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Analgesia Maintenance With Oral Methylnaltrexone in Patients With Opioid-Induced Constipation and Chronic Noncancer Pain in a Phase 3, Randomized, Controlled Trial

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INTRODUCTION

- Opioid use for treatment of chronic noncancer pain is frequently associated with opioid-induced constipation (OIC), which may lead patients to reduce or discontinue opioid use and thereby compromise pain control[1-3]
- OIC is caused largely by activation of enteric μ-opioid receptors resulting in decreased neurotransmitter release that alters gastrointestinal (GI) function[4,5]
- Tolerance to OIC does not develop over time, and laxatives/enemas are generally suboptimal in providing relief as they do not address the underlying pathophysiology or may themselves cause side effects[1-3]
- Methylnaltrexone (Relistor®, Salix Pharmaceuticals, Bridgewater, NJ) is a selective, peripherally acting μ-opioid receptor antagonist that improves GI motility and transit time without affecting μ-opioid receptor–mediated analgesia[6-8]
- Meta-analyses confirm the efficacy and safety of methylnaltrexone as a subcutaneous treatment for OIC[9,10]
- An oral formulation of methylnaltrexone was approved by the US Food and Drug Administration in 2016 for the treatment of OIC in adults with chronic noncancer pain[11]
- In a phase 3, randomized, controlled trial, oral methylnaltrexone (300 mg/d and 450 mg/d) was significantly more efficacious than placebo in increasing the number of dosing days with rescue-free bowel movements (RFBMs) within 4 hours of dosing ($P \leq 0.002$)[12]
- Although peripherally acting, it is important to confirm that methylnaltrexone does not alter centrally mediated opioid analgesia

OBJECTIVE

- To determine whether oral methylnaltrexone affects centrally mediated opioid analgesia or precipitates withdrawal symptoms in adults with chronic noncancer pain and OIC in a randomized controlled trial

METHODS

Key Inclusion Criteria

- Aged ≥18 years, chronic noncancer pain for ≥2 months, and receiving ≥50 mg of oral morphine equivalents per day for ≥14 days before screening
- History of OIC for ≥30 days confirmed during screening and defined as <3 RFBMs per week on average and ≥1 of the following:
  - ≥25% of RFBMs categorized as type 1 or type 2 on the Bristol Stool Form Scale
  - Straining during ≥25% of RFBMs
  - ≥25% of RFBMs with a sensation of incomplete evacuation
- Laxative therapy for ≥30 days before screening (discontinued during screening)

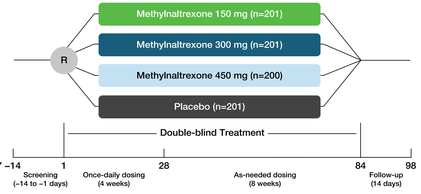
Key Exclusion Criteria

- History of mechanical bowel obstruction or megacolon or clinically significant gastrointestinal disorders (eg, fecal incontinence, rectal prolapse, fecal ostomy, and inflammatory bowel disease)
- Rectal bleeding not associated with hemorrhoids or fissures within 60 days of screening
- Planned surgery during the study

Study Design

- This was a phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel-group study (NCT01186770)
- After a 14-day screening period, patients were randomized (1:1:1:1) to receive oral methylnaltrexone 150 mg, 300 mg, 450 mg, or placebo once daily (QD) for 4 weeks, followed by as-needed (PRN) dosing (not to exceed QD) for 8 weeks (**Figure 1**)
  - Throughout the study, patients received the same dose of methylnaltrexone or placebo and double-blinding was maintained
  - Patients were followed for 14 days after the double-blind period

Figure 1. Study Design



R = randomization.

Assessments and Statistical Analyses

- Pain intensity and opioid withdrawal symptoms were assessed at baseline (day 1 predose), days 14 and 28 (QD period), and days 42, 56, and 84 (PRN period). Opioid withdrawal was also evaluated at 1 hour postdose on day 1
- Pain intensity during the previous 24-hour period was measured using an 11-point numerical rating of pain intensity scale (0=no pain; 10=worst pain possible)
- Opioid withdrawal was assessed using the 13-item Objective Opioid Withdrawal Scale (OOWS, completed by trained clinician) and 19-item Subjective Opioid Withdrawal Scale (SOWS, completed by patient)[13]
  - Items on OOWS were scored as 0 (absent) or 1 (present), with a total score from 0 to 13
  - Items on SOWS were scored as 0 (not at all), 1 (a little), 2 (moderate), 3 (quite a bit), or 4 (extremely), with a total score from 0 to 76
- Safety analyses were performed in the safety population, which consisted of all randomized patients who received ≥1 dose of methylnaltrexone or placebo
- Changes from baseline in pain intensity score, total OOWS score, and total SOWS score were compared between each methylnaltrexone dose group and placebo using the Wilcoxon-Mann-Whitney test
  - Because abdominal cramping may also be caused by induction of laxation with methylnaltrexone, the OOWS and SOWS analyses were performed with and without items relating to cramping

RESULTS

Patients

- A total of 803 patients received ≥1 dose of study medication; demographic and baseline characteristics were generally similar across the 4 treatment groups (**Table 1**)
- Back pain was the most common condition for opioid use, reported by 68.2% of the study cohort
  - The baseline morphine-equivalent dose (MED) was slightly higher in the methylnaltrexone 300-mg group than in the other groups as it included 2 patients who reported higher daily morphine doses than the other patients

Table 1. Demographic and Baseline Characteristics (ITT Population)[a]

Characteristic	Methylnaltrexone 150 mg (n=201)	Methylnaltrexone 300 mg (n=201)	Methylnaltrexone 450 mg (n=200)	Placebo (n=201)
Mean age (SD), years	50.9 (10.3)	51.5 (10.5)	51.4 (10.5)	52.6 (10.3)
Age ≥65 years, n (%)	15 (7.5)	19 (9.5)	19 (9.5)	22 (10.9)
Sex, n (%)				
Male	68 (33.8)	87 (43.3)	72 (36.0)	71 (35.3)
Female	133 (66.2)	114 (56.7)	128 (64.0)	130 (64.7)
Race, n (%)				
White	164 (81.6)	158 (78.6)	172 (86.0)	166 (82.6)
Black/African American	30 (14.9)	38 (18.9)	25 (12.5)	27 (13.4)
Other	7 (3.5)	5 (2.5)	3 (1.5)	8 (4.0)
Primary pain condition, n (%)				
Back pain	132 (65.7)	136 (67.7)	135 (67.5)	145 (72.1)
Arthritis	20 (10.0)	15 (7.5)	19 (9.5)	12 (6.0)
Neurologic/neuropathic pain	16 (8.0)	13 (6.5)	16 (8.0)	11 (5.5)
Joint/extremity pain	13 (6.5)	16 (8.0)	11 (5.5)	10 (5.0)
Fibromyalgia	15 (7.5)	8 (4.0)	11 (5.5)	12 (6.0)
Other	5 (2.5)	13 (6.5)	8 (4.0)	11 (5.5)
Baseline MED, mg[b]				
Median (range)	141.1 (30.0–1280.0)	177.5 (47.4–2289.3)	155.6 (27.0–1272.0)	132.0 (42.6–1077.3)
Mean (SD)	200.0 (205.2)	252.6 (298.1)	218.0 (189.1)	209.7 (199.1)
Mean pain intensity score (SD)	6.4 (1.8)	6.4 (1.9)	6.4 (1.9)	6.2 (2.1)

MED = morphine-equivalent dose; SD = standard deviation.
[a]The ITT population includes all randomized patients who received ≥1 dose of study drug.
[b]Baseline opioid dose was defined as the average daily oral MED during the screening period.

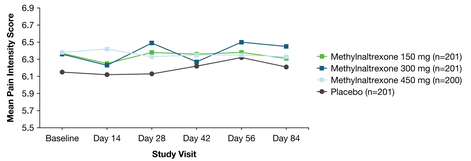
Exposure to Study Drug

- Median exposure to study drug was 83 days in each treatment group; the range of exposure was 1 to 94 days in the methylnaltrexone 150-mg group, 1 to 91 days in the methylnaltrexone 300-mg group, 1 to 99 days in the methylnaltrexone 450-mg group, and 3 to 91 days in the placebo group

Pain Intensity

- Pain intensity scores were similar among groups at baseline (**Table 1**) and remained stable during the 4-week QD dosing period and 8-week PRN dosing period (**Figure 2**)
  - No significant changes from baseline occurred in any treatment group

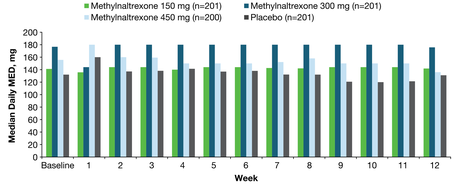
Figure 2. Mean Pain Intensity Score During Treatment With Oral Methylnaltrexone



Mean pain intensity was evaluated on an 11-point scale from 0 (no pain) to 10 (worst possible pain).

- The mean change from baseline in pain intensity score did not differ between each oral methylnaltrexone dose group and the placebo group ($P \geq 0.29$ at day 14; $P \geq 0.11$ at day 28; $P \geq 0.57$ at day 42; $P \geq 0.40$ at day 56; and $P \geq 0.22$ at day 84)
- The median MED in study patients remained relatively unchanged during the QD and PRN dosing periods (**Figure 3**)
  - Similarly, there were minimal changes in mean MED across the 4 treatment groups from baseline (range, 200.0–242.4 mg) to 4 weeks of QD dosing (range, 214.5–235.6 mg) and through 8 weeks of PRN dosing (range, 202.3–234.9 mg)

Figure 3. Median Daily MED Over Time

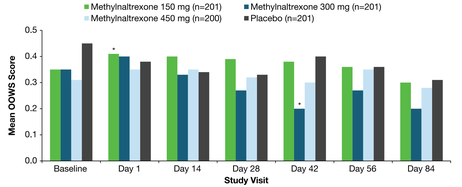


MED = morphine-equivalent dose.

Opioid Withdrawal

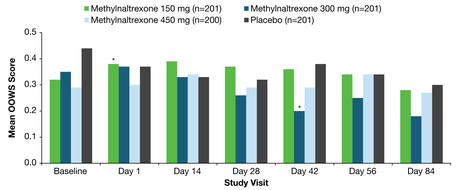
- Mean changes from baseline in OOWS score were minimal in all treatment groups (**Figure 4**). Comparable results were obtained when items relating to abdominal cramping were excluded from the analysis (**Figure 5**)
- Mean changes from baseline in SOWS score were also minimal in all treatment groups (**Figure 6**), including when abdominal cramping was excluded from the analysis (**Figure 7**)

Figure 4. Mean OOWS Score Over Time



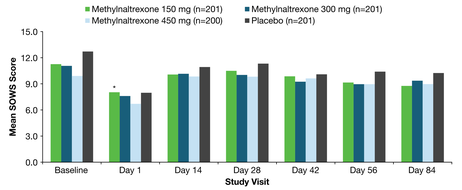
OOWS = Objective Opioid Withdrawal Scale.
*P<0.05 for change from baseline in mean OOWS score versus placebo.

Figure 5. Mean OOWS Score Over Time Excluding Items Related to Abdominal Cramping



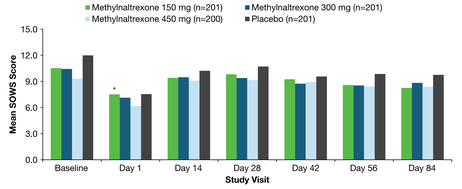
OOWS = Objective Opioid Withdrawal Scale.
*P<0.05 for change from baseline in mean OOWS score versus placebo.

Figure 6. Mean SOWS Score Over Time



SOWS = Subjective Opioid Withdrawal Scale.
*P<0.05 for change from baseline in mean SOWS score versus placebo.

Figure 7. Mean SOWS Score Over Time Excluding Items Related to Abdominal Cramping



SOWS = Subjective Opioid Withdrawal Scale.
*P<0.05 for change from baseline in mean SOWS score versus placebo.

CONCLUSIONS

- **Oral methylnaltrexone did not interfere with opioid analgesia and was not associated with opioid withdrawal signs or symptoms in this randomized controlled trial**
- **Oral methylnaltrexone can be considered as a treatment option for OIC that does not compromise pain management in patients with chronic noncancer pain**

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