Original Article

Long-Term Safety and Efficacy of Morphine Sulfate and Naltrexone Hydrochloride Extended Release Capsules, a Novel Formulation Containing Morphine and Sequestered Naltrexone, in Patients with Chronic, Moderate to Severe Pain

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Abstract

Context. Morphine sulfate and naltrexone hydrochloride extended release capsules contain extended-release pellets of morphine with a sequestered naltrexone core (MS-sNT). Taken whole, as intended, morphine is released to provide pain relief; if tampered with by crushing, naltrexone is released to mitigate subjective effects of morphine.

Objectives. This open-label study assessed long-term (12-month) safety of MS-sNT in patients with chronic, moderate to severe pain.

Methods. Safety assessments included determining adverse events (AEs), laboratory assessments, and the Clinical Opiate Withdrawal Scale (COWS). Analgesic efficacy was assessed (diary) as worst, least, average, and current pain using an 11-point numeric scale (0 = none; 10 = worst).

Results. Of 465 patients receiving one or more doses, 160 completed the study. Most patients (81.3%) experienced one or more AEs, most commonly constipation (31.8%) or nausea (25.2%). Thirty-three patients (7.1%) reported serious AEs; one patient’s severe gastrointestinal inflammation and colitis were considered possibly study drug-related. Most discontinuations (30%) occurred in the first month, most often because of AEs (23.7%). There were no clinically relevant changes in laboratory results or vital signs, and no clinically significant electrocardiogram changes deemed study drug-related. During each visit after Week 1, 5% or fewer patients had COWS scores indicating mild withdrawal.

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symptoms (range, 0%–4.8%). Five patients, who did not take the study drug as instructed, had scores consistent with moderate withdrawal. MS-sNT yielded statistically significant improvements from baseline in mean scores for all pain diary items for all visits, except Week 1 for least pain.

**Conclusion.** In this study population, when MS-sNT was taken as directed for chronic, moderate to severe pain for up to 12 months, most AEs were typical opioid-related side effects. Mean COWS scores remained low, indicating lack of withdrawal symptoms and appropriate transition off the study drug at completion. J Pain Symptom Manage 2010;40:734–746. © 2010 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

**Key Words**
Opioid, morphine, naltrexone, chronic pain

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**Introduction**

Chronic pain is a highly prevalent medical condition in the United States; it afflicts 9% of U.S. adults and is the leading cause of disability among the working population.\(^1,2\) When undertreated and undercontrolled, chronic pain can have significant physical, emotional, and financial consequences, including difficulties in working, concentrating, sleeping, exercising, social functioning, personal relationships, and mental health, all of which can contribute to a diminished quality of life.\(^3,4\)

Clinical guidelines, including those developed by the American Pain Society and the American Academy of Pain Medicine, for the treatment of various types of chronic pain, advocate a systematic approach to pain management that includes the use of opioids for patients with moderate to severe pain who have not responded to nonopioid therapies.\(^5\)–\(^10\) Opioids are generally considered part of a multimodal plan for relieving chronic pain.\(^6,11\) Immediate-release opioid formulations typically provide pain relief for four to six hours and are suitable for the treatment of acute pain.\(^2\) Extended-release formulations enable effective pain relief to be achieved with less frequent dosing than immediate-release formulations and are more suitable for treating chronic, moderate to severe pain that requires continuous around-the-clock opioid therapy.\(^12\)–\(^15\)

Treatment paradigms for the effective management of chronic pain often involve the use of long-term opioid therapy. The resulting increased use of opioids has been associated with a significant increase in opioid abuse and diversion.\(^16\)–\(^19\) As extended-release formulations contain higher opioid content per unit dose than immediate-release preparations, they consequently could be targeted for abuse by tampering to rapidly release the full dose.\(^2\)

Various physical and pharmacological strategies have been proposed to create resistance to tampering or to mitigate the subjective effects caused by rapid release of the opioid in the event of tampering. One strategy is to include a sequestered, orally bioavailable opioid antagonist that is released only when the product is subjected to tampering.\(^2\) Morphine sulfate and naltrexone hydrochloride extended release capsules (EMBEDA\(^\text{®}\), King Pharmaceuticals\(^\text{®}\), Inc., Bristol, TN) contain pellets of extended-release morphine sulfate, each with a sequestered core of naltrexone (MS-sNT). When the product is taken orally as directed, naltrexone remains sequestered in the pellet core and only trace systemic concentrations are detected. However, the product is designed such that tampering by crushing the pellets releases the naltrexone to mitigate the positive subjective effects of morphine.\(^20,21\)

Controlled clinical trials have demonstrated that MS-sNT is effective in the treatment of chronic pain.\(^22,23\) Results of a randomized, double-blind, crossover study of patients with chronic pain because of osteoarthritis indicated that MS-sNT has an efficacy and safety profile comparable to that provided by a marketed extended-release morphine sulfate formulation (KADIAN\(^\text{®}\) Capsules, Actavis, Hafnarfjordur, Iceland) that contains polymer-coated, extended-release morphine pellets but with an inert core.\(^22,24\) In a randomized, double-blind, placebo-controlled, multicenter trial of patients
with chronic pain because of osteoarthritis of the hip or knee, MS-sNT maintained a greater degree of pain relief vs. placebo over a 12-week maintenance period.\textsuperscript{23}

This study was designed to evaluate the long-term safety of MS-sNT when administered for up to 12 months to patients with chronic, moderate to severe pain. Secondary objectives were to evaluate the long-term efficacy of treatment with MS-sNT and to assess for the presence of any opioid withdrawal symptoms.

**Methods**

This was an open-label, multicenter study (sponsor study number ALO-KNT-302) assessing the safety and efficacy of MS-sNT for the management of chronic (three months or longer), moderate to severe pain (e.g., osteoarthritis, chronic low back pain with or without radiculopathy, diabetic peripheral neuropathy, postherpetic neuralgia) in men and women aged 18–70 years who were otherwise healthy. The study was conducted in compliance with the Declaration of Helsinki and its amendments, the International Conference of Harmonisation Principles of Good Clinical Practice, and all local regulatory statutes. The protocol and related study materials were approved by an institutional review board or independent ethics committee at each study site before patients were enrolled. All patients provided written informed consent before entering the study.

Patients were excluded if they had a diagnosis of cancer within the past three years (except squamous or basal cell carcinoma of the skin) or had pain in the target area because of cancer, fibromyalgia, migraine, recent trauma or fracture, or infection. Other exclusion criteria included a documented history of allergy or clinically significant intolerance to morphine or other opioids; a history of alcohol or drug abuse within the past five years; clinically significant abnormalities unrelated to the source of pain; medical or psychiatric illness or diagnostic abnormality that, in the investigator’s opinion, would interfere with the study or pose a risk to the patient, for example, morbid obesity (body mass index > 45 kg/m\(^2\)); and any clinically significant laboratory abnormalities. Of note, entry criteria allowed patients with liver function tests up to but not including three times the upper limit of normal (ULN).

Patients also were excluded if they had received pain interventions, including an implanted spinal cord stimulator, intraspinal infusion of any medication within the previous month, epidural or local corticosteroid injections into the target joint within two months, oral or intramuscular corticosteroids within 90 days (except stable doses of prednisone of \(\leq 10\) mg), surgical intervention to the back within six months, elective surgery within eight weeks, or any investigational product within 30 days. Treatment with phenothiazines; monoamine oxidase inhibitors; or high doses of sedatives, hypnotics, or tranquilizers was not allowed. Women of childbearing potential were required to have a negative urine pregnancy test for \(b\)-human chorionic gonadotropin at screening and at monthly intervals, and agreed to practice an acceptable method of contraception.

Patients were evaluated for eligibility at a baseline visit, and then returned to the study site within seven days for enrollment and initiation of study treatment. They were asked to choose the most painful joint or body area to serve as the target site for assessing the efficacy of study treatment, and were asked to rate the intensity of pain in the target joint on a numerical rating scale of 0 (no pain) to 10 (worst pain) over the previous 24 hours.

The initial dose of MS-sNT was based on the patient’s previous treatment for chronic pain. Patients who were not taking opioids at study entry were started on MS-sNT at a dose of 20 mg twice daily, and could be titrated upward or switched to once-daily dosing after three days. Patients who were already receiving an opioid medication started MS-sNT at a dose equivalent to 50\%–75\% of their current daily opioid dose because of the potential for incomplete cross-tolerance. All patients returned to the clinic one week after the initial drug dispensing visit and monthly thereafter, for the remainder of the study.

Throughout the study, dosage of MS-sNT could be adjusted in accordance with the investigator’s best medical judgment. MS-sNT could be administered 12 hours apart or once daily. Capsules were available in dosage strengths of 20, 30, 40, 50, 60, 80, and 100 mg, which could be combined to achieve the desired daily
dosage. Dose could be adjusted at each study visit, based on pain score and adverse event (AE) profile, or between visits if the patient had been on a dose for three or more days and pain relief was inadequate. In such cases, the patient went to the clinic for an unscheduled visit to assess pain intensity and AEs and to return unused capsules. If the increased dose resulted in unacceptable AEs, the dose was reduced. At each study visit, investigators followed drug accountability procedures, which included documenting the return of any unused drug and the dispensing of drug for use until the next scheduled visit.

Patients agreed to refrain from taking nonstudy opioid medications. Use of other analgesics, including acetaminophen, aspirin, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors, was allowed as rescue medication. However, patients were encouraged to refrain from using these additional analgesics as their primary source of pain relief and, instead, were instructed to call the clinic to adjust the MS-sNT dosage in the event of inadequate analgesia. In addition, patients were instructed not to use any rescue medication within 24 hours before a clinic visit. Low-dose aspirin (≤325 mg/day) was allowed for cardiovascular prophylaxis, providing the patient had been on a stable dose regimen for 30 or more days before the baseline visit. In addition, investigators were instructed to direct patients to use prophylactic laxatives to relieve opioid-induced constipation.

At the completion of the treatment period, patients were tapered off opioid therapy using morphine sulfate extended-release capsules (half of the last effective MS-sNT dose taken twice daily for three days, then half of the reduced dose for the next three days, and then dose discontinuation on the seventh day). Alternatively, MS-sNT therapy was changed to currently approved extended-release opioids at the discretion of the investigator. Patients were required to return for a final visit 28–32 days after the completion of the treatment period.

**Assessments**

**Safety.** AEs were recorded at each study visit or evaluation. All AEs were classified by the investigator in terms of their intensity (mild, moderate, or severe); relationship to study drug (definite, probable, possible, unlikely, not related); actions taken; and outcome. An AE was considered serious if it was deemed to cause any of the following: death, a life-threatening condition, hospitalization or prolonged existing hospitalization, a permanent disability or incapacity, a congenital anomaly in an infant born to a mother who was exposed to the study drug during pregnancy, or an important medical event requiring intervention to prevent permanent impairment or damage. Vital signs were measured at every visit from baseline through last treatment visit. A complete physical examination and a 12-lead electrocardiogram (ECG) were performed at baseline and at the six-month and final treatment visits. Clinical laboratory testing was ordered at baseline; the end of Months 3, 6, and 9 of treatment; and at the final treatment visit.

The Clinical Opiate Withdrawal Scale (COWS), an 11-item assessment tool completed by the clinician evaluating signs or symptoms of opioid withdrawal, was administered at all study visits beginning at Month 1 of treatment and in the event of early termination. Total COWS scores of 5–12 indicate mild withdrawal; 13–24, moderate withdrawal; 25–36, moderately severe withdrawal; and greater than 36, severe withdrawal. After completion of the treatment period (12-month study visit), follow-up telephone contact was made for four consecutive days to record AEs and concomitant medications and to monitor for subjective signs of opioid withdrawal. At the posttreatment follow-up visit (30±2 days) after the last dose of study medication, AEs and concomitant medications since the previous visit were recorded, and a final assessment for signs and symptoms of withdrawal using COWS was performed. Any AE and any new abnormal laboratory result considered clinically significant were followed to a satisfactory resolution, until stable, or until they could be explained by other known cause (s) (i.e., concurrent condition or medication) and clinical judgment indicated that further evaluation was not warranted. Evaluation using a prespecified list of opioid-associated AEs, including dry mouth, constipation, dizziness, somnolence, pruritus, nausea, and vomiting, was also performed.

**Efficacy.** Efficacy was assessed as a prespecified secondary outcome. During study visits,
patients were asked to rate the pain intensity at the target joint or area using an 11-point numeric rating scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine), as is used on the Brief Pain Inventory Short Form questionnaire to assess the worst, least, and average pain in the last 24 hours, as well as current pain. Patients also provided a global assessment of the study drug using a five-point numeric rating scale ranging from 1 (poor) to 5 (excellent) during each scheduled study visit beginning one week after study drug was dispensed.

Pharmacokinetics. An exploratory pharmacokinetic (PK) analysis during long-term use of MS-sNT also was conducted in a subset of patients. Planned sample size was up to 20 patients for each of the following four groups: total starting daily dose of less than 80 mg; 80–120 mg; greater than 120 mg; and aged 65 years or older. Patients were selected sequentially from each group and were asked to provide a separate informed consent for participation in the PK study. Predose blood samples were collected at each monthly visit. Plasma concentrations of morphine, naltrexone, and 6-β-naltrexol, the major metabolite of naltrexone, were measured by validated liquid chromatography/mass spectrometry methods (CEDRA Corporation, Austin, TX). The limits of quantification (LOQ) for morphine, naltrexone, and 6-β-naltrexol were 0.200 ng/mL, 4 pg/mL, and 0.25 pg/mL, respectively. The intra- and inter-run coefficient of variability values were, respectively, 1.7%–10.7% and 4.9%–9.3% for the morphine assay, 1.4%–26.9% and 4.8%–13.6% for naltrexone, and 0.7%–7.7% and 1.9%–5.3% for the 6-β-naltrexol assay.

Statistics

A sample size of 400 patients was selected to allow for a 75% dropout rate and have 100 patients complete six months of treatment and for an 87.5% dropout rate and have 50 patients complete the entire 12-month study. Safety was assessed in all patients who received study medication. Treatment-emergent AEs were categorized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA®) v9.1. The incidence of AEs and changes in vital signs, ECGs, and clinical laboratory test results were summarized using descriptive statistics. Shifts in laboratory values were evaluated based on the minimum value reported, the maximum value reported, and the value obtained at the end of the study, with number and percentage of subjects with shift values within normal range, greater than normal range, and less than normal range reported. Changes were reviewed by the investigator at each site and then by the medical monitor to determine whether they were clinically relevant. The incidence and severity of selected opioid-associated AEs, including dry mouth, constipation, dizziness, somnolence, pruritus, nausea, and vomiting, also were tabulated. COWS scores, both actual values and changes from the first evaluation, were summarized using descriptive statistics.

Efficacy was summarized descriptively based on the pain intensity scales in all patients who received study drug and had at least one postbaseline pain intensity measure or global assessment. Each of the four pain intensity scales was analyzed at each visit in terms of the actual value and the change from baseline. A paired t-test was used to compare differences between each postbaseline and baseline assessment. Comparisons with baseline were based on values for those patients who had values for baseline and at the respective visit. Average daily dose of rescue medication was determined based on the number of pills dispensed and date returned. However, given the wide range and variability in these numbers, the analysis was not considered an accurate representation of daily consumption, and results are not included.

The average daily dose of morphine was calculated as the capsule dosage × (number of capsules dispensed − number of capsules returned)/(date returned − date dispensed + 1). If there were multiple dosages dispensed at a visit, the average daily dose was the sum of the averages for each dosage. For the exploratory PK analysis, data were analyzed by dose (dose normalized to account for changes in dose during study), and age groups and sex were represented graphically over time and in tabular format.

Results

Three populations of patients were analyzed: 1) the safety population consisted of
all patients who received at least one dose of study drug; 2) the intent-to-treat (ITT) population consisted of all patients receiving at least one dose of study drug and having at least one postbaseline efficacy assessment; and 3) the PK population consisted of all patients from whom PK samples were drawn and from whom sufficient plasma concentrations were available to allow the calculation of PK parameters.

Baseline demographic and clinical characteristics are displayed in Table 1. Of 467 patients enrolled, 465 received at least one dose of study drug (safety population), and all of these completed at least one postdose efficacy assessment (ITT population). Therefore, the safety and ITT populations were the same (465). A total of 160 patients completed the study. The mean age was 51.7 years; 52.7% were women and 88.2% were white (Table 1). The most common pain sources were lower back (265 out of 465, 57.0%); hip (52 out of 465, 11.2%); anterior knee (50 out of 465, 10.8%); and posterior neck (25 out of 465, 5.4%). The most common concurrent medical conditions reported at baseline were hypertension (183 out of 465, 39.4%); depression (140 out of 465, 30.1%); osteoarthritis (140 out of 465, 30.1%); insomnia (110 out of 465, 23.7%); back pain (108 out of 465, 23.2%); drug hypersensitivity (107 out of 465, 23.0%); and hysterectomy (101 out of 465, 21.7%). Of the 465 patients treated, 297 (63.9%) had used opioids within 30 days before the first dose of study drug; 168 (36.1%) had not. Of those patients who had been taking opioids (patients could have used more than one), 195 (66%) had used hydrocodone, 49 (16%) had used oxycodone, 41 (14%) had used morphine, 36 (12%) had used tramadol, 16 (5%) had used methadone, 16 (5%) had used fentanyl, 14 (5%) had used controlled-release morphine sulfate, and four (1%) had used hydromorphone.

Patient disposition is shown in Fig. 1. The most common reasons for discontinuation were AEs (110, 23.6%); noncompliance (64, 13.7%); withdrawal of consent (52, 11.1%); lack of efficacy (39, 8.4%); and lost to follow-up (28, 6.0%). Approximately 30% (129 out of 465) of patients discontinued in the first 30 days of treatment. The discontinuation rates were similar between those patients who were opioid naive (108 out of 168, 64.3%) and those who were not (197 out of 297, 66.3%). Among opioid-naive patients, 50 (29.8%) discontinued because of AEs and four (2.4%) because of lack of efficacy. Among opioid-experienced patients, 60 (20.2%) discontinued because of AEs and four (2.4%) because of lack of efficacy. Among opioid-experienced patients, 60 (20.2%) discontinued because of AEs and 35 (11.8%) because of lack of efficacy.

The median average daily dose of morphine in MS-sNT over the course of study in the safety population was 58.6 mg, with 25th-
75th-percentile doses at 39.2 and 98.0 mg, respectively. For the completor population, the median average daily dose of morphine was 76.9 mg, and the 25th- and 75th-percentile doses were 51.3 and 110.8 mg, respectively. The mean duration of exposure was 180.3 ± 152.1 days (median, 135 days), with a maximum duration of exposure of 380 days.

Primary Outcome: Safety

Overall, 378 patients (81.3%) reported AEs; of these 288 (61.9%) reported AEs considered to be treatment related by the investigator. The most common AEs were constipation (n = 148, 31.8%); nausea (n = 117, 25.2%); headache (n = 56, 12.0%); and vomiting (n = 55, 11.8%). Incidence of treatment-related AEs is shown in Table 2. The incidence of prespecified opioid-associated AEs that were classified as severe is shown in Table 3. The event-incidence rate per interval was determined for AEs that began in that interval; thus, ongoing AEs were not counted in subsequent intervals. Using this method, incidence of AEs was highest in the first 30 days (66.2%) of treatment and decreased thereafter. There were 33 patients (7.1%) who reported one or more serious AEs (SAEs), but no SAE was reported more than twice. SAEs reported by two patients each were colitis, chest pain, bacterial arthritis, osteoarthritis, and deep vein thrombosis. One patient had an SAE (severe gastrointestinal inflammation and severe colitis) judged possibly related to the study drug. No other SAE was considered related to the study drug. Of note, one SAE reported as acute myocardial infarction had been reported on the patient’s case report form as having occurred four years before treatment with MS-sNT in this study and was considered unrelated to the study drug. No deaths were reported during the study.

Among the 110 patients (23.7%) who discontinued because of AEs, the most common AEs were considered to be opioid related (nausea, 5.4%; constipation, 3.4%; vomiting, 2.6%). There were no notable changes in the mean percent change from baseline or clinically important pattern of vital sign changes in any individual sign. There were 79 patients (20.5%) who had an ECG tracing that was changed from baseline; of these, only one was reported as clinically significant but judged by the investigator as not clinically related to the study drug (the patient was diagnosed with an incomplete right bundle branch). Five other ECG abnormalities were reported as AEs (acute myocardial infarction, angina pectoris, bradycardia, bundle branch right block, congestive cardiac failure) and were considered unrelated to the study drug.

There were no clinically relevant mean changes from baseline in hematology, clinical chemistry, or urinalysis. The most common hematology changes from baseline were normal to high shifts for neutrophils (8.4%) and normal to low shifts in lymphocytes (11.2%), RBC count (8.8%), hemoglobin (8.2%), and hematocrit (7.1%). There were no clinically notable patterns in the number of patients with normal to abnormal shifts in urinalysis. The most common clinical chemistry shifts were normal to high shifts in alanine aminotransferase (ALT) (8.0% during study and 4.5% at study end) and aspartate aminotransferase (AST) (8.8% during study and 4.5% at

Table 2
Summary of Treatment-Related Adverse Reactions* Reported by 2% or More of Patients

<table>
<thead>
<tr>
<th>Event</th>
<th>n (%) of Overall N = 465</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>145 (31.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>103 (22.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>37 (8.0)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>34 (7.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>32 (6.9)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>26 (5.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19 (4.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19 (4.1)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>17 (3.7)</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>16 (3.4)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>13 (2.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (2.2)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>10 (2.2)</td>
</tr>
</tbody>
</table>

*Defined as an adverse event attributed to study drug by the investigator; determined from sum of all probably, possibly, and definitely related to treatment-emergent adverse events.

Table 3
Frequency of Preselected Opioid-Associated Adverse Events Classified as Severe (All Causality)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>n (%) of Overall N = 465</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>14 (3.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (1.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (0.9)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>
study end), based on the highest value reported in the study and at study end. Of the more than 400 patients included in this study, only four patients accounted for five values of ALT and AST > 3 × ULN.

Four patients had moderate elevations of hepatic enzymes. A 59-year-old woman had an isolated elevation of AST (4.1 × ULN) at three months, which returned to normal despite increasing doses of MS-sNT; the patient discontinued after 10 months because of a positive alcohol screen, consistent with her history of alcoholism. The second patient, a 60-year-old woman with a concomitant diagnosis of gastroenteritis, had elevated ALT (3.4 × ULN), AST (2.0 × ULN), and alkaline phosphatase (1.5 × ULN) at 8.5 months. During the previous three months, daily dose of MS-sNT was 80 mg. Liver function enzymes returned to normal values when MS-sNT dose was reduced to 40 mg/day and the patient completed the study. A third patient, a 49-year-old woman who discontinued from the study after less than four days on MS-sNT because of nausea, had elevated ALT (3.4 × ULN) and AST (4.9 × ULN); there was no documented follow-up. The fourth patient, a 34-year-old woman with concomitant upper respiratory infection who discontinued treatment after six days because of increasing shortness of breath, noncardiac chest pain, and nausea, had an isolated significant elevation of ALT that was reported as normal while off study drug at follow-up. An additional six patients had ALT values that were greater than 2 × ULN at study entry that normalized during the study.

At baseline, the mean COWS score was 1.2 (baseline range, 0–17); 34 patients (7.8%) had scores of 5–12 consistent with mild withdrawal, and one patient (0.2%) had a score between 13–24 consistent with moderate withdrawal, possibly because of insufficient dosing at baseline. A small number of patients had COWS scores consistent with mild withdrawal at Week 4 (n = 16, 4.8%) to Month 6 (n = 3, 1.4%). There was no elevation in COWS scores at the end of the study. All five patients with COWS scores consistent with moderate withdrawal symptoms did not take study drug as instructed: they adjusted their own dose of study drug, did not take study drug, used incorrect dosing, reported loss of study drug, or ran out of study drug before the next visit. There was no correlation between COWS scores and quantifiable naltrexone concentrations in those patients who had PK assessments. Four patients had at least one outlying plasma naltrexone concentration during the study (ranging up to 145 pg/mL). These levels were not associated with increased COWS scores.

**Prespecified Secondary (Efficacy) Outcomes**

The mean change from baseline in all four pain diary items (worst, least, average, and current) was significant for all visits (Fig. 2). The mean percent change from baseline also was significant for all four pain diary items at all visits, except Week 1 for least pain. The percent change from baseline pain scores decreased until Week 28 and remained stable thereafter. Decrease from baseline in pain intensity curves for the ITT and completer populations were similar, indicating that patient discontinuations did not impact mean decreases in pain intensity scores (Fig. 2).

Among patients remaining in the study at each visit, the proportion rating medication as good, very good, or excellent was 223 out of 390 (57.2%) after Week 1, 244 out of 318 (76.7%) after Week 4, and greater than 90% from Week 12 (n = 253) through study completion (n = 162).

**Plasma Pharmacokinetics Assessment**

Ninety-three patients, a subset of the ITT population, participated in the PK study (there were fewer than 20 patients in the group receiving an MS-sNT dose >120 mg). Plasma morphine concentrations were highly variable, because of dose titrations up or down during the study; most of the dosing changes were made in the first three months of the study, and the greatest increase in morphine levels occurred during the first three months of treatment and then remained within the range of 18.6–26.9 ng/mL (Fig. 3). Accurate assessment of the effect of MS-sNT dose on plasma morphine, naltrexone, and 6-β-naltrexol concentrations required dose normalization to account for changes in dose during the study. There was no increase in dose-normalized plasma morphine concentrations over time, indicating that morphine did not accumulate during the study.

Of 444 samples analyzed for plasma naltrexone over a full year of dosing, 49 (11%) had
quantifiable concentrations, and the median of these 49 quantifiable concentrations was 10.1 pg/mL. Three patients had at least one outlying plasma naltrexone concentration (>1 standard deviation [SD] of the mean, 49.4 pg/mL) during the study (69.7–145 pg/mL). At times when naltrexone concentrations were highest, COWS scores remained low (≤4). A fourth patient had plasma naltrexone concentrations of 14.4 and 44.1 pg/mL at Weeks 36 and 52, respectively; COWS score was 0 at 52 weeks when the naltrexone concentration was highest. Quantifiable plasma naltrexone concentrations had no observable clinical effects.

Of 457 samples analyzed for 6-β-naltrexol, 338 (74.0%) had quantifiable concentrations. The median quantifiable 6-β-naltrexol concentration over the entire study was 18.5 pg/mL. The maximum plasma 6-β-naltrexol concentration was 3720 pg/mL. The highest 6-β-naltrexol concentrations were consistent with the highest naltrexone concentrations. As was the case with naltrexone, there was no observable clinical effect of 6-β-naltrexol on withdrawal symptoms, as measured by COWS scores. Neither plasma naltrexone nor 6-β-naltrexol accumulated over the 52 weeks of the study. Although there were very weakly positive correlations to increase in naltrexone dose, the increases in plasma naltrexone ($R^2 = 0.102$) and 6-β-naltrexol ($R^2 = 0.121$) concentrations were considered clinically negligible. There were no positive correlations for age and sex to plasma naltrexone and 6-β-naltrexol concentrations. Not surprisingly, plasma morphine concentrations positively correlated with increasing dose ($R^2 = 0.4585$).

**Discussion**

In this open-label study in patients with chronic pain, once- or twice-daily treatment with MS-sNT for up to one year was generally safe. AEs characteristic of a morphine-containing product were reported. There were no clinically relevant changes from baseline in mean hematology or clinical chemistry values and no shift from normal reported by more than 10% of the patients. We specifically monitored the hepatic enzymes ALT and AST because of previous reports of dose-related hepatotoxicity in patients treated daily with naltrexone at doses higher than 50 mg and ranging to 300 mg. While the dosage of naltrexone sequestered in MS-sNT capsules was significantly lower and taken as directed, only trace amounts in plasma would be expected, the decision was made to allow enrollment of patients with elevations of ALT and/or
AST of up to 3 × ULN to increase the likelihood of identifying changes in these liver function tests. Four patients had isolated changes (>3 × ULN) in liver enzymes. Three were transient and may have been related to concomitant conditions; one patient, who discontinued after four days of treatment because of nausea, was lost to follow-up. Six patients with elevations at baseline (>2 × ULN) of either AST or ALT had levels that normalized during the study.

Because trace amounts of naltrexone and its metabolite 6-ß-naltrexol have been previously detected after MS-sNT administration,

because it was important to determine if these molecules would accumulate and whether signs of opioid withdrawal could be observed in patients during chronic exposure to MS-sNT. During MS-sNT treatment or after its discontinuation, there was no clear evidence of withdrawal syndrome, as assessed using COWS scores. No patient taking MS-sNT as instructed reported clinically relevant COWS scores; post-study investigation revealed that those five patients reporting COWS scores greater than or equal to 13 did not adhere to instructions for use or had a discrepancy with study medication.

PK analyses demonstrated that morphine, naltrexone, and 6-ß-naltrexol did not accumulate in plasma during the 12 months of treatment with MS-sNT. Additionally, in patients with quantifiable plasma naltrexone concentrations, COWS scores remained low and did not correlate with plasma naltrexone concentrations. A higher percentage of patients had quantifiable 6-ß-naltrexol than naltrexone because of the rapid metabolism of naltrexone and the greater sensitivity of the assay method used for 6-ß-naltrexol vs. naltrexone. The major metabolite of naltrexone, 6-ß-naltrexol is a weaker opioid antagonist (1/12th to 1/50th depending on species) than its parent compound.

Because a pharmacologically active dose of naltrexone would be expected to precipitate potentially severe symptoms of opioid withdrawal syndrome in opioid-dependent patients, it is important to put the plasma naltrexone and 6-ß-naltrexol concentrations reported in this study into perspective. The bioanalytical assay used for naltrexone in this study (LOQ = 4 pg/mL [0.004 ng/mL]) was highly sensitive compared with other common methods with an LOQ of 0.1 ng/mL.30,31

The plasma naltrexone and 6-ß-naltrexol concentrations observed in this study ranged up to 145 pg/mL (0.145 ng/mL) and 3720 pg/mL (3.720 ng/mL), respectively, and did not accumulate over time. These concentrations are much lower than those known to have a clinical effect. In a randomized crossover study demonstrating dose proportionality across the 50- to 200-mg dose range in 24 healthy male volunteers, mean (SD) Cmax for the naltrexone 50-mg dose was 8.6 (4.8) ng/mL for naltrexone and 99.3 (30.2) ng/mL for 6-ß-naltrexol. For the naltrexone 100-mg dose (two 50-mg tablets), the mean Cmax was 19.6 (17.9) ng/mL for naltrexone and 206.8 (78) ng/mL for 6-ß-naltrexol.32 The steady-state equilibrium concentration of plasma naltrexone after 100 mg daily oral doses of naltrexone was 10.9 ng/mL, with steady-state concentrations after 24 hours of 2.1 ng/mL for naltrexone and 17.6 ng/mL for 6-ß-naltrexol.33 Additionally, a receptor binding study using positron-emission tomography scans to assess opioid receptor occupancy by naltrexone at daily doses of 16, 32, and 48 mg estimated that a plasma naltrexone half maximum effective concentration of 1.6 ng/mL is required for occupancy of 90% of human central nervous system opiate receptor sites. Therefore, the trace naltrexone and 6-ß-naltrexol exposure resulting from long-term MS-sNT therapy would not be expected to exert a pharmacological effect.

The median daily dose of morphine in this study was 58.6 mg, a relatively low daily dose. Because the ratio of naltrexone to morphine in MS-sNT is 4%, the exposure to naltrexone would be very low. Although there is a possibility that patients taking higher doses of MS-sNT, with a potentially higher exposure to naltrexone, might experience opioid withdrawal syndrome, there is no evidence at present to indicate that the trace exposure to naltrexone is dose related or that this would be likely. However, tampering by crushing would be expected to release all of the naltrexone, expose the patient to high levels of naltrexone, and may precipitate opioid withdrawal syndrome.

While previous short-term trials have demonstrated the efficacy of MS-sNT in managing chronic pain symptoms, results from this study demonstrate that MS-sNT provided effective pain relief during treatment up to 12
months. Only 39 patients (8.4%) specified lack of efficacy as a reason for discontinuation. Mean improvements from baseline in worst, least, average, and current pain were significant over the 12 months of the trial. The similarity in the decrease from baseline pain intensity curves for the ITT and the completer populations suggests that patient discontinuations did not affect the profile of mean decreases in pain intensity scores. While global assessment scores were favorable throughout the study, an important caveat is that only those patients remaining in the study provided assessments.

There is limited published literature on the outcomes of long-term opioid therapy in patients with chronic noncancer pain. Clinical evidence for long-term efficacy of opioids is based largely on surveys, case studies, and open-label studies, whereas clinical recommendations are based largely on expert consensus.

Although nonrandomized and open label, this trial does contribute up to 12 months of evidence that at least a subgroup of patients can attain and maintain long-term reduction of chronic pain while taking M斯特;NT. The rates of discontinuation (56% at six months [465 – 205 = 260 discontinued = 56%] and 65.6% at 12 months [465 – 160 = 305 discontinued = 65.6%]) in this trial were similar to the rates of discontinuation in other reported long-term opioid studies. The most common AEs in this study, which included gastrointestinal effects (constipation, nausea, vomiting); somnolence; headache; and pruritus, were similar to those reported in previous opioid studies.

As with other open-label studies of pain medications, there are several study limitations. Dose adjustments were made according to the best judgment of the investigators as to whether pain relief was inadequate or AEs were intolerable. There was no comparator arm to place safety and efficacy outcomes into perspective. Although a broad range of pain was included in the study, it was still restrictive. The characteristics of the patients included in the study may not be representative of the range of those typically treated in a clinical practice, and results may not be generalized to other populations of patients with chronic pain who may have concomitant conditions, such as a history of drug abuse, personality disorders, or other medical conditions.

Additional long-term controlled trials and prospective studies are needed to address the issues surrounding long-term opioid therapy.

In conclusion, long-term once- or twice-daily treatment with M斯特;NT (median average daily dose of 58.6 mg) for up to 12 months (mean = 180.3 ± 152.1 days; median = 135 days) in patients with chronic, moderate to severe pain was generally safe and efficacious in this open-label study.

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