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Oral Methylnaltrexone for Adults With Chronic Noncancer Pain and Opioid-Induced Constipation (OIC): Timing and Characterization of Clinical Symptoms Do Not Suggest Opioid Withdrawal With Daily Treatment

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BACKGROUND

- Opioids activate receptors in the gastrointestinal (GI) tract causing slow GI transit and constipation[1]
- Opioid-induced constipation (OIC) disrupts patients' quality of life[2,3] and may prompt patients to decrease or discontinue use of opioids,[2] potentially leading to inadequate pain control
- Methylnaltrexone is a peripherally acting μ-opioid receptor antagonist that has been approved in subcutaneous and oral formulations for the treatment of OIC in patients with chronic noncancer pain (CNCP)
- Results from phase 3, randomized, double-blind trials demonstrated a statistically significant reduction in OIC symptoms and few adverse events (AEs) with subcutaneous[4] and oral[5] methylnaltrexone versus placebo
- No significant changes from baseline in mean pain intensity scores and minimal changes in Objective Opioid Withdrawal Scale (OOWS) scores were observed in patients treated with methylnaltrexone[6]

AIM

- To evaluate the timing of AEs suggestive of opioid withdrawal in patients with CNCP and OIC

METHODS

Patients and Study Design

- Phase 3, randomized, double-blind, placebo-controlled study with a 14-day (±2 days) screening period, a 28-day period of once-daily (QD) treatment, a 56-day period of as needed (PRN) treatment, and a 14-day follow-up period
- Patients were randomly assigned in a 1:1:1:1 fashion to receive oral methylnaltrexone 150 mg/d, 300 mg/d, or 450 mg/d or placebo QD for 4 weeks
- During the 8-week PRN period, patients continued to receive the same treatment to which they were assigned at randomization (QD period)
- Patient population: ≥18 years of age with CNCP for ≥2 months and requiring ≥50 mg oral morphine equivalents per day for ≥14 days before screening
  - OIC was confirmed during screening, defined as a mean of <3 rescue-free bowel movements (RFBMs; defined as no laxative use within 24 hours prior to bowel movement) per week associated with ≥1 of the following:
    - Bristol Stool Form Scale type 1 or 2 for ≥25% of RFBMs
    - Straining during ≥25% of RFBMs
    - Sensation of incomplete evacuation after ≥25% of RFBMs

Assessments and Statistics

- Oral morphine equivalent dosages (MED) were recorded daily
- Occurrence of AEs of interest (abdominal pain, diarrhea, hyperhidrosis, anxiety, nausea) after each dose was analyzed
- Incidence of withdrawal-related AEs (abdominal pain, nausea, diarrhea, vomiting, hot flush, chills, anxiety, piloerection, hyperhidrosis, yawning, and insomnia; not reported here individually) for each dose was assessed and the following are presented here:
  - Percentage of patients having ≥3 withdrawal-related AEs for the same dose
  - Discontinuation because of withdrawal-related AEs
- Occurrence of clusters of AEs involving possible opioid withdrawal symptoms as defined by *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V) criteria[7] were determined throughout the study
  - Patients met DSM-V criteria for opioid withdrawal if they had ≥3 of the following after administration of study drug: dysphoric mood, nausea or vomiting, muscle aches, lacrimation or rhinorrhea, pupillary dilation, piloerection, sweating, diarrhea, yawning, fever, or insomnia
- Opioid withdrawal was assessed using the OOWS[8] at baseline (pre-dose on Day1), Day 1 (1 hour post-dose), Weeks 2 and 4 (QD period), and Weeks 6, 8, and 12 (PRN period)
- Opioid withdrawal was analyzed with and without items related to GI symptoms (nausea or vomiting and diarrhea for DSM-V criteria and abdominal cramping for OOWS) because such symptoms were considered potential confounding factors (ie, occurred frequently in patients with OIC and potential side effects of methylnaltrexone treatment, not indicative of withdrawal)
- Pain intensity was assessed throughout the study using an 11-point numerical rating scale (PI-NRS), evaluating pain during the previous 24 hours (score, 0 = no pain; 10 = worst possible pain)[9]
- The Wilcoxon-Mann-Whitney test was performed to compare changes from baseline in the pain intensity score and OOWS for each oral methylnaltrexone dose versus placebo

RESULTS

- Demographic and baseline characteristics of the study population were similar across all treatment groups (**Table 1**)[5]

Table 1. Demographic and Baseline Characteristics

Characteristics	Methylnaltrexone 150 mg/d (N=201)	Methylnaltrexone 300 mg/d (N=201)	Methylnaltrexone 450 mg/d (N=200)	Placebo (N=201)
Mean age, y (SD)	50.9 (10.3)	51.5 (10.5)	51.4 (10.5)	52.6 (10.3)
Sex, n (%)				
Female	133 (66.2)	114 (56.7)	128 (64.0)	130 (64.7)
Male	68 (33.8)	87 (43.3)	72 (36.0)	71 (35.3)
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)
Median baseline MED, mg/d (range)*	141.1 (30–1280.0)	177.5 (47.4–2289.3)	155.6 (27–1272.0)	132.0 (42.6–1077.3)
RFBMs per week, mean (SD)	1.5 (0.9)	1.4 (0.9)	1.4 (0.8)	1.5 (1.0)

*150 mg/d, N=200; 300 mg/d, N=201; 450 mg/d, N=200; placebo, N=201.
MED = morphine equivalent dose; RFBM = rescue-free bowel movement; SD = standard deviation.
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- After the first dose of study medication, abdominal pain, diarrhea, and nausea were more prevalent with oral methylnaltrexone 450 mg/d compared with placebo and lower methylnaltrexone doses (**Table 2**)

Table 2. Occurrence of AEs of Interest By Dose of Study Medication

Study Medication	AE, n (%) Abdominal Pain	Diarrhea	Hyperhydrosis	Anxiety	Nausea
After first dose					
Oral Methylnaltrexone					
150 mg/d (N=201)	4 (2.0)	0	1 (0.5)	0	1 (0.5)
300 mg/d (N=201)	7 (3.5)	0	2 (1.0)	5 (2.5)	5 (2.5)
450 mg/d (N=200)	13 (6.5)	3 (1.5)	2 (1.0)	2 (1.0)	6 (3.0)
Placebo (N=201)	4 (2.0)	0	0	0	2 (1.0)
After second dose					
Oral Methylnaltrexone					
150 mg/d (N=201)	2 (1.0)	0	0	0	0
300 mg/d (N=201)	3 (1.5)	1 (0.5)	1 (0.5)	0	2 (1.0)
450 mg/d (N=200)	1 (0.5)	0	0	0	1 (0.5)
Placebo (N=201)	2 (1.0)	0	1 (0.5)	0	3 (1.5)

AE = adverse event.

RESULTS

- Following the second dose of study medication, the incidence of abdominal pain, diarrhea, and nausea were similar among all treatment groups
- The incidences of AEs of interest (abdominal pain, diarrhea, hyperhidrosis, anxiety, nausea) were ≤1.0% in all treatment groups for each dose >2 through dose 28
- For the first dose, 1 patient treated with methylnaltrexone 300 mg/d and 3 patients treated with methylnaltrexone 450 mg/d experienced ≥3 AEs that could be suggestive of opioid withdrawal (withdrawal-related AEs)
- After the first dose of study medication, 3 patients treated with methylnaltrexone 450 mg/d discontinued from the study because of withdrawal-related AEs; 1 patient in the placebo group discontinued the study after the second dose
- DSM-V criteria for opioid withdrawal (including GI symptoms) was met in 5 patients who received methylnaltrexone and no patients who received placebo
  - GI symptoms consistent with the mechanism of action of methylnaltrexone in the GI tract in reversing the peripheral action of opioids may mimic withdrawal symptoms
  - When GI symptoms were excluded from the criteria, no patients in any treatment group met DSM-V opioid withdrawal criteria
- Mean changes in OOWS scores from baseline were minimal throughout the study in all treatment groups, with or without the inclusion of GI symptoms (**Table 3**)

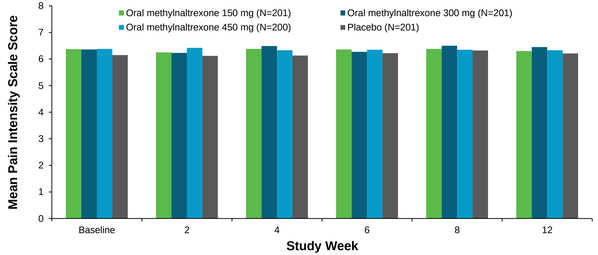
Table 3. Objective Opioid Withdrawal Scale Score

Characteristics	Methylnaltrexone 150 mg/d (N=201)	Methylnaltrexone 300 mg/d (N=201)	Methylnaltrexone 450 mg/d (N=200)	Placebo (N=201)
OOWS score (excluding GI symptoms)				
Baseline, mean (SD)	0.32 (0.9)	0.35 (0.8)	0.29 (0.9)	0.44 (1.1)
Mean change from baseline (SD)				
Day 1	0.06 (0.6)	0.02 (0.6)	0.02 (0.4)	−0.07 (0.6)
Week 2	0.07 (0.7)	−0.02 (0.7)	0.06 (0.7)	−0.07 (0.7)
Week 4	0.03 (0.7)	−0.08 (0.9)	0.02 (0.6)	−0.10 (0.7)
Week 6	0.01 (0.6)	−0.13 (0.8)	0.0 (0.6)	−0.02 (0.8)
Week 8	0.01 (0.7)	−0.10 (1.1)	0.04 (0.7)	−0.06 (0.8)
Week 12	−0.08 (0.7)	−0.16 (0.8)	−0.01 (0.8)	−0.11 (0.7)
OOWS Score (including GI symptoms)				
Baseline, mean (SD)	0.35 (1.0)	0.35 (0.8)	0.31 (1.0)	0.45 (1.1)
Mean change from baseline (SD)				
Day 1	0.06 (0.6)	0.04 (0.6)	0.05 (0.4)	−0.07 (0.6)
Week 2	0.04 (0.7)	−0.02 (0.7)	0.06 (0.7)	−0.07 (0.7)
Week 4	0.01 (0.7)	−0.07 (0.9)	0.03 (0.6)	−0.10 (0.7)
Week 6	−0.01 (0.6)	−0.13 (0.9)	−0.02 (0.6)	−0.02 (0.8)
Week 8	0.0 (0.8)	−0.08 (1.1)	0.03 (0.7)	−0.06 (0.7)
Week 12	−0.09 (0.8)	−0.14 (0.8)	−0.02 (0.9)	−0.11 (0.7)

GI = gastrointestinal; OOWS = Objective Opioid Withdrawal Scale; SD = standard deviation.

- Mean pain scores remained stable throughout the study (**Figure**); there were minimal changes in daily opioid use across treatment groups (mean MED of ~200–240 mg/d) throughout the study

Figure. Mean Pain Intensity Scores With Oral Methylnaltrexone



CONCLUSIONS

- Daily oral methylnaltrexone did not elicit opioid withdrawal or reduce central analgesia in adults with CNCP and OIC
- Although abdominal pain, diarrhea, and nausea were more prevalent with oral methylnaltrexone 450 mg/d compared with placebo and lower methylnaltrexone doses after the first dose of study medication, the incidences of these AEs were similar among all treatment groups following the second dose of the study medication
- Lack of withdrawal effects of methylnaltrexone is expected given the mechanism of action of methylnaltrexone (ie, peripheral μ-opioid receptor antagonism)
- The lack of opioid withdrawal effects of oral methylnaltrexone combined with its demonstrated efficacy and favorable safety profile indicates that oral methylnaltrexone may be a valuable oral therapy for patients with OIC

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