexone. In fact, although oxycodone or its metabolite concentrations did not correlate with efficacy, there was a significant negative correlation between increased efficacy and plasma concentrations of β -naltrexol, the major metabolite and marker of naltrexone in the Oxytrex groups, that is, the lower plasma concentrations of β -naltrexol correlated with a greater reduction in pain intensity.

Besides dosing regimen, the difference between the Oxytrex bid and Oxytrex qid groups was the daily dose of naltrexone. (With the naltrexone dose fixed at 0.001 mg per dose, the Oxytrex qid dose group received 0.004 mg/day, and the bid dose group received 0.002 mg/day.) Oxytrex bid, with a total daily naltrexone dose of 0.002 mg, achieved significantly greater analgesia than the placebo group and both QID groups, either with or without naltrexone at 0.004 mg/day. It is possible that the total daily naltrexone dose in the Oxytrex qid group was too high to enhance analgesia. It should also be noted that the greatest difference between Oxytrex bid and the other groups occurred at week 3, when the opiate dose was highest, and the ratio of naltrexone to oxycodone was, therefore, the lowest.

The present finding of enhanced and prolonged analgesia confirms previous clinical reports of the effects of ultralow-dose opioid antagonists combined with opi-

ates.^{9,12} When considering the clinical studies that did not demonstrate enhanced analgesia by the addition of low doses of naloxone to morphine PCA, it should be noted that the naloxone doses in those studies were considerably higher than the naltrexone doses in this clinical trial. Although naloxone and naltrexone might not be equipotent, the dosing differences in the current clinical trial versus previous studies are substantial and are further augmented by the increased bioavailability of intravenous administration of the earlier studies compared to the 20% bioavailability of oral naltrexone¹³ used in this clinical trial. Although the present data show that 2 but not 4 μ g/day of oral naltrexone enhanced the analgesia of oxycodone, prior clinical studies that did not show enhanced analgesia used intravenous naloxone doses of approximately 20 μ g/day,³ 475 μ g/day,² and 540 μ g/day,¹⁰ assuming similar patient weights between studies. In addition, although pharmacokinetic differences make dose comparisons between clinical and preclinical data difficult, experiments in mice showed that antagonist to agonist ratios that enhance analgesia were 1:100,000 or lower, whereas a ratio of 1:1000 or higher decreased analgesia.⁷ The ratio of naltrexone to oxycodone in the Oxytrex bid group ranged from 1:5,000 to 1:20,000, depending on the dose of oxycodone, and the low oral bioavailability of naltrexone versus the 90% bioavailability of oxycodone slightly widens this ratio.

The enhanced and prolonged analgesia by Oxytrex bid in this clinical trial is supported by preclinical data showing that ultralow-dose opioid antagonists enhance and prolong opioid analgesia and attenuate tolerance. The mechanism of ultralow-dose opioid antagonists in enhancing analgesia has been suggested to be the prevention of excitatory signaling of opioid receptors that occurs during opioid tolerance and counteracts analgesia.^{4-8,24,27} Agonist stimulation of opioid receptors normally activates an inhibitory signal transduction cascade that inhibits the cell. In animals chronically treated with an opiate, the μ opioid receptor switches its G protein coupling profile to initiate an excitatory signaling pathway that produces the opposite effect on the cell, and chronic co-treatment with an ultralow-dose opioid antagonist attenuates this alteration in signaling.²⁷ This mechanism of action might also explain recent preclinical data showing that ultralow-dose NTX reduces the acute rewarding or "euphoric" effects of opiates, as well as the aversive effects of their withdrawal.¹⁶ The present clinical results suggest that the prevention of excitatory signaling of opioid receptors by ultralow-dose opioid antagonists might also occur in human beings to enhance the analgesic effect of the opiate.

In summary, Oxytrex bid, despite less frequent dosing, resulted in significantly lower pain scores than oxycodone qid and significant separation from placebo by the end of the study on all other measures in which oxycodone alone did not. The effects of Oxytrex on analgesia as well as analgesic tolerance and withdrawal are currently being investigated in larger numbers of patients and with longer treatment durations in 2 Phase III clinical trials in osteoarthritis and low back pain.

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