

## ORIGINAL ARTICLE

# Methylnaltrexone for Opioid-Induced Constipation in Advanced Illness

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## ABSTRACT

**BACKGROUND**

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Constipation is a distressing side effect of opioid treatment. As a quaternary amine, methylnaltrexone, a  $\mu$ -opioid-receptor antagonist, has restricted ability to cross the blood-brain barrier. We investigated the safety and efficacy of subcutaneous methylnaltrexone for treating opioid-induced constipation in patients with advanced illness.

**METHODS**

A total of 133 patients who had received opioids for 2 or more weeks and who had received stable doses of opioids and laxatives for 3 or more days without relief of opioid-induced constipation were randomly assigned to receive subcutaneous methylnaltrexone (at a dose of 0.15 mg per kilogram of body weight) or placebo every other day for 2 weeks. Coprimary outcomes were laxation (defecation) within 4 hours after the first dose of the study drug and laxation within 4 hours after two or more of the first four doses. Patients who completed this phase were eligible to enter a 3-month, open-label extension trial.

**RESULTS**

In the methylnaltrexone group, 48% of patients had laxation within 4 hours after the first study dose, as compared with 15% in the placebo group, and 52% had laxation without the use of a rescue laxative within 4 hours after two or more of the first four doses, as compared with 8% in the placebo group ( $P < 0.001$  for both comparisons). The response rate remained consistent throughout the extension trial. The median time to laxation was significantly shorter in the methylnaltrexone group than in the placebo group. Evidence of withdrawal mediated by central nervous system opioid receptors or changes in pain scores was not observed. Abdominal pain and flatulence were the most common adverse events.

**CONCLUSIONS**

Subcutaneous methylnaltrexone rapidly induced laxation in patients with advanced illness and opioid-induced constipation. Treatment did not appear to affect central analgesia or precipitate opioid withdrawal. (ClinicalTrials.gov number, NCT00402038.)

**C**LINICIANS OFTEN USE OPIOIDS TO TREAT moderate-to-severe pain; however, opioids frequently induce or aggravate constipation. Empirically, laxative therapy may be burdensome and ineffective and result in temporally unpredictable responses. In addition, severe opioid-induced constipation may limit opioid therapy, worsening analgesia. These drawbacks can substantially compromise the quality of life, especially in patients with advanced illness.

Opioid-induced constipation is predominantly mediated by gastrointestinal  $\mu$ -opioid receptors.<sup>1,2</sup> Selective blockade of these peripheral receptors might relieve constipation without compromising centrally mediated effects of opioid analgesia or precipitating withdrawal. N-methylation of the uncharged systemic opioid antagonist, naltrexone,<sup>3</sup> results in a charged derivative, methylnaltrexone, which has restricted ability to cross the blood-brain barrier in humans because of its polarity and low lipid solubility.<sup>4</sup>

In healthy volunteers, methylnaltrexone reversed the morphine-induced delay in both gastric emptying and oral-cecal transit time without affecting analgesia.<sup>5-8</sup> A small, randomized, placebo-controlled trial involving long-term methadone users also showed that methylnaltrexone induced laxation (defecation).<sup>9</sup>

Our randomized, placebo-controlled, phase 3 trial was designed to determine the efficacy and safety of subcutaneous methylnaltrexone, as compared with placebo, in relieving opioid-induced constipation in patients with advanced illness. An open-label extension trial provided additional data on the use of methylnaltrexone for up to 3 months.

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## METHODS

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### PATIENTS

From February 28, 2004, to October 16, 2005, we conducted both a 2-week, double-blind, randomized, placebo-controlled phase and a subsequent 3-month, open-label extension phase at 27 U.S. and Canadian nursing homes, hospice sites, and palliative care centers. Patients who were 18 years of age or older and had advanced illness, which was defined as a terminal disease (incurable cancer or other end-stage disease) with a life expectancy of 1 month or more, were eligible. Qualifying patients received opioids for analgesia for 2 weeks or more and a stable regimen of opioids

and laxatives for 3 or more days before study entry. Patients also had opioid-induced constipation with either fewer than three laxations during the preceding week and no clinically meaningful laxation (as determined by the investigator) within 24 hours before the first study dose or no clinically meaningful laxation within 48 hours before the first study dose. Women of childbearing potential had negative pregnancy tests.

Exclusion criteria were constipation that was not primarily caused by opioids (as determined by the investigator), mechanical gastrointestinal obstruction, an indwelling peritoneal catheter, clinically active diverticular disease, fecal impaction, acute surgical abdomen, and fecal ostomy. On completion of the double-blind phase of the study, patients could enroll in the open-label phase (Table 1 in the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)).

In collaboration with the principal academic investigators, Progenics Pharmaceuticals designed the protocol and collected and analyzed the data. All authors had independent access to the primary data and vouch for the data's integrity and completeness. The decision to publish was made by the academic investigators. In addition, a consultant who was paid by the sponsor participated in the writing and editing of the manuscript.

The study was approved by either a central or a local institutional review board and followed Good Clinical Practice and Declaration of Helsinki principles. Each patient provided written informed consent before enrollment in the study.

### STUDY DESIGN

In the double-blind phase, a computer-generated randomization schedule, blocked according to study center, was used to assign patients in a 1:1 ratio to methylnaltrexone (at a dose of 0.15 mg per kilogram of body weight) or an equal volume of placebo administered subcutaneously on alternate days for 2 weeks. Patients could continue their baseline laxative regimen throughout the study and take rescue laxatives as needed, though not within 4 hours before or after receiving a dose of the study drug. The study drugs (40 mg of methylnaltrexone per milliliter or placebo) were provided in identically appearing vials. Study staff administered the first dose. Trained caregivers administered subsequent doses. By day 8, if patients had had fewer than three rescue-free laxations

(defined as laxation without the use of a rescue laxative, such as an enema or a suppository, after receipt of the study drug), the initial volume of the study drug could be doubled (to 0.30 mg of methylnaltrexone per kilogram) (Fig. 1).

In the open-label extension trial, patients received subcutaneous methylnaltrexone as needed up to every 24 hours for up to 3 months. The first open-label extension dose (0.15 mg per kilogram) was administered more than 14 days after the first double-blind dose and more than 24 hours after the last double-blind dose. Subsequent doses could be increased to 0.30 mg per kilogram if no laxation occurred within 4 hours or could be decreased to 0.075 mg per kilogram if drug-related adverse events occurred. Safety follow-up was scheduled 30 days after the last study dose.

#### EVALUATIONS

Patients were assessed daily for laxation, including consistency (with six categories, ranging from watery to very hard) and difficulty (with five categories, ranging from no difficulty to great difficulty); concomitant medications; and adverse events. We report adverse events occurring at any time after the administration of the first dose of the study drug. The severity of adverse events was assessed with the use of the National Cancer Institute's Common Toxicity Criteria (CTC), version 2.0. Constipation-related distress (rated on a scale from "none" to "very much") was assessed on days 1, 7, and 14. Patients and investigators completed the Global Clinical Impression of Change (a scale ranging from 1 to 7, with higher scores indicating better bowel function) on days 7 and 14 and monthly to assess any change in bowel status. Opioid doses were compared by converting doses to oral morphine equivalents with the use of standard formulas.<sup>10-17</sup>

A complete blood count and comprehensive metabolic measurements were obtained at screening, on days 7 and 14, and monthly during the open-label extension, and all tests were performed by a central laboratory. Vital signs were monitored before and after the administration of the study drug on day 1 and for patients with a dose escalation on day 9. Patients rated their current pain and worst pain in the preceding 24 hours (on a scale of 0 to 10, with higher scores indicating greater severity) on days 1, 7, and 14.

Patients also used the Modified Himmels-

#### Figure 1 (facing page). Enrollment and Outcomes.

By day 8 of the double-blind phase of the study, if patients had had fewer than three rescue-free laxations, the initial volume of the study drug could be doubled (from 0.15 to 0.30 mg of methylnaltrexone per kilogram of body weight or an equivalent volume of placebo) at the investigator's discretion.

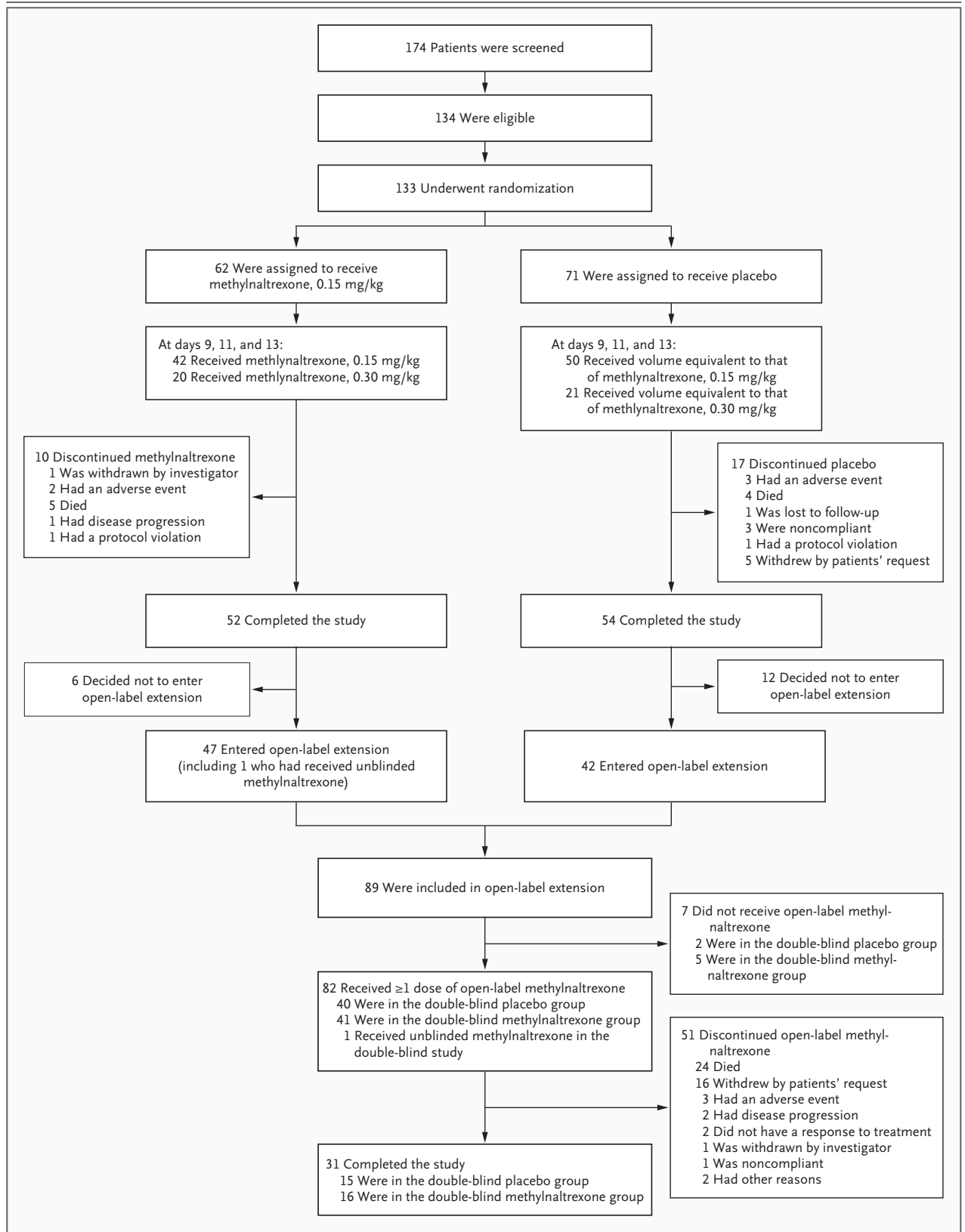
bach Withdrawal Scale (on which scores range from 1 to 4, with higher scores indicating greater severity of symptoms) for each of seven symptoms of opioid withdrawal: yawning, lacrimation, rhinorrhea, perspiration, tremor, piloerection, and restlessness. The total withdrawal score was the sum of the ratings, ranging from 7 to 28.<sup>18</sup>

#### EFFICACY

The coprimary outcomes of the double-blind phase were the proportion of patients with rescue-free laxation within 4 hours after the first dose of the study drug and the proportion of patients with rescue-free laxation within 4 hours after two or more of the first four doses. Additional efficacy outcomes included the proportion of patients with rescue-free laxation within 4 hours after four or more of seven doses, the proportion of patients with rescue-free laxation within 4 or 24 hours after each dose, the proportion of patients with three or more laxations per week, the time to laxation, overall pain scores, and symptoms of opioid withdrawal. There was no primary outcome for the open-label extension trial, given its intent.

#### STATISTICAL ANALYSIS

The primary statistical analysis evaluated rescue-free laxation in the intention-to-treat population (i.e., all patients who underwent randomization and who received one or more doses of the study drug). Missing values were imputed from the last observation carried forward. Primary outcomes in the study groups were compared with the use of the chi-square test after the confirmation of nonsignificant interaction according to center with the use of the Breslow-Day test within a Cochran-Mantel-Haenszel analysis. The chi-square test was also used to analyze the laxation response for each of the seven doses and the proportion of patients with three or more laxations per week. After adjustment for the planned interim analyses of efficacy, an alpha level of 0.0249 for each comparison of the coprimary outcomes



in the two study groups was considered to indicate statistical significance.

The number of patients needed for the study was based on the results of a previous phase 2 study.<sup>19</sup> Using a chi-square test with a two-sided alpha of 0.025 and a power (1-beta) of 0.9 and

with various assumptions regarding study-group responses, we estimated that the enrollment of 65 patients in each study group (a total of 130 patients) would allow us to detect a difference of 30 to 35% in the proportion of patients who had a laxation response.

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Placebo (N=71)	Methylnaltrexone (N=63)
Age — yr		
Median	70	72
Range	39–98	34–93
Sex — no. (%)		
Male	31 (44)	27 (43)
Female	40 (56)	36 (57)
Race or ethnic group — no. (%)†		
White	65 (92)	61 (97)
Black	5 (7)	1 (2)
Asian	0	1 (2)
Other	1 (1)	0
Primary diagnosis — no. (%)		
Cancer	41 (58)	37 (59)
Cardiovascular disease	7 (10)	8 (13)
COPD or emphysema	5 (7)	9 (14)
Alzheimer's disease or dementia	4 (6)	4 (6)
Other‡	14 (20)	5 (8)
Laxatives taken — median (range)		
No. of drug classes	2 (1–5)	2 (1–4)
No. of generic drugs	3 (1–6)	2 (1–5)
Laxative use — no. (%)	70 (99)	62 (98)
Bulk producer	3 (4)	1 (2)
Contact laxative	58 (82)	51 (81)
Enema§	10 (14)	8 (13)
Osmotic agent	24 (34)	19 (30)
Stool softener	28 (39)	26 (41)
Constipation-related distress — no. (%)		
None	8 (11)	7 (11)
A little bit	6 (8)	6 (10)
Somewhat	11 (15)	9 (14)
Quite a bit	18 (25)	16 (25)
Very much	27 (38)	22 (35)
Not reported	1 (1)	3 (5)
Opioid dose — mg/day		
Mean	339±1214	417±787
Median (range)	100 (10–10,160)	150 (9–4160)

Table 1. (Continued.)

Characteristic	Placebo (N = 71)	Methylnaltrexone (N = 63)
WHO performance status — no. (%)¶		
1	6 (8)	3 (5)
2	16 (23)	14 (22)
3	36 (51)	28 (44)
4	13 (18)	18 (29)

\* Plus–minus values are means  $\pm$ SD. All patients were enrolled in the double-blind study; one patient was enrolled but received an unblinded study drug and was excluded from the intention-to-treat analysis. Percentages may not total 100 because of rounding. COPD denotes chronic obstructive pulmonary disease, and WHO World Health Organization.

† Patients selected race or ethnic group from the following options: white, black, Asian, Native Hawaiian or Pacific Islander, American Indian or Alaskan Native, and other.

‡ Other diagnoses included failure to thrive, amyotrophic lateral sclerosis, end-stage multiple sclerosis, malabsorption syndrome, pernicious anemia, rheumatoid arthritis, Buerger's disease, cerebral vascular accident, idiopathic pulmonary fibrosis, peripheral vascular disease, diabetes mellitus, hypoxic brain injury, multiple systems failure, chronic pain or multiple fractures, and end-stage Parkinson's disease.

§ This category included enemas that the patient or caregiver remembered during the week before signing the informed-consent form plus the regular use of enemas as part of the patient's stable laxative regimen on entering the study.

¶ According to the WHO performance criteria, 1 denotes restricted in physically strenuous activity but ambulatory and able to carry out work; 2, ambulatory and capable of all self-care but unable to carry out any work, with less than 50% of waking hours in bed or chair; 3, capable of only limited self-care and confined to bed or chair more than 50% of waking hours; and 4, completely disabled, not capable of any self-care, and confined to bed or chair.

Secondary outcomes were considered to be exploratory, and no correction for multiplicity of testing was made. Post hoc analyses were performed with the use of a logistic-regression model to explore the effects of baseline characteristics on the rescue-free laxation response within 4 hours after the first dose in the double-blind phase of the study. The logistic-regression model included age and baseline opioid dose (oral morphine equivalent) as continuous variables and performance status (World Health Organization class 1 or 2 vs. class 3 or 4) and primary diagnosis (cancer vs. noncancer) as categorical variables.

Since the extension phase was not designed to assess efficacy definitively, no inferential data analyses were performed. All data are presented with the use of summary statistics and frequency distributions. Baseline values were obtained before the administration of the first dose of a study drug in the double-blind phase. Adverse events, laboratory data, and vital signs were summarized after the first exposure to the study drug.

## RESULTS

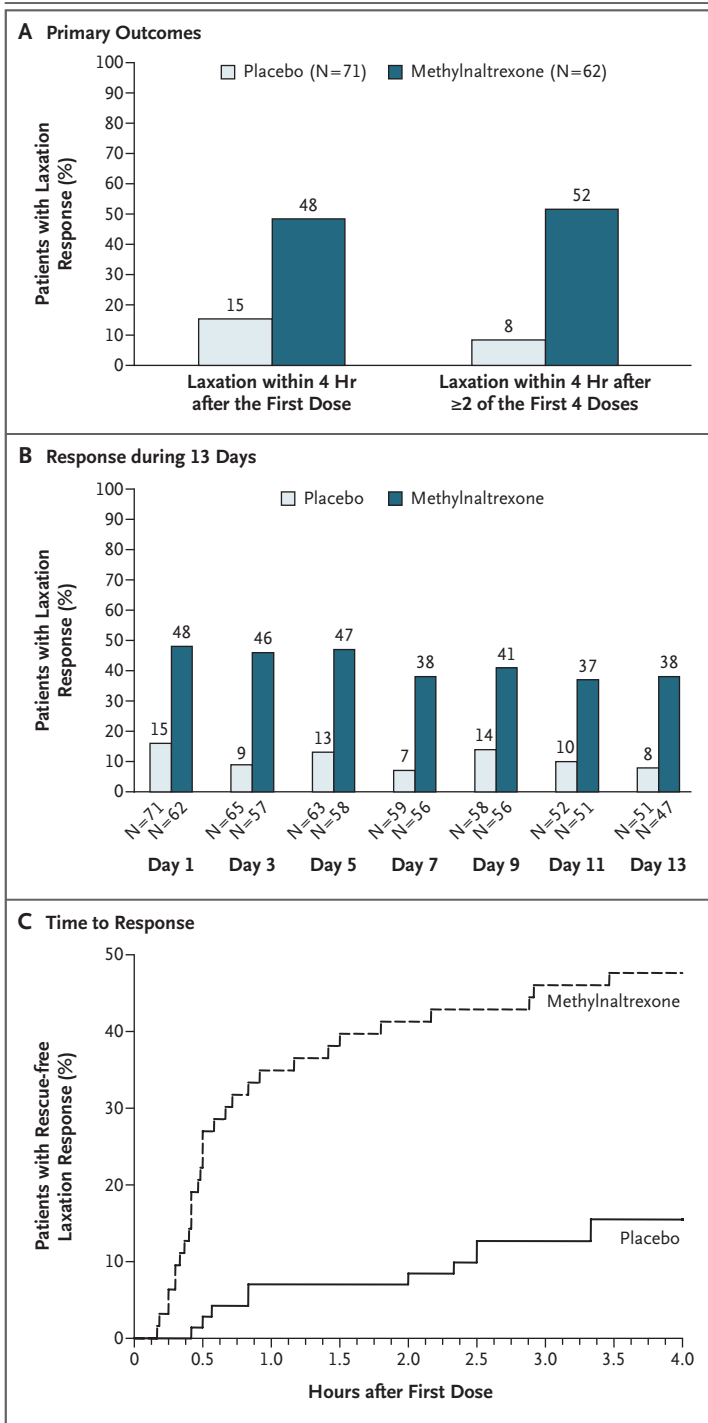
### DOUBLE-BLIND PHASE

In the double-blind phase of the study, 134 patients completed screening and received a study drug. One patient received methylnaltrexone in an

unblinded fashion and was included only in the safety analysis. Thus, the efficacy analysis included 133 patients (71 in the placebo group and 62 in the methylnaltrexone group) (Fig. 1). There were no major differences between the two study groups in baseline demographic or clinical characteristics and performance-status ratings (Table 1). At baseline, the median oral morphine-equivalent dose was 150 mg per day in the methylnaltrexone group and 100 mg per day in the placebo group. In both groups, the median number of laxative drug classes used was two.

### Efficacy

The proportion of patients who had rescue-free laxation within 4 hours after receiving the first dose of the study drug was 48% in the methylnaltrexone group, as compared with 15% in the placebo group; similarly, significantly more patients in the methylnaltrexone group had rescue-free laxation within 4 hours after two or more of the first four doses, as compared with the placebo group ( $P < 0.001$  for both comparisons) (Fig. 2A). Results remained significant for observed responses rather than last observation carried forward. The differences between the study groups remained significant for both outcomes after adjustment for characteristics of the baseline opioid dose ( $P < 0.001$ ).



**Figure 2. Primary Outcomes, Response at 13 Days, and the Time to Response.**

Panel A shows the results of the primary efficacy outcomes — laxation within 4 hours after the first dose of the study drug and laxation within the first 4 hours after two or more of the first four doses — in the methylnaltrexone group and the placebo group.  $P < 0.001$  for both comparisons between the methylnaltrexone group and the placebo group. Panel B shows rescue-free laxation within 4 hours after each dose during a 13-day period.  $P < 0.005$  for all comparisons. On days 9, 11, and 13, variations in doses were permitted on the basis of efficacy and adverse events. Panel C shows Kaplan–Meier curves for the time to laxation within 4 hours after the first dose of the study drug in the two groups ( $P < 0.001$ ).

rescue-free laxation, as compared with 7 to 14% of the placebo group (Fig. 2B). Differences between the study groups were significant for each of the seven doses ( $P < 0.005$  for all comparisons). During the double-blind study, 79% of the methylnaltrexone group and 46% of the placebo group had a laxation response within 4 hours after one or more doses.

Rescue-free laxation within 24 hours after each of the seven doses occurred in 55 to 66% of the methylnaltrexone group and in 29 to 39% of the placebo group. These differences were significant ( $P < 0.05$ ) for doses 1 through 4 but did not reach statistical significance for doses 5 through 7. In addition, the proportion of patients with three or more rescue-free laxations per week was significantly higher in the methylnaltrexone group than in the placebo group (68% vs. 45%,  $P = 0.009$ ). Among doses linked to rescue-free laxation within 4 hours, watery bowel movements occurred after 28 of 176 doses of methylnaltrexone (16%) and after 8 of 48 doses of placebo (17%).

Post hoc logistic-regression model analysis of data in the methylnaltrexone group showed that rescue-free laxation within 4 hours after the first dose did not vary according to age, functional status, a diagnosis of cancer (as compared with noncancer), or the baseline opioid dose (oral morphine equivalent) (Table 2 in the Supplementary Appendix).

The time to laxation after the first dose was rapid (Fig. 2C); among patients in the methylnaltrexone group who had a response within 4 hours, half had a response within 30 minutes. Among all patients, the median time to laxation after the first dose was 6.3 hours in the methylnal-

In the methylnaltrexone group, 24 patients (39%) had rescue-free laxation within 4 hours after four or more of seven doses during a 13-day period, as compared with 4 patients in the placebo group (6%) ( $P < 0.001$ ); after doses 2 through 7, 37 to 47% of the methylnaltrexone group had

trexone group and more than 48 hours in the placebo group ( $P<0.001$ ). The shorter time to laxation in the methylnaltrexone group persisted for each of the seven doses ( $P<0.002$  for all comparisons).

Forty-one patients had a dose escalation during the second week (20 who received 0.3 mg per kilogram in the methylnaltrexone group and 21 in the placebo group at an equivalent volume). In the methylnaltrexone subgroup that received a dose escalation, the rescue-free laxation response rate (percent of doses) was 15% within 4 hours at the previous dose of 0.15 mg per kilogram, whereas the rate was 24% after the dose was increased to 0.3 mg per kilogram. In contrast, in the placebo subgroup, the rates of rescue-free laxation were 8% in patients before a dose escalation and 7% in patients after a dose escalation.

Among patients with laxation within 24 hours after receiving a dose of the study drug, stool consistency improved from hard or very hard at baseline to slightly hard, firm, or soft or formed in similar percentages of patients in the two study groups. More patients in the methylnaltrexone group than in the placebo group had reductions in the difficulty of laxation and distress associated with constipation. Scores on the Global Clinical Impression of Change scale on days 7 and 14 showed that the majority of patients in the methylnaltrexone group considered that their bowel status had improved, but a majority of patients in the placebo group considered that their status was unchanged (Table 3 in the Supplementary Appendix).

#### Pain Scores and Opioid Withdrawal

Patients in the two study groups had similar mean pain scores at baseline and at each evaluation, with minimal changes over time (Table 2). Similarly, in both study groups, scores on the Modified Himmelsbach Withdrawal Scale remained stable throughout the study (Table 2).

#### Adverse Events

Similar percentages of patients in the two study groups had at least one adverse event. Of the adverse events occurring in 5% or more of patients in either study group, abdominal pain, flatulence, nausea, increased body temperature, and dizziness occurred more frequently in the methylnaltrexone group, with an increase in incidence of 3 percentage points or more over that in the

**Table 2. Mean Scores for Pain Assessment and Symptoms of Opioid Withdrawal.\***

Assessment	Placebo (N=71)	Methylnaltrexone (N=62)
Score for worst pain within 24 hr†		
Baseline‡	5.5±2.6	5.1±2.7
Day 1	5.6±2.7	4.9±2.2
Day 7	5.2±2.6	5.2±2.4
Day 14	4.8±2.7	5.0±2.5
Score for current level of pain†		
Baseline‡	3.5±2.6	3.6±2.7
Day 1	3.6±2.5	3.4±2.3
Day 7	3.5±2.6	3.4±2.4
Day 14	2.7±2.2	3.4±2.6
Score on Modified Himmelsbach Withdrawal Scale§		
Baseline‡	8.2±1.8	8.3±1.5
Day 1	7.8±1.5	7.8±1.2
Day 7	8.1±1.8	7.9±1.7
Day 14	8.3±2.4	8.2±1.8

\* Plus-minus values are means ±SD.

† Pain was rated on a scale of 0 to 10, with higher scores indicating greater severity.

‡ Baseline scores were recorded on day 1 before the administration of a study drug. If the predose value was missing, the measurement recorded at screening was substituted.

§ The Modified Himmelsbach Withdrawal Scale ranges from 7 to 28, with higher scores indicating greater severity of symptoms. The scale consists of scores (ranging from 1 to 4) for seven symptoms of opioid withdrawal: yawning, lacrimation, rhinorrhea, perspiration, tremor, piloerection, and restlessness.

placebo group (Table 3). Adverse events that occurred more frequently in the placebo group than in the methylnaltrexone group included falls and hypotension. The pattern of adverse events in patients who had a dose escalation to 0.3 mg per kilogram during the second week showed no meaningful differences between groups. Reactions at the injection site did not differ between the study groups, with three patients in each group reporting such effects.

Investigators rated most adverse events as mild or moderate. Severe adverse events (grade 3 on the CTC scale) occurred in 8% of patients in the methylnaltrexone group and 13% of those in the placebo group. Life-threatening adverse events (grade 4) occurred in 16% of patients in the methylnaltrexone group and 15% of those in the placebo group. All grade 4 adverse events were judged to be related to the primary illness (e.g., progression of an underlying cancer).

**Table 3. Incidence of Adverse Events Occurring in at Least 5% of Patients in Either Study Group during the Double-Blind Phase.\***

Adverse Event	Placebo (N = 71)	Methylal- trexone (N = 63)
Any event	57 (80)	51 (81)
Abdominal pain	9 (13)	11 (17)
Flatulence	5 (7)	8 (13)
Vomiting	9 (13)	8 (13)
Malignant-neoplasm progression	9 (13)	7 (11)
Nausea	5 (7)	7 (11)
Increase in body temperature	2 (3)	5 (8)
Dizziness	2 (3)	5 (8)
Peripheral edema	8 (11)	5 (8)
Asthenia	4 (6)	4 (6)
Diarrhea	3 (4)	4 (6)
Lethargy	4 (6)	4 (6)
Dehydration	4 (6)	2 (3)
Pain exacerbation	7 (10)	2 (3)
Restlessness	4 (6)	2 (3)
Abdominal distention	6 (8)	1 (2)
Abdominal tenderness	4 (6)	1 (2)
Fall	7 (10)	1 (2)
Somnolence	4 (6)	1 (2)
Tachycardia	4 (6)	1 (2)
Hypotension	4 (6)	0

\* Patients were counted only once for each adverse event.

Serious adverse events occurred in 17% of patients in the methylal-trexone group and 28% of those in the placebo group (Table 4 in the Supplementary Appendix). The most commonly reported serious adverse event in both study groups was the progression of a malignant neoplasm (in 11% of patients in the methylal-trexone group and 17% of those in the placebo group). A majority of the remaining serious adverse events also reflected underlying disease progression. Investigators deemed that all serious adverse events were either not related or unlikely to be related to the study drug. Discontinuations that were associated with adverse events occurred in 6% of patients in the methylal-trexone group and 7% of those in the placebo group.

There were 10 deaths (16%) in the methylal-trexone group and 16 (23%) in the placebo group. Five deaths in the methylal-trexone group and

12 in the placebo group occurred during the 30-day follow-up after administration of the last study dose. During the double-blind phase, the investigators considered all deaths to be related to underlying disease progression and none to a study drug. Most laboratory measures were similar in the two study groups at baseline and at each subsequent evaluation. No laboratory measure showed clinically relevant changes from baseline.

#### OPEN-LABEL EXTENSION

Eighty-nine patients who completed the 2-week double-blind study entered the open-label extension phase, and 82 patients (42 who had previously received methylal-trexone and 40 who had previously received placebo) received at least one dose of methylal-trexone during the extension phase. Table 4 shows the laxation response during the open-label phase. Among patients who had received methylal-trexone during the double-blind phase, the rates of rescue-free laxation during the open-label phase in months 1 through 3 for all doses were 45 to 58%. For patients who had received placebo during the double-blind phase, the response rates were 48 to 52%. Among patients who had rescue-free laxation within 4 hours after receiving a dose of open-label methylal-trexone, the median times to laxation for each individual dose were all less than 45 minutes.

During the extension phase, the most common adverse events were abdominal pain (30%), progression of malignant neoplasm (24%), nausea (21%), and vomiting (20%). Serious adverse events occurred in 36 patients (44%); most of the events were consistent with underlying disease progression. Serious adverse events that were deemed to be related to the study drug were muscle spasms (in one patient) and abdominal pain and exacerbated pain (both in one patient). There were 32 deaths during the extension phase, including 8 during the 30-day follow-up. Investigators deemed that all deaths were consistent with underlying disease progression.

#### DISCUSSION

In advanced illness, opioid-induced constipation can rival distress caused by pain.<sup>20,21</sup> Current laxative therapy for opioid-induced constipation, even optimally titrated, may be burdensome or ineffective for some patients. Opioid antagonists,

**Table 4. Rate of Rescue-free Laxation during the Open-Label Extension Phase, According to Study-Group Assignment in the Double-Blind Phase.\***

Variable	Placebo (N = 40)			Methylnaltrexone (N = 42)		
	No. of Patients	Total No. of Doses	Response Rate %	No. of Patients	Total No. of Doses	Response Rate %
Double-blind phase	40	277	11	42	287	45
Open-label extension phase						
Month 1	40	294	48	42	330	45
Month 2	23	147	48	25	156	58
Month 3	13	94	52	12	96	57

\* The response rate equals the number of doses for which there was a laxation response divided by the total number of doses.

such as naloxone,<sup>22</sup> can cross the blood–brain barrier, resulting in pain and opioid withdrawal.<sup>23–25</sup> In contrast, methylnaltrexone belongs to a new drug class with selective antagonism of peripheral  $\mu$ -opioid receptors and might help relieve opioid-induced constipation but maintain analgesia. As a charged naltrexone derivative, methylnaltrexone does not affect the central nervous system in humans.<sup>26</sup> Previous studies showed methylnaltrexone reversal in opioid-induced delay in the oral–cecal transit time in both healthy subjects and patients.<sup>6,8,9,27</sup> Moreover, because methylnaltrexone induced laxation in a pilot study involving long-term methadone users<sup>9</sup> and in a phase 2 trial involving patients with advanced illness and opioid-induced constipation,<sup>19</sup> the drug may reverse opioid-induced constipation without affecting analgesia or triggering opioid withdrawal mediated by central nervous system receptors.

Patients with advanced illness in our study were receiving a median opioid dose of about 100 mg of oral morphine equivalent and were constipated at baseline, despite receiving a median of two classes of laxatives. Patients may have had a response to adjustment of their baseline laxatives; therefore, the study population cannot be described as one in which optimal therapy was a failure. However, this population represents a clinically relevant group of patients who do not have a response to a reasonable laxative regimen and either may continue to have constipation while laxatives are adjusted or may be subjected to invasive rectal interventions. In this population, subcutaneous methylnaltrexone induced laxation within 4 hours after administration in a significantly higher proportion of patients than

did placebo, a benefit that persisted during the administration of all seven double-blind doses. Overall, the rate of a laxation response persisted throughout the 2-week double-blind phase and the 3-month open-label extension.

The response to methylnaltrexone was rapid; among patients who had a response within 4 hours after receiving a dose, half had laxation within 30 minutes, and most had laxation within 1 hour. This rapid onset of action may be a desirable feature for both patients and caregivers, considering that other laxatives often have a longer or unpredictable onset of action.

Approximately half the patients did not have a response to the first methylnaltrexone dose. It is unlikely that this nonresponse was explained by the antagonist–agonist ratio, because the laxation response did not vary over a large range of opioid doses, and there was a weak dose–response relationship. Another placebo-controlled trial showed that subcutaneous injections of methylnaltrexone in doses of 0.15 mg or 0.3 mg per kilogram were equally effective.<sup>28</sup> Furthermore, some patients may have opioid-induced constipation mediated by central  $\mu$  receptors. However, intravenous methylnaltrexone induced laxation in 100% of patients who were long-term users of methadone and who had opioid-induced constipation.<sup>9</sup> This finding suggests that peripheral  $\mu$  receptors largely mediate opioid-induced constipation. Patients with advanced illness may have other causes of constipation, including immobility, decreased oral intake, a low-fiber diet, metabolic and endocrine imbalances, neurologic disorders, concomitant drug side effects, inadequate toileting arrangements, sedation, depression, and

advanced age.<sup>29</sup> In our study, logistic-regression analysis showed no correlation between laxation response and age, functional status, or cancer versus a noncancer diagnosis. Thus, the lack of response in a subgroup of patients remains unexplained. Nevertheless, the response to methylnaltrexone suggests that even in our study population of patients with advanced illness, peripheral  $\mu$ -receptor activity was a major factor in constipation, whether as a result of exogenous or endogenous opioids.

In our study, methylnaltrexone did not increase pain or trigger opioid withdrawal, findings that are supportive of the peripheral action of methylnaltrexone. Although oral naloxone, in the absence of systemic withdrawal, triggered diarrhea that was hypothesized to be a manifestation of local withdrawal in the gastrointestinal tract,<sup>30,31</sup> methylnaltrexone did not increase the incidence of watery stools. It is not known whether this observation reflects a difference in the mechanism of action between methylnaltrexone and naloxone or is related to the ratio between the dose of methylnaltrexone and the opioid dose.

Abdominal pain and flatulence were the most common adverse events in the methylnaltrexone group during the double-blind phase of our study.

All methylnaltrexone-treated patients reported that such symptoms were mild or moderate. The overall incidence of adverse events and treatment discontinuations that were associated with adverse events were similar in the two study groups. As expected in patients who are seriously ill, many serious adverse events and deaths occurred. However, the incidence of such events was similar in the two groups, and all deaths were related to underlying disease progression.

Opioid-induced constipation is an important problem for patients with advanced illness and poses therapeutic challenges for clinicians. Our study showed that in this population methylnaltrexone rapidly induced laxation without compromising analgesia. Methylnaltrexone may represent an important therapeutic option for patients with advanced illness who are suffering from opioid-induced constipation.

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#### APPENDIX

The following principal investigators, listed alphabetically, participated in this study: *Miami Jewish Home and Hospital for the Aged, Miami*: M. Agronin; *Senior Adult Specialty Research, Houston*: L. Borrell; *Henry Ford Hospital, Detroit*: L. Bricker; *Segal Institute for Clinical Research, North Miami, FL*: E. Burdick; *Nathan Adelson Hospice, Las Vegas*: K. Cross; *Physicians Administrative Support Services, Tucker, GA*: P. Erdman; *British Columbia Cancer Agency, Centre for the Southern Interior, Kelowna, BC, Canada*: G. Fyles; *McGill University Health Centre, Montreal*: B. Gagnon; *Palliative Medicine Consultants, Rockville, MD*: C. Harrison; *American Health Network, Avon, IN*: J. Kerlin; *Independent Psychiatric Consultants, Waukesha, WI*: C. Kohlenberg; *Penn State Milton S. Hershey Medical Center, Hershey, PA*: M. Kreher; *Linden Research Consultants, Oklahoma City*: D. Linden; *Care Source Hospice—Home Health Palliative Care, Salt Lake City*: A. Lipman; *Hospice and Palliative Physician Services, Springhill, FL*: D. McGrew; *LifePath Hospice and Palliative Care, Tampa, FL*: M. Moehl-Boatwright; *Arizona Research Center, Phoenix*: M.D. Mollen; *Valley Medical Primary Care, Centerville, OH*: M. Patel; *Iowa Pain Management Clinic, West Des Moines*: J.F. Peppin; *Millennium Psychiatric Associates, St. Louis*: F. Sicuro; *Bridgeport Manor, Bridgeport, CT*: B.A. Sloan; *Hospice of the Western Reserve, Cleveland*: C. Wellman; *Senior Adult Specialty Research, Austin, TX*: J. Winston.

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