

Oxytrex™: a New Opioid Analgesic With Minimal Physical Dependence And Better Overall Safety

Lynn R. Webster¹, Peter G. Butera², Nancy Wu², Lauren V. Moran², Lindsay H. Burns² and Nadav Friedmann²

¹Lifetree Clinical Research, Salt Lake City, UT; ²Pain Therapeutics, Inc., South San Francisco, CA

ABSTRACT

Physical dependence is an expected effect of prolonged, high-dose opioid therapy and is characterized by physical signs of withdrawal. Oxytrex (oxycodone + ultra-low-dose naltrexone) is a new opioid drug candidate shown here to minimize the adverse effects of long-term opioid therapy, including physical dependence. In a 719-patient, multi-center, placebo- and active-controlled Phase III clinical trial in chronic moderate-to-severe low-back pain, Oxytrex provided strong analgesia yet reduced withdrawal, constipation, somnolence and pruritis compared to oxycodone. Patients were randomized to receive placebo, oxycodone q.i.d., or Oxytrex™ q.i.d or b.i.d. The Oxytrex BID group received 2 micrograms/day of naltrexone and Oxytrex QID group received 4 micrograms/day formulated into their daily dose of oxycodone. Following a wash-out period, patients with moderate-to-severe low-back pain (≥ 5 on a 0-10 scale) were dose escalated every week up to 6 weeks until they attained adequate pain relief (≤ 2) or just bearable side-effects using 10 to 80 mg of drug (or placebo) per day. Patients then remained on that daily dose for 12 weeks. Demographics, baseline pain scores and pain relief in week 12 were similar in all drug groups. However, compared to patients on oxycodone, patients on Oxytrex BID reported a) significantly less drug use to achieve equal analgesia ($p=0.03$) b) 44% less moderate-to-severe constipation ($p=0.01$) c) 33% less somnolence ($p=0.03$) and d) 51% less moderate-to-severe pruritis ($p<0.001$). In addition, patients in the Oxytrex b.i.d. group reported dramatically (55%) less physical dependence as measured by the short opioid withdrawal scale compared to patients in the oxycodone group upon cessation of opioid therapy. This is the first study to show adequate opioid analgesia with minimal opioid withdrawal effects and better safety compared to oxycodone.

INTRODUCTION

The present randomized, double-blind, placebo- and active-controlled Phase III clinical trial compared Oxytrex™ (oxycodone + ultra-low-dose naltrexone), at two different total daily naltrexone doses, to oxycodone alone in patients with chronic low-back pain. Previous preclinical and clinical reports have shown that a variety of ultra-low-dose opioid antagonists paradoxically enhance and prolong the analgesic effect of opiates.^{3, 4, 6, 10, 11, 16, 18, 19} Extensive preclinical data have also shown ultra-low-dose opioid antagonists to attenuate opioid analgesic tolerance and withdrawal effects.^{4, 13-16, 18, 19}

Preclinical studies clearly show that within an “ultra-low” dose range of pg/kg to µg/kg, the lower doses of opioid antagonists are more effective than the higher doses at enhancing analgesia and reducing tolerance and dependence.^{16, 17} In clinical reports, the studies that have demonstrated enhanced analgesia^{3, 6, 10, 11} or opioid-sparing effects when using patient-controlled analgesia⁸ have used far lower opioid antagonist doses than clinical studies that have failed to demonstrate beneficial effects of low doses of opioid antagonists.^{1, 2} In addition, in a pharmacokinetic analysis of plasma samples from a subset of patients in a Phase II clinical trial of Oxytrex, analgesic efficacy negatively correlated with plasma levels of 6β-naltrexol, the major metabolite of naltrexone, i.e. the lower the 6β-naltrexol, the greater the analgesia.^{3, 7}

In the earlier clinical trial, the Oxytrex BID treatment, with 0.002 mg/day of naltrexone, produced significantly greater pain relief than both oxycodone QID and Oxytrex QID, which included 0.004 mg/day naltrexone ($p < 0.01$ for both comparisons). The total daily dose of oxycodone escalated over the 3 weeks but was identical in all active treatment groups. Moreover, that trial demonstrated greater efficacy of the Oxytrex treatment containing the lower naltrexone dose as well as the effectiveness of less frequent dosing with this treatment.

In this Phase III trial, after randomization to receive placebo, oxycodone QID, Oxytrex QID or Oxytrex BID, patients titrated their daily dose over 1-6 weeks to a pain score ≤ 2 , or to a just bearable level of side effects, or to a maximum of 80 mg/day. After titration, patients remained on their individual fixed doses for an additional 12 weeks. Treatment was abruptly stopped at the end of the study, and withdrawal signs were measured for 4 days. This design was intended to compare Oxytrex to oxycodone by assessing 1) the dose needed for maximal pain relief, 2) side effects experienced during treatment, 3) any analgesic tolerance developed over the 3-month fixed-dose period, and 4) an assessment of the extent of physical dependence.

METHODS

Patients

Patients were between the ages of 18 and 70 with persistent low-back pain for at least 6 months requiring daily analgesics. Eligible patients had a baseline Pain Intensity (PI) score ≥ 5 (on a 0-10 Likert Scale). Patients taking opioid doses equivalent to ≥ 20 mg oxycodone were tapered off, and a 72-hr period of no opioid medication was required of all patients before study entry.

Treatment Groups

Qualifying patients were randomized in a 1:2:2:2 ratio to receive placebo, oxycodone QID, Oxytrex QID or Oxytrex BID. Randomization was stratified by sex. Besides the dosing regimen, Oxytrex BID differed from Oxytrex QID by the total daily dose of NTX:

each active dose contained 0.001 mg NTX so that the Oxytrex BID group received 0.002 mg/day and the Oxytrex QID received 0.004 mg/day. Oxytrex BID patients received 2 placebo pills alternating with Oxytrex tablets in order to maintain blinding.

Clinical Protocol

All patients in active treatment groups started at a total daily oxycodone dose of 10 mg/day (divided b.i.d. or q.i.d.). No other analgesics (NSAIDs, COX-2 inhibitors, opioids, acetaminophen, etc.) were allowed during the treatment period. Over 1-6 weeks, patients titrated their daily dose to a pain score ≤ 2 , or to a level of just bearable side effects, or to a maximum of 80 mg/day. Dose titration occurred at weekly visits according to the following schedule: 10 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 60 mg/day and 80 mg/day. After titration, patients remained on their final dose for 12 weeks. Treatment was abruptly stopped at the end of the treatment period to allow assessment of withdrawal by the Short Opioid Withdrawal Scale (SOWS)⁹ for 4 days.

RESULTS

Discontinuations

Of the 719 patients randomized to treatment, 54% did not complete the study, and most of these discontinuations (65%) occurred during the titration period. There was no difference in discontinuation rates between oxycodone QID and Oxytrex BID (51% and 52%, respectively), although placebo and Oxytrex QID had slightly higher rates (58% for both). The primary reason for discontinuation in active treatment groups was adverse events (24 – 31%), predominantly common opioid-related side effects. There were no differences between active treatment groups in discontinuations due to inadequate pain relief (7 – 11%). Inadequate pain relief was the primary reason for discontinuation in the placebo group (40%).

Analgesia

All active treatment groups separated from placebo, and no group developed analgesic tolerance over this 3-month fixed-dose treatment period. The percent reductions in pain scores from baseline to the end of the study were not significantly different among active treatment groups (46%, 41%, 43% for oxycodone QID, Oxytrex QID and Oxytrex BID, respectively, versus 32% for placebo). However, compared to oxycodone QID, the total average daily dose of oxycodone was 12% lower for both Oxytrex QID and Oxytrex BID arms ($p=0.03$ for both).

Physical Dependence

The SOWS scores, indicating severity of withdrawal, were used to assess physical dependence. The distribution of patients reporting mild, moderate or severe withdrawal, according to first day SOWS scores, showed an overall reduction in moderate to severe physical dependence by Oxytrex BID compared to oxycodone QID, with an intermediate distribution for Oxytrex QID (Fig. 1). In addition, the mean SOWS score for Oxytrex BID was reduced by 55% compared to oxycodone the day after treatment ended ($p=0.01$), and by 42% averaged over the first 2 days ($p=0.04$, Fig. 2).

Fig. 1 Patients showing mild, moderate and severe withdrawal

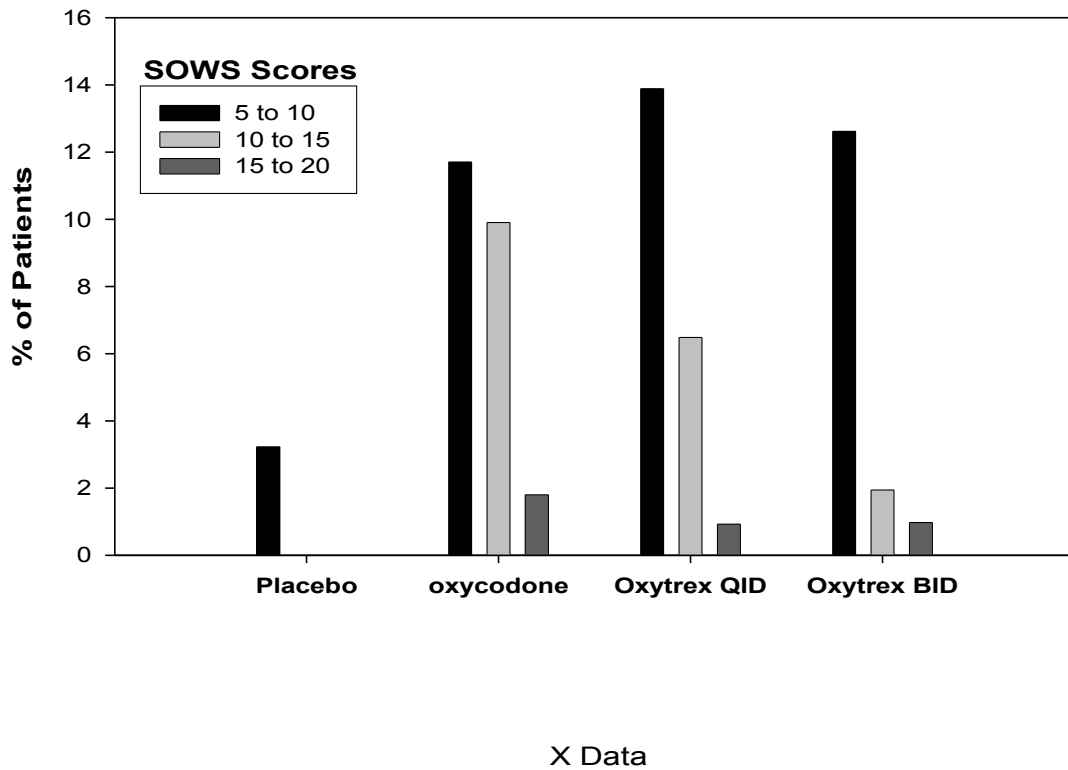
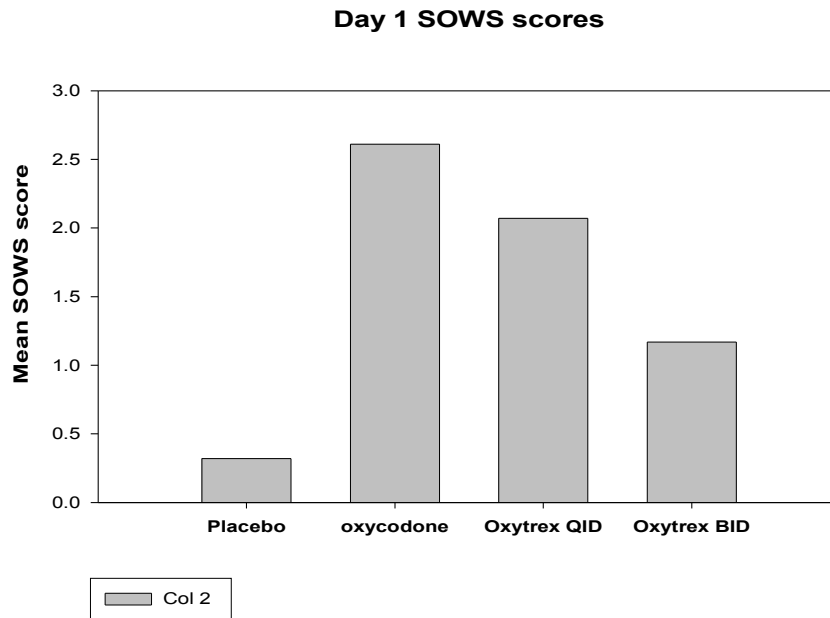


Fig. 2

Day 1 SOWS scores



Adverse Events

Oxytrex BID significantly reduced three moderate-to-severe opioid-related adverse events (Table 1). Oxytrex BID significantly reduced the mean number of moderate-to-severe incidents per patient of constipation by 44% (p=0.01), of somnolence by 33% (p=0.03), and of pruritus by 51% (p<0.001). Oxytrex QID produced intermediate reductions in these adverse events, significantly reducing the incidence of moderate-to-severe pruritus (p=0.002).

Table 1. Number of moderate-to-severe opioid-related adverse events per patient

	Placebo	Oxycodone ^{QID}	Oxytrex ^{QID}	Oxytrex ^{BID}
Constipation	0.28	0.71 [‡]	0.55	0.40*
Dizziness	0.13	0.37 [‡]	0.32 [‡]	0.35 [‡]
Somnolence	0.50	0.83 [‡]	0.61	0.56*
Pruritus	0.05	0.51 [‡]	0.28 ^{‡*}	0.25 ^{‡*}
Nausea	0.21	0.60 [‡]	0.53 [‡]	0.52 [‡]
Vomiting	0.09	0.23 [‡]	0.19	0.22

[‡] p < 0.05 compared to placebo

*p < 0.05 compared to Oxycodone QID group

DISCUSSION

To our knowledge, this double-blind, randomized, placebo- and active-controlled Phase III clinical trial in low-back pain is the first to demonstrate a significant reduction in physical dependence following cessation of prolonged opioid therapy. We attribute this clinical benefit to the addition of 2 micrograms/day of naltrexone to the oxycodone in the Oxytrex BID treatment. The decrease in physical dependence by Oxytrex BID vs. oxycodone was demonstrated by a significant reduction in mean SOWS scores in the first and first two days following cessation of treatment. Oxytrex BID also reduced the number of patients experiencing moderate or severe withdrawal, illustrating the reduction in severity of withdrawal.

In addition to reducing withdrawal, the Oxytrex BID treatment provided a better safety profile than oxycodone QID by significantly decreasing moderate-to-severe incidents of three major opioid-related adverse events: constipation, somnolence and pruritis. The reduction in severity of these adverse events concurrent with equivalent analgesia at a lower dose demonstrates an improved therapeutic index for Oxytrex versus oxycodone.

In this trial, all active treatments separated from placebo in the percent reduction of Pain Intensity scores. Compared to oxycodone QID, both Oxytrex groups demonstrated equivalent analgesia at a significantly lower dose, and Oxytrex BID did so with less frequent dosing. All active treatment groups maintained this level of pain relief from the end of titration to week 12. Hence, the lack of analgesic tolerance in the oxycodone active control group in this trial of mostly opioid-naïve patients prevented the assessment of whether Oxytrex alleviates opioid tolerance, a property suggested by preclinical data^{4, 16, 18, 19} and a clinical case report in a severely opioid-tolerant patient.⁶

The earlier Phase II clinical trial of Oxytrex in osteoarthritis pain demonstrated enhanced and prolonged analgesia by Oxytrex BID compared to oxycodone alone with identical total daily doses between groups.³ The current Phase III trial also supports enhanced analgesic efficacy by Oxytrex since equivalent analgesia was achieved with a significantly lower average total daily dose of oxycodone.

In summary, the addition of ultra-low-dose naltrexone to oxycodone in the Oxytrex BID formulation was shown to reduce physical dependence, moderate-to-severe constipation, somnolence and pruritis, and to achieve equivalent analgesia with a lower dose of oxycodone, demonstrating enhanced analgesic potency. These benefits were achieved with convenient twice daily dosing. These Phase III clinical data are the first demonstration of reduced physical dependence on opioids in a controlled clinical trial. Although physical dependence is distinct from but often associated with addiction, recent preclinical data have also demonstrated reductions in the addictive potential and in the acute rewarding or “euphoric” effect when ultra-low-dose naltrexone is added to oxycodone in doses that also enhance oxycodone analgesia.^{12, 14} While the mechanism of action of ultra-low-dose opioid antagonists in combination with opioids is not yet fully understood, *in vitro* electrophysiology data has demonstrated that their addition prevents the excitatory effects of opiates, a phenomenon that increases with chronic opioid

treatment and is thought to contribute to opioid tolerance and dependence.^{4,5} More recent molecular pharmacology data has confirmed that chronic opioid treatment *in vivo* alters the normal G protein coupling profile of mu opioid receptors, so that their activation leads to excitatory rather than inhibitory signaling, and that ultra-low-dose opioid antagonist co-treatment suppresses these changes, restoring the normal G protein coupling pattern of these opioid receptors.²⁰

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