Controlled-release oxycodone and naloxone in the treatment of chronic low back pain: A placebo-controlled, randomized study

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BACKGROUND: For Canadian regulatory purposes, an analgesic study was required to complement previously completed, pivotal studies on bowel effects and analgesia associated with controlled-release (CR) oxycodone/CR naloxone.

OBJECTIVES: To compare the analgesic efficacy and safety of CR oxycodone/CR naloxone versus placebo in patients with chronic low back pain.

METHODS: Patients requiring opioid therapy underwent a two- to seven-day opioid washout before being randomly assigned to receive either 10 mg/5 mg CR oxycodone/CR naloxone or placebo every 12 h, titrated weekly according to efficacy and tolerability to 20 mg/10 mg, 30 mg/15 mg or 40 mg/20 mg every 12 h. After four weeks, patients crossed over to the alternative treatment for an additional four weeks. Acetaminophen/codeine (300 mg/30 mg every 4 h to 6 h as needed) was provided as rescue medication.

RESULTS: Of the 83 randomized patients, 54 (65%) comprised the per-protocol population. According to per-protocol analysis, CR oxycodone/CR naloxone resulted in significantly lower mean (± SD) pain scores measured on a visual analogue scale (48.6±23.1 mm versus 55.9±25.4 mm; P=0.0296) and five-point ordinal pain intensity scores (2.1±0.8 versus 2.4±0.9; P=0.0415) compared with placebo. After the double-blinded phase, patients and investigators both preferred CR oxycodone/CR naloxone over placebo. These outcomes continued in the 79% of patients who chose to continue receiving CR oxycodone/CR naloxone in a six-month, open-label evaluation.

CONCLUSIONS: In patients complying with treatment as per protocol, CR oxycodone/CR naloxone was effective for the management of chronic low back pain of moderate or severe intensity.

Key Words: Controlled-release; Low back pain; Naloxone; Oxycodone

A pproximately four of five Canadian adults experience at least one episode of back pain during their lifetime (1). Chronic back pain is generally defined as pain lasting longer than three (2) or six (3) months, although the pain may never fully resolve; patients may experience repeated exacerbations, with lifetime recurrences in up to 85% of individuals (2). Accordingly, the economic consequences of treatment decisions for low back pain are substantial (4,5). While the evidence to support many of the treatments used for low back pain varies in quality (6-8), a recurring premise in consensus norms for evidence to support many of the treatments used for low back pain is that the use of opioids in the treatment of chronic noncancer pain has recently been published by the American College of Physicians and the American Pain Society (11). The National Opioid Use Guideline Group, in collaboration with most provincial Colleges of Physicians and Surgeons, have issued a Canadian opioid guideline to aid medical practice for chronic noncancer pain in adults (12).

Controlled release (CR) oxycodone/CR naloxone (Targin, Purdue Pharma, Canada) is a formulation of CR oxycodone and CR naloxone in a 2:1 ratio. The oxycodone component is indicated for the relief of pain, and the naloxone component is indicated for the relief of opioid-induced constipation (OIC) (13). The combination of oral CR oxycodone and CR naloxone provides systemically available oxycodone to address pain control, while the naloxone component provides opioid antagonist effects locally in the gut, preventing activation of the μ-receptor in the intestinal lining.
submucosal and mesenteric plexuses. Activation of these receptors by oxycodone decreases gastric emptying and intestinal peristalsis, reduces the secretion of digestive enzymes and increases fluid absorption. This can lead to nausea, vomiting, loss of appetite and, in the colon, the formation of hard, dry stools and constipation. The presence of naloxone at the gut receptors reduces these effects of oxycodone. In addition, oral naloxone has been demonstrated to have a very low (<3%) systemic bioavailability due to first-pass metabolism by the liver. The major product is naloxone glucuronide, an inactive form of naloxone (14).

Double-blinded studies of CR oxycodone/CR naloxone in patients with noncancer pain demonstrated a level of pain relief comparable with that provided by CR oxycodone (OxyContin, Purdue Pharma, Canada) as well as reduced OIC (14-16). Open-label extension studies demonstrated the long-term efficacy and tolerability of fixed combination CR oxycodone/CR naloxone over 52 weeks, with clinically relevant improvements in OIC (17). The results from a large (n=7836), four-week, observational study were consistent with the findings of earlier pivotal clinical trials for analgesia and bowel outcomes (18).

METHODS
To address Canadian regulatory requirements, an additional analgesic study involving patients with chronic noncancer pain was required. The present trial complements three previously completed, pivotal studies on the safety and efficacy of CR oxycodone/CR naloxone (14-16). Thus, the purpose of the present study was to compare the clinical efficacy and safety of CR oxycodone/CR naloxone with placebo in a randomized, double-blinded, crossover titration-to-effect study in patients with chronic low back pain who had previously not responded adequately to nonopioid therapy and required the use of opioids to control their pain.

Patients
Adult (>18 years of age) men and nonpregnant (negative pregnancy test), non-nursing women with low back pain of moderate or greater intensity (as assessed by the investigator and the patient using a 5-point ordinal scale: 0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = excruciating) for the previous three months or longer were enrolled in the present study. Patients currently taking opioids or patients who had not previously responded to nonopioid therapy and now required opioids to control their pain were randomized following a two- to seven-day washout from all pre-study opioid analgesics. Patients who were receiving nonopioid analgesics (nonsteroidal anti-inflammatory drugs or muscle relaxants) that were stably dosed for two weeks and antidepressants or anticonvulsants that were stably dosed for eight weeks were permitted to continue these medications, provided the doses remained unchanged throughout the study.

Eligible patients underwent a two- to seven-day washout of previous opioid analgesics and stimulant laxatives to establish baseline pain and bowel function. Patients who experienced at least moderate pain (score of 2 on a 5-point scale) after the washout period were eligible to continue in the study. Patients were provided with acetaminophen plus codeine 300 mg/30 mg tablets to take for unrelieved pain (one to two tablets every 4 h as needed) and 8.6 mg senna/docusate sodium tablets (Senokot®S, Purdue Pharma, USA) for constipation (maximum four tablets twice per day) during the washout period.

After the washout period, patients were randomly assigned to receive either CR oxycodone/CR naloxone or placebo at an initial dose of 10 mg/5 mg every 12 h. A computer-generated random allocation listing of patient numbers was generated by the biostatistician and patients entering the study were centrally allocated to the associated treatment condition. Blinding was achieved using the double dummy technique. The patients, investigator and all clinical research staff were blinded. Patients were titrated at weekly clinic visits according to pain control and side effects to 20 mg/10 mg, 30 mg/15 mg or a maximum of 40 mg/20 mg every 12 h. After four weeks of treatment in the first phase, patients again received the initial dose of 10 mg/5 mg CR oxycodone/CR naloxone or placebo every 12 h, and were titrated as in the first phase. Patients were provided with acetaminophen plus codeine 300 mg/30 mg to be taken every 4 h to 6 h as required for rescue analgesia in both phases. If a patient experienced dose-limiting side effects or attained complete pain relief, investigators maintained the study drug at the existing dose. Patients were provided with senna/docusate sodium tablets to treat constipation as required. Investigators were requested to evaluate patients for whether they had neuropathic, nociceptive or both sources of pain under study and whether the patient was expected to respond to opioid therapy.

Patients who successfully completed both phases of the double-blinded study were eligible to receive CR oxycodone/CR naloxone for a period of six months in an open-label extension, with the investigator’s concurrence.

Study evaluations
Analgesic efficacy was assessed using a 5-point categorical scale for pain intensity (0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = excruciating) and a 100 mm visual analogue scale (VAS) twice daily in the patient diary at 08:00 and 20:00. Patients also recorded rescue medication use, rescue laxative use, stool frequency (date and time of each bowel movement) and stool consistency (Bristol Stool Form Scale) in their diaries.

At baseline, crossover and end of study, the impact of pain on sleep (since the last evaluation) was assessed using the Pain and Sleep Questionnaire (PSQ) (19-24). Pain and sleep (since the last evaluation) were assessed with a 100 mm VAS (anchors never to always): ‘How often have you needed pain medication to fall asleep?’; ‘How often have you had trouble falling asleep because of pain?’; ‘How often have you needed sleep medication to help you fall asleep?’; ‘How often have you been awakened by pain during the night?’; ‘How often have you been awakened by pain in the morning?’; ‘If you are sleeping with a partner,
### TABLE 1
Mean dose, rescue medication dose, treatment preference, treatment effectiveness and Global Impression of Change scores

<table>
<thead>
<tr>
<th></th>
<th>CR oxycodone/CR naloxone</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication dose every 12 h, mg</td>
<td>36.5±7.3/18.2±3.7</td>
<td>38.1±5.5/19.1±2.8</td>
<td>0.1050</td>
</tr>
<tr>
<td>Rescue dose, number of acetaminophen/codeine</td>
<td>2.6±3.1 (790/78)</td>
<td>4.3±3.5 (1290/129)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Treatment effectiveness*</td>
<td>1.4±1.0</td>
<td>0.9±1.0</td>
<td>0.0216</td>
</tr>
<tr>
<td>Treatment preference, %</td>
<td>1.4±1.0</td>
<td>1.0±1.0</td>
<td>0.0258</td>
</tr>
<tr>
<td>Patient (20% no preference)</td>
<td>56</td>
<td>24</td>
<td>0.0127</td>
</tr>
<tr>
<td>Investigator (15% no preference)</td>
<td>57</td>
<td>28</td>
<td>0.0218</td>
</tr>
<tr>
<td>Global Impression of Change scores†</td>
<td>3.2±1.4</td>
<td>3.9±1.5</td>
<td>0.0102</td>
</tr>
<tr>
<td>Patient</td>
<td>3.1±1.4</td>
<td>4.0±1.6</td>
<td>0.0035</td>
</tr>
<tr>
<td>Investigator</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data presented as mean ± SD unless otherwise indicated. *4-point scale: 0 = not effective; 1 = slightly effective; 2 = moderately effective; 3 = highly effective; †7-point scale: 1 = very much improved to 7 = very much worse

how often was your partner awakened from his/her sleep?". The duration and quality of sleep was assessed by asking the patients (anchors very poor to excellent): ‘On average, how many hours of sleep have you been getting each night?’ and ‘Overall, how would you rate the quality of your sleep?’. Items 1 through 5 were summed to derive an overall score.

Patients were asked to rate their pain-related disability at baseline using the Pain Disability Index (PDI) questionnaire at crossover and end of study (25,19). The PDI consists of seven disability subscales, each representing a different area of everyday functioning: family/ home responsibilities; recreation; social activity; occupation; sexual behaviour; self-care; and life support activity. Each scale is graded from zero to 10, zero indicating no disability and 10 indicating total disability. The first five disability subscales address discretionary activities and the remaining two address obligatory activities (26,27). An overall disability score is determined by summing the numerical ratings of the seven disability scales (range zero to 70).

At baseline, crossover and end of study, the Quebec Back Pain Disability questionnaire, which consists of 20 items rated on a 5-point categorical scale (0 = not difficult at all; 1 = minimally difficult; 2 = somewhat difficult; 3 = fairly difficult; 4 = very difficult; 5 = unable to do) was administered (28).

At baseline and at the weekly clinic visits, patients were asked to complete the Bowel Function Index (BFI) (29). The BFI consists of three items scored on a 100-point numerical analogue scale: difficulty of bowel movement (0 = easy or no difficulty; 100 = severe difficulty); feeling of incomplete bowel evacuation (0 = not at all; 100 = very strong); and judgement of constipation (0 = not at all; 100 = very strong) over the past week.

At baseline, crossover and end of study visits, the general health status outcome measure (the Short Form 36 [SF-36] health survey), was administered (30,31). Effectiveness of Treatment (19,20,32) and Global Impression of Change (GIC) (33) were assessed by the patient and the investigator at crossover and end of study. Effectiveness of treatment was assessed using a 4-point categorical scale to describe the effectiveness of the analgesic treatment based on the degree of pain relief over the past seven days (not effective, slightly effective, moderately effective, highly effective).

Overall treatment preference was assessed by the patient and the investigator at the end of the study before unblinding the treatment allocation (Table 1) by asking, ‘Which treatment period did you prefer?’ The initial period of the study (phase I); the second period of the study (phase II); or no preference. For GIC, a 7-point ordinal scale was used (1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse).
RESULTS

One hundred patients were screened and 83 patients were included in the present study (Figure 1). Twenty patients discontinued the study, with nine dropping out during active treatment and 11 during placebo treatment. The reasons for dropout were due to adverse events (n=11), consent withdrawn (n=6), protocol violation (n=1) or lost to follow-up (n=2). Of those discontinuing the study due to adverse events, six were during active treatment and five were during placebo administration. Withdrawal of consent was equally split, with three in each phase. Ten patients were disqualified from per-protocol analysis due to initiation or adjustment of antidepressant doses during the study (n=5), noncompliance with study medication dosing (n=2), use of prestudy anesthetics that were considered likely to change the patient’s pain during the study period (n=2); paraspinal injections [mancaine 0.5% solution] are felt within 24 h and have a duration of approximately four weeks, thereby altering the patient’s pain over the course of the study), and reported opioid dependence and abuse during the study (n=1). Forty-four patients that completed at least two weeks in each phase and met all the criteria for evalability (Figure 1) were included in the in-protocol analysis (27 men, 27 women, mean ± SD age 50.6±10.9 years; 94.4% were Caucasian, 1.9% Asian and 3.7% other). The average duration of low back pain was 13.8±10.3 years, with 51% of the patients reporting not working (unemployed or not attending work). Sixty-nine per cent (n=37) were assessed as having a neuropathic component to their back pain.

In the ITT population, the majority (n=75 [80.4%]) of the patients were taking opioid analgesics for their chronic low back pain before the trial, while eight patients (9.6%) were opioid naive. Twenty patients (24%) were taking an oxycodone/acetaminophen combination, 12 patients (14%) were taking CR oxycodone and four patients (5%) a different oxycodone product. Other prestudy treatments included acetylsalicylic acid/ibuprofen/acetaminophen (33.7%), other nonsteroidal anti-inflammatory drugs (31.3%), antidepressants/anticonvulsants (19.3%), muscle relaxants (12.0%), local anesthetic injections (9.6%) and other (7.2%).

The mean (± SD) daily dose of study medication during the final week of each treatment phase was 36.5±7.3 mg/18.2±3.7 mg every 12 h in the CR oxycodone/CR naloxone treatment group and 38.1±7.5 mg/20.0±3.8 mg every 12 h in the placebo group for the per-protocol population (P=0.1050) (Table 1).

The mean baseline daily VAS and ordinal pain scores were 61.4±16.3 mm and 2.5±0.6 for the per-protocol population. In the final week of treatment, mean VAS pain scores decreased to 48.6±23.1 mm and 55.9±25.4 mm in the CR oxycodone/CR naloxone and placebo groups, respectively. The difference between the treatment groups was statistically significant (P=0.0296) (Figure 2). Similar results were observed with the ordinal pain scores after the final week of treatment (active versus placebo 2.1±0.8 versus 2.4±0.9, respectively; P=0.0415).

There was no indication of a carryover effect for both the per-protocol and ITT populations (P=0.6989 and P=0.6179).

Overall PSQ scores were significantly improved with CR oxycodone/CR naloxone compared with placebo (P=0.0046).
TABLE 3  
Pain and Disability Index (PDI) scores during the final week of treatment (per-protocol population n=54)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>CR oxycodone</th>
<th>CR naloxone</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family/home responsibility</td>
<td>6.2±2.1</td>
<td>5.4±2.5</td>
<td>5.6±2.3</td>
<td>3.9±0.2</td>
<td></td>
</tr>
<tr>
<td>Recreation</td>
<td>7.1±2.5</td>
<td>6.2±2.9</td>
<td>6.5±3.0</td>
<td>0.3167</td>
<td></td>
</tr>
<tr>
<td>Social activity</td>
<td>6.2±2.7</td>
<td>5.4±2.6</td>
<td>5.8±2.9</td>
<td>0.0815</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td>6.9±2.4</td>
<td>5.9±3.0</td>
<td>6.3±2.9</td>
<td>0.1592</td>
<td></td>
</tr>
<tr>
<td>Sexual behaviour</td>
<td>6.7±2.7</td>
<td>5.2±3.2</td>
<td>5.3±3.3</td>
<td>0.5419</td>
<td></td>
</tr>
<tr>
<td>Self care</td>
<td>4.4±2.7</td>
<td>3.4±2.9</td>
<td>4.1±2.9</td>
<td>0.0500</td>
<td></td>
</tr>
<tr>
<td>Life support</td>
<td>4.5±2.8</td>
<td>3.0±2.8</td>
<td>4.0±2.9</td>
<td>0.0190</td>
<td></td>
</tr>
<tr>
<td>Total pain and disability index scores</td>
<td>42.0±13.2</td>
<td>34.3±15.6</td>
<td>37.5±15.2</td>
<td>0.0511</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as mean ± SD unless otherwise indicated. There were statistically significant improvements after controlled release (CR) oxycodone/CR naloxone treatment compared with placebo treatment for two items (self care and life support), and the total PDI scores approached statistical significance between treatments (P=0.0511). There were statistically significant improvements from baseline in all seven subscales following treatment with CR oxycodone/CR naloxone (P<0.0264) and in only two subscales following placebo treatment (P=0.0142). The decreases from baseline for the total PDI scores were 18.7% (P=0.0001) and 10.6% (P=0.005) following CR oxycodone/CR naloxone and placebo treatments, respectively.

(Tables 2). PDI scores are listed in Table 3 and the overall PDI scores approached statistical significance (P=0.0511). There were no differences between treatment groups for all of the SF-36 domains and total Quebec Back Pain scores or individual items at the end of the study.

Mean BFI scores did not change during the final week of treatment compared with baseline (39.3±33.0) for CR oxycodone/CR naloxone or placebo (33.6±30.2; P=0.2412 and 32.4±29.5; P=0.1586, respectively), and the difference between treatment groups was not statistically significant (P=0.8729) (Figure 3).

The mean frequency of bowel evacuation was similar to baseline (1.0±0.5/day), with no difference between the treatment groups at the end of the study (0.9±0.5 tablets/day for the CR oxycodone/CR naloxone group and 1.0±0.6 tablets/day for the placebo group; P=0.1152).

Stool consistency, as measured by the Bristol Stool Score, also did not change from baseline (3.6±1.1) and was similar between treatment groups at the end of the study (3.7±1.1 for the CR oxycodone/CR naloxone group and 3.6±1.0 for the placebo group; P=0.8394).

There was no difference in the use of rescue laxatives (senosan/docusate sodium tablets) during the final week of treatment (0.4±0.7 tablets/day for the CR oxycodone/naloxone group and 0.4±0.8 for the placebo group; P=0.4439).

At baseline, one week after withdrawal of pre-study opioid analgesics, the mean SOWS score was 0.85±0.59. One week after the end of each treatment phase, the mean SOWS scores for the CR oxycodone/CR naloxone and placebo groups were 0.76±0.60 and 0.79±0.60, respectively (P=0.5595).

Table 4 lists the incidence of the most common adverse events. There were no significant differences between treatment groups in the overall incidence of adverse events (P=0.0079). Among common adverse events, significantly more somnolence was reported during the active treatment phases (P=0.0045). There were four patients who reported serious adverse events during the trial. Two occurred during placebo treatment (one fracture in association with an accidental fall, and suspected recurrent transient ischemic attacks with weakness, lack of coordination of hands and difficulty speaking) and two occurred during CR oxycodone/CR naloxone treatment (hospitalization for abdominal cramps, gas, nausea, diarrhea and fever, and for diverticulitis and irritable bowel syndrome). The investigator’s assessments in all four cases were “not related to study medication”.

The ITT population included 83 patients (39 men, 44 women mean ± SD) age 51.3±12.5 years, 91.6% were Caucasian, 2.4% Asian and 6.0% other. Mean daily doses observed in the ITT population were 18.7% (P=0.0001) and 10.6% (P=0.005) following CR oxycodone/CR naloxone and placebo treatments, respectively.

(36.5 mg/18.2 mg) were similar to the per-protocol population (34.2 mg/17.1 mg; P=0.2595), with significantly less rescue medication (acetaminophen/codeine 300 mg/30 mg tablets) used in the CR oxycodone/CR naloxone treatment group compared with the placebo group (P=0.0003) (Table 1). VAS and 5-point ordinal pain intensity scores during the final week of treatment with CR oxycodone/CR naloxone compared with placebo were 52.2±23.0 mm versus 57.8±24.2 mm (P=0.0527) and 2.3±0.8 versus 2.5±0.9 (P=0.0862), respectively.

Fifty patients were enrolled in the open-label extension, during which they received treatment with CR oxycodone/CR naloxone for up to six months. The mean duration of treatment was 163.3±41.6 days, and 40 patients completed a full six months of treatment. The reasons for withdrawal from the open-label study were: adverse events (n=3), insufficient therapeutic effect (n=2), protocol violation (n=1) and other (n=2). There was one patient who underwent less than one day of treatment in open-label (started and stopped on the same day) but was nevertheless included in the analysis, and one patient was lost to follow-up. Only an ITT analysis was applied to the open-label phase.

The mean oxycodone dose per day did not vary greatly from the end of the double period (36.0 mg/18.0 mg ± 8.3 mg/4.15 mg) to the end of open-label period (35.10 mg/17.55 mg ± 9.30 mg/4.65 mg). Ordinal pain scores decreased from 2.5±0.83 at the final double-blinded assessment to 1.8±0.71 at the end of the open-label period.

DISCUSSION

The results of the present randomized, double-blinded, crossover study showed that CR oxycodone/CR naloxone was significantly more...
effective than placebo in the treatment of chronic low back pain when
injected at a dose of 10 mg/5 mg and titrated to effect to a maximum
dose of 40 mg/20 mg every 12 h. This treatment effect was demon-
strated despite a significantly greater use of rescue analgesia in the
placebo group.

For both primary assessments of pain intensity (VAS and ordinal),
CR oxycodone/CR naloxone produced significantly lower scores than
placebo treatment in titrated patients taking study medications as pre-
scribed. The difference in 100 mm VAS score between CR oxycodone/CR
naloxone and placebo was 7.3 mm, and there was a difference of 0.3 on the
ordinal scale. Reductions in chronic pain intensity of 10% to 20% are
considered to reflect minimally important changes (37). The improvement in
pain from baseline for CR oxycodone/CR naloxone was 21% on the 100 mm VAS and 16% on the
ordinal scale. The finding that a statistically significant majority of patients
and investigators preferred the CR oxycodone/CR naloxone treatment
phase for the management of pain, when asked before unblinding of the
treatment allocation, demonstrates that the differences in treatment
outcomes between CR oxycodone/CR naloxone and placebo treat-
ments were clinically evident to the patients and investigators. In addi-
tion, both patients and investigators rated the effectiveness and GIC of
CR oxycodone/CR naloxone as significantly greater than placebo. CR
oxycodone/CR naloxone also provided a statistically significant
benefit for patients’ sleep and improvement in the overall PSQ score
compared with placebo, which was accompanied by significant improve-
ments from baseline in three of eight items on the questionnaire for CR
oxycodone/CR naloxone treatment. Sleep disturbance is a common
complaint among patients with chronic pain (38) and changes in sleep
affect pain reporting (39); therefore, sleep quality is an important goal
in pain management.

The corresponding differences in pain scores in the ITT population
trended in the direction observed in the per-protocol analysis, with
differences of 5.6 mm and 0.2 relative to placebo on VAS and ordinal
pain scores, respectively. However, the differences did not reach statis-
tical significance for VAS (P=0.0527) or ordinal pain (P=0.0862)
scores. With the study powered for a per-protocol analysis, potential
factors for these outcomes include a lack of sufficient within-patient
data available from subjects in the ITT analyses.

Due to the ethical concerns that may be associated with placebo-
controlled studies, an active opioid rescue medication was used. In
the present study, the higher consumption of active rescue medication
in the placebo group reached statistical significance, with the placebo
group using approximately two additional tablets of
codeine/acetaminophen daily compared with the CR oxycodone/CR
naloxone group. The use of an active opioid rescue as a pro re nata
regimen in a placebo-controlled study helps patients to cope with
placebo therapy. The significantly lower use of opioid rescue medica-
tion in the CR oxycodone/CR naloxone group is consistent with the
finding of superior analgesia versus placebo. Additionally, and consist-
ent with the observed pain scores, all of the secondary measures
trended in the same direction.

Most chronic low back pain is musculoskeletal and mechanically
induced and, thus, nociceptive in nature, but many patients may have
symptoms consistent with an additional neuropathic component. In
the present study, approximately 67% of the patients were assessed as
having a neuropathic component to their pain. Previously, it was
believed that opioids were not as effective for neuropathic pain as for
nociceptive pain, but based on a growing number of randomized
placebo-controlled studies, it is now accepted that opioids, including
CR oxycodone, are effective in treating neuropathic pain (19,20,40-42).
Approximately 90% of the patients had previously been treated with
an opioid, including 40% on oxycodone. Analyses did not subdivide
patients based on previous use of oxycodone versus those with no
recent use. With practice of medicine documents as a guide, the exclu-
sion of populations with a history of substance misuse or severe mental
illness was made in the present double-blinded, randomized clinical
trial.

There was no statistically significant difference between treatment
groups with regard to BFI scales, stool frequency and consistency, or
laxative usage, and there were no significant changes from baseline in
any of these assessments. There was, however, no enrollment require-
ment for pre-existing constipation for the present study, and, on average,
the study population was not constipated at the outset, as demonstrated
by the mean bowel evacuation scores of 1.0±0.5 per day. An excessive
taxation effect of CR oxycodone/CR naloxone was not observed in treat-
ment groups that were not constipated at the outset. Moreover, before
study entry, less than one-half of the patients (42%) were using single-
entity opioids (although 68% of patients had been using a combination
opioid preparation). By the end of the study, patients in the active treat-
group were receiving a mean daily dose of approximately 7.3 mg CR
oxycodone (plus approximately 750 mg/75 mg per day of acetaminophen
plus codeine in the form of rescue medication). Given that CR oxy-
codone/CR naloxone yields oxycodone plasma levels comparable with
CR oxycodone, it is noteworthy that CR oxycodone/CR naloxone was
not associated with a statistically significant change in bowel function.
However, the design of the present trial is not suitable to prove that the
naloxone component of CR oxycodone/CR naloxone pre-empted the
development of OIC.

The most common reason for withdrawal from the study was
adverse events (see Figure 1). The overall rate of withdrawal in the
present study was 24%. Five patients in the placebo group and six
patients in the CR oxycodone/CR naloxone group dropped out due to
adverse events. Overall dropouts were relatively balanced between
the treatment groups and therefore not considered to be biasing the
primary analysis. This equates to a withdrawal rate due to adverse
events in the CR oxycodone/CR naloxone treatment phase of
7.2%.

Although there were two serious adverse events during
CR oxycodone/CR naloxone treatment, investigators deemed these
to be unrelated to study medication. There were no statistically
significant differences in adverse events between CR oxycodone/
CR naloxone and placebo treatments except for somnolence, which
occurred more frequently in patients receiving CR oxycodone/
CR naloxone. Adverse events, such as asthenia, constipation, dizzi-
ness, dry mouth, headache, nausea, pruritus, somnolence, sweating
and vomiting, are common for oxycodone-containing products (43).
Overall, the rate of adverse events was low, with all adverse events
reported by ≤12.2% of patients. The low incidence of adverse events
compared with placebo for CR oxycodone/CR naloxone in the present
study is consistent with a favourable safety profile.

CR oxycodone/CR naloxone is unique in containing both an agon-
ist and an antagonist with a low systemic bioavailability; therefore, the
question arises as to whether opioid withdrawal effects may be observed
during the course of the study. No statistically significant differences were
observed between treatments with respect to the symptom listing on a
modified SOWS scale, either during the study treatment phases or on
discontinuation of CR oxycodone/CR naloxone before crossover to pla-
cebo in the double-blinded phase. The purpose of the modified SOWS
questionnaire was to provide a structured probe of symptoms commonly
associated with the syndrome of opioid withdrawal in patients under-
going pain therapy. In addition, there were no reports of withdrawal
symptoms by the investigators at any time during the study. This is
consistent with findings in other clinical trials with CR oxycodone/CR
naloxone, in which discontinuation of treatment did not result in opioid
withdrawal in controlled use for up to three months (14,16).

As noted by Martell et al (44), most published controlled studies of
opioids for chronic low back pain are of relatively short duration, pro-
viding little evidence regarding the efficacy or safety of long-term
opioid treatment (45-48). However, a three-month, double-blinded
controlled study demonstrated a statistically significant improvement
in pain intensity and pain relief scores with CR oxycodone compared
with placebo (49). Similar conclusions were reached in a study of CR
oxycodone involving more than 200 patients with chronic noncancer
pain for periods of up to three years (50). Approximately equal
numbers of patients with osteoarthritis, neuropathic pain or low back pain were enrolled. While nearly one-half of the patients required a dose increase in the first three months, further increases thereafter were gradual and minimal, and were associated with stable levels of pain control. Based on observer reports of drug-seeking behaviour, six patients were assessed as having probable drug abuse or dependence, although none met formal diagnostic criteria for substance abuse. Findings of stable pain control and absence of statistically significant dose escalation have also been reported in other studies with CR oxycodone (51) or CR morphine (52) for treatment periods of up to three to 4.5 years and one year, respectively.

The improvements in pain scores observed during the randomized phase of the present study in patients taking the product as prescribed were sustained for the treatment period of up to six months. Moreover, the mean dose of CR oxycodone/CR naloxone at the end of the open-label phase was comparable with the mean dose during the corresponding double-blinded phase. The tolerability of CR oxycodone/CR naloxone was maintained throughout the open-label phase of the study. In the results of the long-term extension phase of the present study, it was observed that patients stabilized on CR oxycodone/CR naloxone maintained efficacy and tolerability for an extended period of time without dose increases.

The present study was adequately powered to detect a difference between treatments, and the target sample size was consistent with power calculations for crossover study designs (36). In terms of the length of patient exposure to blinded treatment, the randomized portion of the study was eight weeks in duration. An effort was made to keep the enrollment criteria as broad as possible while remaining within clinical practice norms for the use of opioids in suitable patients with chronic low back pain. Enrolled subjects met these criteria, but a skewed distribution of subjects according to race for Caucasians emerged. This is reflective of the catchment populations at the investigational sites.

CONCLUSION

In patients who had previously been treated with opioids or were scheduled for opioid treatment, on the primary measure of analgesic efficacy, pain control was significantly better in the CR oxycodone/CR naloxone treatment phase compared with the placebo phase in patients adherent to the protocol, including their taking of blinded study medications. Independent of the increased use of rescue medication in the blinded placebo arm, patient and investigator ratings of treatment effectiveness and preference indicated a meaningful therapeutic benefit of CR oxycodone/CR naloxone. There were no statistically significant differences in reported adverse events in patients receiving active treatment compared with placebo, except for somnolence, which occurred more frequently with CR oxycodone/CR naloxone. The analgesic response profile from the double-blinded phase of the trial continued over the six-month open-label phase. CR oxycodone/CR naloxone was effective for analgesic treatment, with an acceptable tolerability profile, in patients with chronic low back pain when initiated at a dose of 10 mg/5 mg every 12 h with rescue medication and titrated on this regimen, as necessary, up to 40 mg/20 mg every 12 h.

In patients not constipated at outset, titration to effect with CR oxycodone/CR naloxone in a randomized, double-blinded, crossover trial was not associated with increased constipation or any other deleterious bowel symptoms relative to placebo. The foregoing outcomes are consistent with previously completed, pivotal trials powered for ITT analyses on analgesia (46) and bowel function (47-48). Collectively, these data lay the basis for definitive trials with CR oxycodone/CR naloxone for the prevention of OIC.

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REFERENCES


