ORIGINAL ARTICLE

Oral naltrexone to enhance analgesia in patients receiving continuous intrathecal morphine for chronic pain: A randomized, double-blind, prospective pilot study

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ABSTRACT

Background: *Years' worth of observations suggest that morphine has both inhibitory and excitatory actions, and that selective blockade of excitatory effects by low doses of opioid antagonists (e.g., naltrexone) may paradoxically enhance morphine analgesia. The purpose of this pilot study was to evaluate and compare the analgesic efficacy and safety of two different low doses of oral naltrexone given in addition to chronic intrathecal morphine infusions in patients with chronic nonmalignant pain (CNMP).*

Methods: *After institutional review board approval, 15 patients with CNMP receiving continuous intrathecal morphine were admitted into a prospective, randomized, double-blind, placebo-controlled, seven-day pilot study. Patients were randomized into three treatment groups based on oral naltrexone dose: 100 μg (Group A, n = 3), 10 μg (Group B, n = 7), or placebo (Group C, n = 5). All patients continued with their constant intrathecal morphine infusion, and in addition they received one capsule of study medication every 12 hours for seven days. Other analgesics or coanalgesics were kept at a constant dose level throughout the study. Patients rated pain scores (visual analogue score [VAS]; 0 = no pain, 10 = worst pain imaginable) and side effects three times daily throughout the study period. Efficacy measures included pain intensity difference (PID) scores, constructed so that positive scores indicate a reduction in pain intensity and negative scores indicate a worsening of pain.*

Results: *Fifteen patients (six male, nine female) with a mean (SD) age of 55 (10) years and weight of 81 (21) kg completed the study. The mean (SD) baseline VAS pain intensity rating was similar in all three groups (6.8 [1.5]). Baseline pain VAS score minus the lowest daily pain VAS score yielded the peak PID score. The peak PID score from Day 1 was statistically ($p < 0.05$) highest (median PID score: 5.9) in Group A compared with Group C. There was a trend in PID scores across Days 2 through 7, with median PID scores higher (i.e., greater pain relief; $p = 0.07$) in Group A. In the daily global pain assessments, the pain scores across Days 2 through 7 approached significance (least pain) in Group A compared to Group C ($p = 0.07$) or B ($p = 0.08$). Side effects were common (93 percent of patients), minor (headache, nausea, sedation, dry mouth), and similar across treatment groups. No serious adverse events were observed, and no evidence of opioid withdrawal was seen.*

Conclusions: *1) Patients with chronic pain who received oral naltrexone 100 μg BID in addition to their chronic intrathecal morphine infusions demonstrated the greatest improvement ($p = 0.07$) in their daily pain scores. Because of the small sample size, the results did not reach traditional levels of significance. 2) Side effects were common, minor, and similar across treatment groups. 3) No serious adverse events were recorded. 4) No evidence of opioid antagonist toxicity or opioid withdrawal was observed.*

Key words: chronic pain, opioid agonists, opioid antagonists, intrathecal analgesics, analgesia

INTRODUCTION

Morphine and other opioids have been prescribed for many years for the treatment of cancer pain and have been found to be effective for the relief of moderate to severe pain.[1] In the last decade, chronic oral or transdermal opioids have gained acceptance as treatments for chronic nonmalignant pain (CNMP).[2] For CNMP patients who do not achieve adequate analgesia with chronic oral opioids or who experience intolerable side effects from opioids, other forms of treatment, such as spinal analgesics, are often used.[3]

Opioids interact with stereospecific, saturable receptors in the brain, spinal cord, and other tissues, with a principal therapeutic effect of analgesia.[4] Morphine binding to inhibitory opioid receptors on nerve cells results in inhibition of the transmission of pain signals into the

brain. It has been observed, however, that while the dominant effect of opioids in their usual clinical doses is to inhibit opioid receptors, opioid agonists simultaneously activate excitatory opioid receptors on sensory nerve cells.[5] This paradoxical excitatory action can weaken opioid-induced analgesia and contribute to dependence and tolerance-related opioid-therapy failures.[5-7] Therefore, medications able to selectively block this excitatory effect on opioid receptors could theoretically enhance opioid analgesia.

The antiexcitatory actions of low-dose opioid antagonists and their potential as possible adjuncts for the enhancement of opioid agonist analgesia have been evaluated through basic and clinical research. Selective antagonism of excitatory opioid receptor function has been shown to enhance the inhibitory potency of opioid agonists in dorsal root ganglion cultures.[8] In rodent nociceptive paradigms, opioid antagonists not only exhibit biphasic dose-response curves[9,10] but also markedly enhance the analgesic potency of morphine when coadministered in remarkably low doses.[11,12]

Several clinical studies and case reports published over the years provide further evidence of this enhancement of opioid analgesia via concurrent use of low doses of opioid antagonists. Levine[13] examined the analgesic actions of naloxone in patients with postoperative dental pain in a controlled, double-blind trial and found that naloxone 400 and 1,000 μg potentiated the analgesic effect of oral pentazocine. A more recent case report demonstrated the opioid-analgesic-enhancing effect of naltrexone when added to chronic methadone therapy in a patient with chronic and refractory painful diabetic neuropathy. For this patient, the addition of naltrexone in the ultra-low dose of 1 μg twice daily not only improved pain relief but also allowed for a modest reduction in methadone dose.[14]

Naltrexone is a pure opioid antagonist that blocks the subjective effects of intravenously administered opioids. It has few, if any, intrinsic actions aside from its opioid-blocking properties. Based on the hypothesis that selective antagonism of opioid excitatory actions may enhance the analgesic potency of opioid agonists, we designed a study to evaluate the safety and efficacy of combined intrathecal morphine and low-dose naltrexone in the treatment of CNMP. Intrathecal opioid therapy delivers low doses of opioids close to the site of action and is often effective in treating CNMP syndromes. However, complete pain relief is not always achieved in all patients, and additional therapies are needed to control chronic pain in the refractory population.[15] Thus, the addition of a low-dose opioid antagonist (i.e., naltrexone) was proposed to enhance analgesia in patients experiencing incomplete pain relief while receiving chronic intrathecal opioids for CNMP. The purpose of this pilot study was to evaluate and compare the analgesic efficacy and safety of two different low doses of oral naltrexone when added to chronic intrathecal morphine therapy in patients with CNMP.

METHODS

Study design

This was a prospective, randomized, double-blind, single-center, placebo-controlled pilot study of the effects of low-dose oral naltrexone on pain relief produced by chronic intrathecal morphine administration. Oral naltrexone was chosen over intrathecal antagonists because of concerns about the unapproved nature of intrathecal naloxone use and the potential for neurotoxicity.

Written informed consent was obtained from all patients. The protocol and informed consent form were reviewed and approved by the Institutional Review Board at the University of Kentucky. The study was conducted in accordance with the provisions of the Declaration of Helsinki and its amendments, and with the International Conference on Harmonization Good Clinical Practice as adopted by the US Food and Drug Administration.[16]

Patients

Adult patients with a history of incompletely relieved CNMP who were using indwelling intrathecal morphine delivery systems were eligible for enrollment. Eligible patients were those with chronic refractory pain and a history of inadequate pain relief following prior use of at least two different opioid analgesic medications. Patients had a baseline visual analogue pain score (VAS) of at least 5 (0 = no pain, 10 = unbearable pain). Premenopausal women testing negative on a serum pregnancy test within seven days of enrollment and either practicing abstinence or using a medically accepted contraception method were eligible for enrollment. Patients had to be willing and able to complete the necessary patient evaluations. Exclusion criteria included any condition that might interfere with the absorption of study medications (e.g., intractable nausea and vomiting, inability to take oral medication, certain gastrointestinal disorders); a history of clinically significant intolerance or hypersensitivity to study medications; a history of (or anticipated) procedures that might confound quantification of analgesia; chronic respiratory insufficiency; severe hepatic or renal impairment; unstable seizure disorder; and any other physical, mental, or psychological condition that might interfere with the study or the interpretation of its results. Patients were not eligible for the study if adjuvant analgesics (e.g., anticonvulsants, antidepressants, NSAIDs) or oral opioids had been started or discontinued within four weeks of study entry.

Study procedures

Fifteen patients were recruited and randomly assigned to one of three naltrexone treatment groups: naltrexone 100 µg (Group A, n = 3), naltrexone 10 µg (Group B, n = 7), or placebo (Group C, n = 5). Oral study medication was provided in the form of identical hard, opaque gelatin capsules. The inactive ingredients were microcrystalline cellulose and magnesium stearate. Both patients and researchers were blinded to the dose of study medication. All bottles, used or unused, were saved for final disposition.

All patients continued their constant intrathecal morphine infusion at the same dose throughout the seven-day study period. Patients receiving adjuvant analgesics continued their medications without change throughout the study period. Prior to administration of oral study drug, baseline assessments were performed, including vital signs, VAS (0 = no pain, 10 = unbearable pain), and evaluation of side effects (sedation, dry mouth, headache, itching, difficulty urinating, constipation, nausea, and vomiting) on a 4-point Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Patients recorded VAS ratings and assessed side effects three times daily throughout the seven-day study period. In addition, patients made a global 24-hour assessment of pain using a VAS scale (0 = no pain, 10 = worst possible pain) once daily. Pain evaluations on Day 1 were made prior to taking study drug, 30 minutes after taking study drug, and hourly post-dose over eight hours.

Patients took study medication every 12 hours throughout the seven-day trial. Acetaminophen was allowed as rescue medication.

Safety and efficacy

Patients recorded their assessments of analgesia, nausea, and sedation, as well as the use of regularly scheduled medications and/or rescue medication. Compliance was determined by review of patient diaries and counts of returned medication. Vital signs, including respiratory rate, heart rate, blood pressure, blood oxygen saturation, and oral temperature, were taken prior to administration of study medication, hourly on the first study day, and once on Day 8 during the patient's exit evaluation. Adverse events were coded using standard methods and recorded in terms of severity and relationship to study drug.

Drug efficacy was estimated via evaluation of pain intensity difference (PID) score, which is the baseline VAS pain intensity rating minus the current pain intensity score. A positive PID score indicates a reduction in pain intensity, and a negative score indicates worsening of pain intensity.[17-19]

Statistical analysis

Results from all enrolled patients were included in the analysis of efficacy data. Statistical evaluation of overall treatment effects was assessed using the exact Kruskal-Wallis procedure. Pairwise comparisons were made using the exact two-sample Wilcoxon procedure. Treatment differences were considered significant at $p < 0.05$. Pairwise testing was considered only if the overall treatment differences were found to be statistically significant ($p < 0.05$) or demonstrated a trend ($p < 0.05$ to $p < 0.10$).

RESULTS

This investigation was considered a Phase I pilot study, intended to capture treatment information to be used in the design of future trials. While all 15 patients completed the study, the resultant uneven numbers of patients between treatment groups made it difficult to generate highly significant statistical results. Nonetheless, several interesting trends were observed in the study data.

Fifteen patients (nine females and six males) completed the protocol (Table 1) and complied with all drug-dosing schedules. The mean (SD) age was 55 (10) years, with a mean (SD) weight of 81 (21) kg. All patients had failed to achieve sustained pain relief on previous oral opioid analgesics, all patients had been previously treated with injective steroid therapy such as epidural or facet injections, and six patients had a history of previous back surgery for pain (one patient in Group A, four patients in Group B, and one patient in Group C). The pain diagnosis, daily intrathecal morphine dose, and concomitant analgesic use for each patient are listed in Table 2.

Mean (SD) baseline oxygen saturations (95.3 percent [3.2]), heart rates (75 bpm [17]), respiratory rate (19 bpm [3.4]), systolic blood pressure (127 mmHg [15.7]), diastolic blood pressure (78 mmHg [12]), and oral temperatures (98.4°F [0.6]) were all unremarkable and exhibited no statistically significant or clinically important changes during the study period.

The mean (SD) baseline VAS pain intensity rating of 6.8 (1.5) was similar in all three groups. Peak PID score was calculated by subtracting the lowest daily pain VAS score from the baseline pain VAS score. Differences in PID scores between all the treatment groups approached statistical significance ($p < 0.07$). The peak PID score from Day 1 was statistically ($p < 0.05$) highest (median PID score: 5.9) in Group A compared with Groups C and B (Figure 1). No difference in reported PID scores was found across time between Groups B and C. The PID scores through eight hours post-dose approached statistical significance ($p < 0.08$), as the median PID scores tended to be highest (i.e., greatest reduction in pain) in Group A and lowest (i.e., least reduction in pain) in Group B.

After Day 1, pain evaluations were made three times daily through Day 7. PID scores were then calculated for

Table 1. Patient demographics				
Characteristic	**Naltrexone 100 µg**	**Naltrexone 10 µg**	**Placebo**	**Total**
Number of patients	3	7	5	15
Age				
Mean	58.0	53.4	55.4	55.0
Median	51.0	52.0	52.0	52.0
Range	48 to 75	49 to 65	42 to 74	42 to 75
Sex				
Males	1 (33 percent)	3 (43 percent)	2 (40 percent)	6 (40 percent)
Females	2 (67 percent)	4 (57 percent)	3 (60 percent)	9 (60 percent)
Height (in)				
Mean	65.8	64.3	64.5	64.6
Median	64.0	61.5	65.0	64.0
Range	62 to 72	58 to 73	56 to 72	56 to 73
Weight (kg)				
Mean	83.8	78.2	81.8	80.5
Median	90.7	79.4	88.4	80.7
Range	54 to 107	47 to 113	57 to 106	47 to 113

each time point in terms of change from Day 1 baseline evaluation (Figure 2). There was a statistically significant difference found among the treatment groups on the afternoon of Day 2 ($p < 0.05$), when Group A had significantly higher PID scores than Groups B and C ($p < 0.05$). A statistically significant difference was also found among the treatment groups on the evening of Day 3, when Group A had higher scores than either Group B or C ($p < 0.05$). The PID scores from Day 2 through Day 7 approached statistical significance ($p < 0.07$), as the median PID scores were higher in Group A than in Group B or C at all pain measurements for Days 2 through 7.

There were no deaths or serious adverse events reported during the one-week study. Side effects related to the gastrointestinal and/or nervous system were most commonly reported, with 14 of 15 patients reporting one or more events in those categories. The most commonly reported adverse events were headache (11 patients), dry mouth (11 patients), sedation (10 patients), and nausea (nine patients). Other side effects included constipation (six patients), pruritus (one patient), and vomiting (two patients). Interestingly, the highest number of reported adverse events per patient (five) occurred in the placebo group. Twenty-five events were reported by the five placebo patients, while 26 events were reported by the seven patients in Group B and seven events were reported by the three patients in Group A.

DISCUSSION

Oral opioids have been recommended recently for the treatment of CNMP such as osteoarthritis and chronic low back pain.[20] This analgesic treatment is often successful, but some patients experience intolerable side effects or inadequate pain relief. For this subset of CNMP patients, spinal analgesics administered via implantable intrathecal pumps are frequently tried.[21] While many patients gain

Table 2. Patient pain diagnosis and analgesic use				
Group	**Patient**	**Pain diagnosis**	**Intrathecal morphine daily dose (mg/d)**	**Concomitant analgesics**
A	1	DJD lumbar spine	8.0	imipramine
	2	Postlaminectomy syndrome	2.7	oxycodone
	3	Chronic low back pain; bilateral hip pain	6.5	hydrocodone
B	1	Postlaminectomy syndrome	2.3	methadone
	2	Postlaminectomy syndrome	7.0	gabapentin
	3	Postlaminectomy syndrome	4.5	gabapentin
	4	DJD cervical spine	12.7	oxycodone
	5	DJD cervical spine	1.8	methadone
	6	DDD lumbar spine	4.4	amitriptyline
	7	Postlaminectomy syndrome	2.5	doxepin
C	1	DJD lumbar spine	23.5	methadone
	2	Postlaminectomy syndrome	3.2	oxycodone
	3	Flank pain (renal stones)	7.5	acetaminophen
	4	Lumbar spondylosis	5.5	NSAID
	5	DJD lumbar spine	9.0	NSAID

DJD = degenerative joint disease; DDD = degenerative disc disease; NSAID = nonsteroidal anti-inflammatory drug.

excellent pain relief from intrathecal analgesics, some do not achieve adequate pain relief, and the occasional patient experiences serious adverse events such as paraplegia and respiratory depression.[22,23] Clearly, additional pain therapies are needed to control chronic pain among patients refractory to oral analgesics and invasive pain treatments. Ultra-low-dose opioid antagonists have occasionally been added to opioid therapy to paradoxically enhance opioid analgesia.[6] With this pilot study, we have reported the first use of oral naltrexone to enhance the analgesia of patients with chronic pain receiving intrathecal morphine.

In this study, patients with chronic pain who received oral naltrexone 100 μg twice daily as an adjunct to chronic intrathecal morphine infusions tended to experience the greatest improvement in their daily pain scores. On the first day of treatment, the highest peak PID scores (greatest pain relief) were seen in the group receiving naltrexone 100 μg BID. Throughout the first day of treatment, there was a trend in the PID scores indicating that the naltrexone 100 μg group tended to have the greatest reduction in pain, with the placebo and naltrexone 10 μg groups experiencing less pain relief. Although these data did not achieve statistical significance, we believe that this trend, even among this small number of patients, is important. Clearly, a larger prospective study needs to be completed to test more fully the hypothesis that oral naltrexone can enhance opioid analgesia among patients with CNMP.

This pilot study is limited chiefly by its small sample size. Because of the small patient numbers, the results did not always reach traditional levels of significance and frequently only suggested a trend. A larger, double-blind, prospective clinical trial is necessary to determine

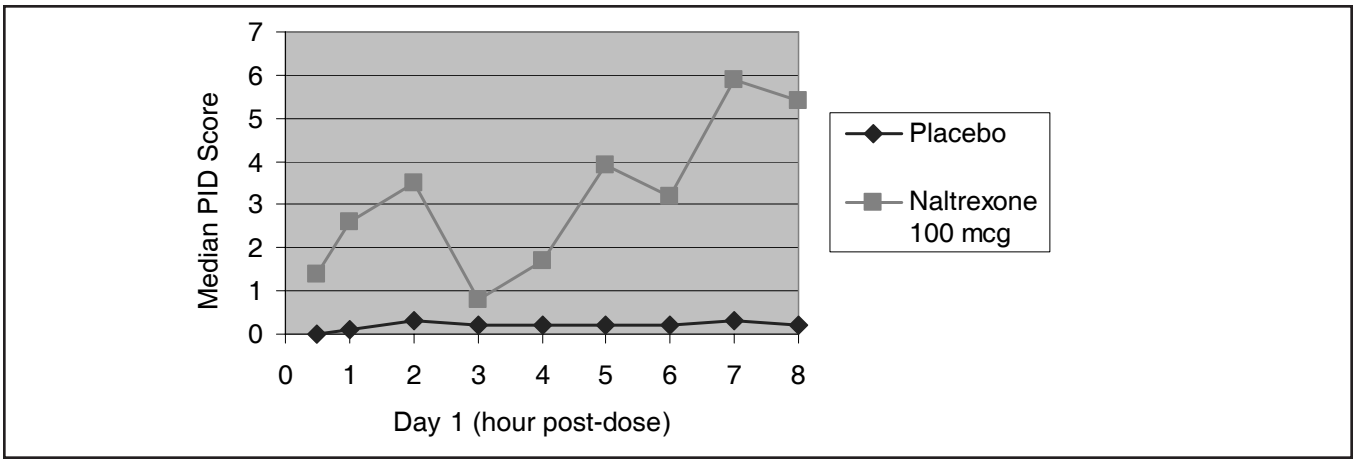

Figure 1. Median pain intensity difference scores over the first eight hours post-dose, with Group A showing higher scores (i.e., greater analgesia) compared with Group C.

whether the efficacy of naltrexone in enhancing intrathecal opioid analgesia can be verified.

The pharmacologic antagonism of excitatory (hyperalgesic), but not inhibitory (analgesic), central nociceptive systems offers a new therapeutic option for anesthesiology, psychiatry, pain management, and palliative medicine. The paradoxical analgesic actions of low doses of opioid antagonists have been demonstrated in both animals and humans.[6,7,11-14] This paradoxical ability of low-dose opioid antagonists to enhance opioid analgesia is not new; in the early 1950s, researchers at Massachusetts General Hospital were already attempting to combine an opioid analgesic with an opioid antagonist in order to enhance morphine analgesia without side effects.[6] Over the next 50 years, various case reports and clinical trials demonstrated that low doses of opioid antagonists enhance opioid analgesia, while large doses of opioid antagonists provide the expected antagonism of opioid effects. Our results indicate that naltrexone's enhancement of intrathecal morphine analgesia may be dose dependent, since only the 100 μg treatment group experienced improved pain relief. Since this pilot study was the first of its kind, the most useful dose of naltrexone was unknown, and our study dose was based on estimations from available animal and human data. Future clinical trials should better define the therapeutic range for naltrexone's analgesic enhancement actions by comparing effects of slightly higher and slightly lower doses of naltrexone to the 200 μg/d shown to be most effective in this pilot trial.

More recent case reports and clinical trials demonstrate the possible usefulness of this new analgesic treatment (naltrexone) in patients with refractory chronic pain.[6] One such case report involves a diabetic patient with painful peripheral neuropathy refractory to methadone 240 mg/d.[14] The patient rated his pain as 9/10 on the VAS scale, in spite of gabapentin adjuvant analgesic therapy, and methylphenidate was necessary in order to combat opioid-related sedation. The patient was given naltrexone 2 μg/d and reported a significant drop in pain score on Day 1, to 3/10. His pain remained controlled with this addition of low-dose naltrexone, and his methadone dose was reduced to 200 mg/d. Our patients responded to a higher—though still classified as low—dose of naltrexone (200 μg/d). This difference may be related to the pain etiology (none of our patients had painful diabetic neuropathy) and to the different route of opioid administration, with all patients in our trial receiving intrathecal opioid analgesics. Since this is the first report of naltrexone enhancing the analgesic effect of intrathecal opioids, the most useful oral dose of naltrexone for enhancing analgesia in CNMP patients remains speculative.

Two clinical trials have been completed using a commercial preparation of oxycodone combined with oral low-dose naltrexone. The first prospective, double-blind, placebo-controlled clinical trial compared the analgesic effect of oxycodone alone versus oxycodone with naltrexone 1 μg among patients with osteoarthritis and chronic pain.[24] Oxycodone combined with low-dose naltrexone gave better pain relief compared with placebo or oxycodone alone over the course of the four-week clinical trial. Another recent clinical trial compared an oxycodone-naltrexone oral preparation with oxycodone alone in patients with chronic nonmalignant low back pain.[25] Patients were allowed to titrate their own opioid doses to achieve adequate pain relief. Both oxycodone-naltrexone and oxycodone alone provided similar analgesia; however, the daily dose of oxycodone was lower in the oxycodone-naltrexone group, suggesting that the naltrexone enhanced opioid analgesia.[20] Furthermore, there were no significant side effects or adverse reactions in the low-dose naltrexone group. Correlation of our pilot study results with these larger clinical trials is difficult, since we added low-dose oral naltrexone to intrathecal morphine analgesia.

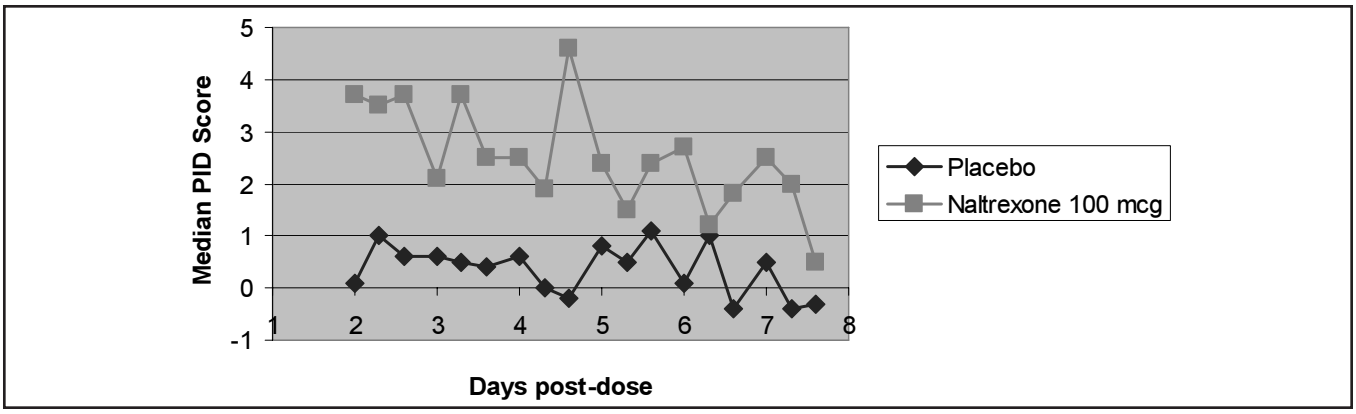

Figure 2. Median pain intensity difference scores over the seven-day pilot study, with Group A showing higher scores (i.e., greater analgesia) compared with Group C.

No deaths or serious adverse events were reported during this pilot study. Side effects were common but minor, with the highest rate of side effects occurring in the placebo group. These are important observations, as the addition of an opioid antagonist to chronic opioid analgesic therapy is potentially harmful.[6] There is always a possibility of precipitating opioid withdrawal, even when using low doses of naltrexone. Also, the opioid-enhancing effect of naltrexone could have precipitated opioid side effects such as sedation or respiratory depression. None of these serious side effects occurred during this clinical trial, however, and no evidence of opioid antagonist toxicity or opioid withdrawal was observed.

In summary, patients with CNMP who received oral naltrexone 100 µg twice daily in conjunction with continuous intrathecal morphine infusions tended to demonstrate the greatest improvement in daily pain scores as compared to patients receiving placebo or naltrexone 10 µg twice daily. We have presented the first pilot study in which low-dose oral naltrexone appears to enhance chronic intrathecal opioid analgesia among patients with chronic pain. Side effects were common, minor, and similar across treatment groups, with no serious adverse events (including opioid withdrawal) observed. While this pilot study involved a small number of patients, it employed rigorous methodology utilizing a prospective, double-blind, placebo-controlled trial design. Future trials need to explore the dose-response character of naltrexone's analgesia-enhancing effects and expand clinical application to patients receiving chronic oral opioids.

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