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Analysis of Impact of Oral Methylnaltrexone for Opioid-Induced Constipation on Opioid Analgesia and Withdrawal Symptoms in Patients With Chronic Noncancer Pain Taking Methadone

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BACKGROUND

- Opioids activate receptors in the gastrointestinal (GI) tract and slow GI transit, leading to constipation, which is commonly called opioid-induced constipation (OIC)[1]
- Stool softeners and laxatives do not disrupt opioid-GI receptor interactions and therefore may be ineffective for OIC[2,3]
- Methylnaltrexone is a peripherally acting μ-opioid receptor antagonist (PAMORA), initially developed as a subcutaneous formulation, that improves transit within the GI tract without centrally mediated effects[4,5]
- An oral formulation of methylnaltrexone has been shown to be efficacious and well tolerated[6] and was approved by the US Food and Drug Administration in 2016, at a recommended dosage of 450 mg once daily, for OIC in adults with chronic noncancer pain (CNCP)[7]
- Symptoms consistent with those of opioid withdrawal have been reported for another PAMORA in patients with OIC taking methadone[8]; this analysis assessed the impact of oral methylnaltrexone for OIC on opioid analgesia in a population with CNCP taking methadone

AIM

- To evaluate the impact of oral methylnaltrexone on opioid analgesia in subgroups of adults with OIC and CNCP taking methadone

METHODS

Patients and Study Design

- Post hoc analysis of a phase 3, randomized, double-blind, placebo-controlled trial[6]
  - 14-day screening period, a 28-day (4-week) once-daily (QD) treatment period, a 56-day (8-week) as needed (PRN) period, and a 14-day follow-up period
  - Double-blinding was maintained throughout the study
- Adults with CNCP for ≥2 months receiving ≥50 mg/d of oral morphine equivalents for ≥14 days who had OIC during screening period (<3 rescue-free bowel movements [RFBMs] per week associated with ≥1 of the following: ≥25% of RFBMs Bristol Stool Form Scale type 1 or type 2; straining during ≥25% of RFBMs; or ≥25% of RFBMs with sensation of incomplete evacuation)
- Eligible patients were randomly assigned to receive oral methylnaltrexone 150 mg, 300 mg, or 450 mg or placebo QD for 4 weeks followed by PRN dosing for 8 weeks

Assessments

- Oral morphine equivalent doses (MEDs) were recorded daily
- Evaluation of pain intensity and opioid withdrawal were conducted at baseline (day 1 predose), 1 hour postdose on day 1 (opioid withdrawal only), days 14 and 28 (QD period), and days 42, 56, and 84 (PRN period)
  - Pain intensity was assessed using an 11-point numerical rating scale evaluating pain during the previous 24 hours (score, 0 = no pain; 10 = worst possible pain)[9]
  - Opioid withdrawal was assessed using the 13-item objective opioid withdrawal scale (OOWS)[10]
    - Higher OOWS scores indicate greater numbers or intensity of symptoms
- Adverse events were monitored throughout the study
- Institutional review board approval was obtained and all patients provided written informed consent

RESULTS

- Overall, 120 of 803 patients reported concomitant methadone use (Table 1)

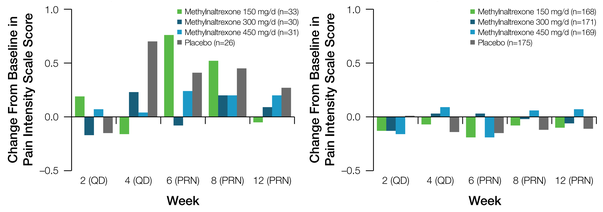
Table 1. Demographic and Baseline Characteristics

	Methadone Population (n=120)				Nonmethadone Population (n=683)			
	Oral Methylnaltrexone				Oral Methylnaltrexone			
Parameter	150 mg (n=33)	300 mg (n=30)	450 mg (n=31)	Placebo (n=26)	150 mg (n=168)	300 mg (n=171)	450 mg (n=169)	Placebo (n=175)
Mean age, y (range)	47.0 (18–68)	48.1 (24–66)	50.8 (25–71)	47.3 (24–61)	51.7 (25–79)	52.1 (24–82)	51.6 (23–78)	53.3 (23–78)
Females, n (%)	21 (63.6)	13 (43.3)	21 (67.7)	13 (50.0)	112 (66.7)	101 (59.1)	107 (63.3)	117 (66.9)
Race, white, n (%)	29 (87.9)	26 (86.7)	28 (90.3)	25 (96.2)	135 (80.4)	132 (77.2)	144 (85.2)	141 (80.6)
Primary pain condition								
Back pain	24 (72.7)	20 (66.7)	19 (61.3)	18 (69.2)	108 (64.3)	116 (67.8)	116 (68.6)	127 (72.6)
Joint/extremity pain	1 (3.0)	3 (10.0)	1 (3.2)	1 (3.8)	12 (7.1)	13 (7.6)	10 (5.9)	9 (5.1)
Arthritis	2 (6.1)	1 (3.3)	3 (9.7)	4 (15.4)	18 (10.7)	14 (8.2)	16 (9.5)	8 (4.6)
Neurologic/neuropathic pain	2 (6.1)	2 (6.7)	3 (9.7)	0	14 (8.3)	11 (6.4)	13 (7.7)	11 (6.3)
Fibromyalgia	3 (9.1)	2 (6.7)	3 (9.7)	1 (3.8)	12 (7.1)	6 (3.5)	8 (4.7)	11 (6.3)
Other	1 (3.0)	2 (6.7)	2 (6.5)	2 (7.7)	4 (2.4)	11 (6.4)	6 (3.6)	9 (5.1)
Median baseline MED, mg/d (range)	186.8 (60–1140)	269.8 (72–2289)	225.0 (90–720)	170.2 (60–600)	127.2 (30–1280)	140.7 (47–1976)	129.0 (27–1272)	126.1 (43–1077)
Mean pain intensity score (SD)	6.4 (1.6)	5.4 (1.8)	6.0 (2.1)	5.6 (2.2)	6.4 (1.9)	6.5 (1.9)	6.5 (1.8)	6.2 (2.1)

MED = morphine equivalent dose; SD = standard deviation.

- There were no significant differences in mean change from baseline in pain intensity scores for any of the 3 methylnaltrexone groups versus placebo in the methadone-treated (Figure 1A; *P*>0.05 vs placebo) or the nonmethadone-treated (Figure 1B; *P*>0.05 vs placebo) populations during the QD and PRN periods
  - As well, when compared with the nonmethadone placebo group, no significant changes from baseline were observed at any timepoints for 3 methylnaltrexone groups in the methadone-treated population (*P*>0.05 vs nonmethadone placebo)

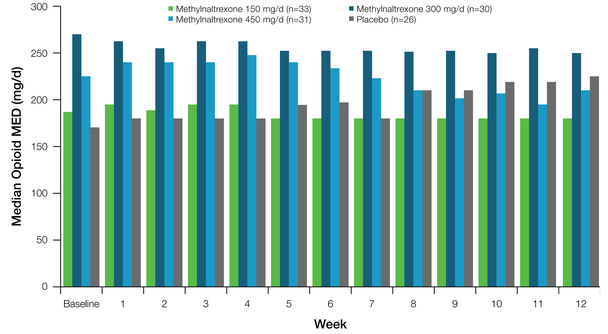
Figure 1. Change From Baseline in Pain Intensity Scale Scores in the Methadone-Treated (A) and Nonmethadone-Treated (B) Populations



*P>0.05 vs placebo for all methylnaltrexone groups.
PRN = as needed; QD = once daily.

- In general, minimal changes in median MED were observed during the 12-week study (Figure 2)

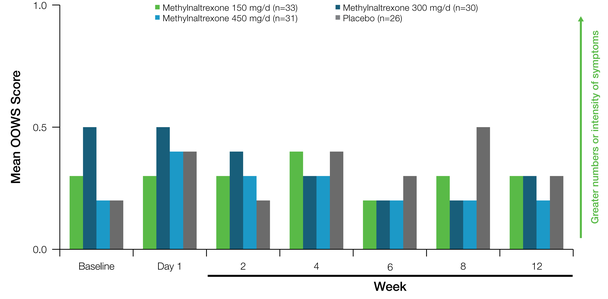
Figure 2. Median Daily MED Over Time



MED = morphine equivalent dose.

- In the methadone-treated population, minimal changes in mean OOWS scores over time were observed (Figure 3) with no significant differences versus placebo at any timepoint (*P*>0.05 vs placebo for each of the 3 methylnaltrexone groups)

Figure 3. Mean OOWS Score Over Time



OOWS = objective opioid withdrawal scale.

- Oral methylnaltrexone was generally well tolerated (Table 2)

Table 2. AE Summary in Methadone-Treated Population (QD, PRN, and Follow-Up Periods)

	Patients, n (%)			
	Oral Methylnaltrexone			
AEs	150 mg (n=33)	300 mg (n=30)	450 mg (n=31)	Placebo (n=26)
Any AE	21 (63.6)	21 (70.0)	23 (74.2)	12 (46.2)
Discontinuations due to AEs	0	1 (3.3)†	1 (3.2)‡	0
Most common AEs*				
Abdominal pain	4 (12.1)	4 (13.3)	10 (32.3)	0
Nausea	2 (6.1)	5 (16.7)	5 (16.1)	0
Diarrhea	1 (3.0)	3 (10.0)	4 (12.9)	0
Flatulence	3 (9.1)	2 (6.7)	1 (3.2)	2 (7.7)
Hyperhidrosis	3 (9.1)	3 (10.0)	1 (3.2)	0
URTI	2 (6.1)	1 (3.3)	0	3 (11.5)
Fall	3 (9.1)	1 (3.3)	0	0
Upper abdominal pain	0	3 (10.0)	0	0

*Reported in ≥6.0% of patients in any treatment group.
†AE of upper abdominal pain.
‡AE of vertigo.
AE = adverse event; PRN = as needed; QD = once daily; URTI = upper respiratory tract infection.

CONCLUSIONS

- **Oral methylnaltrexone does not elicit opioid withdrawal or interfere with opioid analgesia in patients with CNCP and OIC taking methadone**
- **Data further support that methylnaltrexone can be considered as an option for OIC, without clinically significant concerns about compromising pain management strategies in patients with CNCP**

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