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Analysis of Opioid-Mediated Analgesia in Studies With Methylnaltrexone for Opioid-Induced Constipation in Patients With Chronic Noncancer Pain

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INTRODUCTION

- The exact prevalence of opioid-induced constipation (OIC) in patients with chronic noncancer pain (CNCP) is unclear, but it has been reported to be at least 40%[1-4]
- OIC can compromise pain management, with gastrointestinal (GI) adverse effects causing patients to skip opioid doses or reduce their dosage, resulting in inadequate pain control[1,2,5]
- Over-the-counter agents (eg, laxatives) are generally unsatisfactory for relieving OIC in a substantial percentage of patients[1,2,4,6] because they do not target the underlying cause of OIC—μ-opioid receptor activation in the GI tract[7,8]
- Methylnaltrexone (MNTX) is a selective, peripherally acting μ-opioid receptor antagonist that inhibits opioid-induced increases in oral-cecal transit time and delays in gastric emptying[9,10] and has previously been shown to be efficacious and well tolerated for OIC[11-13]

OBJECTIVE

- To examine the potential effects of methylnaltrexone on centrally mediated opioid analgesia in patients with CNCP and OIC treated during a randomized, placebo-controlled trial (RCT)[13] and an open-label trial (OLT)

METHODS

Patient Populations and Study Designs

RCT

- Adults with CNCP ≥2 months, taking a ≥50 mg oral morphine equivalent dose (MED) per day, with ≥1-month history of constipation (<3 rescue-free bowel movements [RFBM] per week on average, plus ≥1 of the following: hard or lumpy stools, straining during bowel movements [BM], sensation of incomplete evacuation)
- Randomized, double-blind, phase 3 study: 2-week screening period, 4-week double-blind period (subcutaneous MNTX 12 mg daily [QD], MNTX 12 mg every other day [QOD], or placebo), 8-week, open-label extension period (MNTX 12 mg as needed [PRN; max, 1 dose/day]), and 2-week follow-up period

OLT

- Similar key patient inclusion and exclusion criteria to those of RCT, including a ≥1-month history of constipation (≥2 of the following: <3 BM/week; hard or lumpy stools for ≥25% of BM; straining during ≥25% of BM; sensation of incomplete evacuation after ≥25% of BM; use of manual maneuvers to facilitate BM ≥25% of time)
- Open-label phase 3 study: 2-week screening period, 48-week treatment period (MNTX 12 mg PRN [min, 1 dose/week; max, 1 dose/day]), and 2-week follow-up period

Assessments and Statistics

- Median and mean daily oral MED taken by patients
- Mean pain intensity scores assessed during 24 hours using an 11-point pain intensity scale (score, 0 = no pain; 10 = worst possible pain)[14]
  - RCT: baseline, Day 1, Weeks 2 and 4 (double-blind period), and Weeks 6, 8, and 12 (open-label period)
  - OLT: baseline, Weeks 4, 8, 12, 16, 24, 32, 40, 48, and early discontinuation/follow-up visit
- For RCT double-blind phase comparisons versus placebo, an ANCOVA model with treatment as a factor and baseline as a covariate was used for pain intensity scores and MED calculations
- Descriptive statistics of observed data were applied for the open-label period of the RCT and the OLT; within-group comparisons were analyzed using paired *t*-tests

RESULTS

- Demographics and baseline characteristics were similar across 3 treatment groups in the RCT and between the 2 studies, with the exception of a lower median baseline MED in the OLT population (120.0; Table 1)

Table 1. Demographics and Baseline Characteristics

	RCT[13]			OLT
Characteristics	MNTX 12 mg QD (n = 150)	MNTX 12 mg QOD (n = 148)	Placebo (n = 162)	MNTX 12 mg PRN (n = 1034)
Mean age, y (range)	48.0 (24–78)	48.6 (23–73)	49.7 (25–83)	51.7 (23–81)
Female, n (%)	93 (62.0)	85 (57.4)	99 (61.1)	669 (64.7)
Race, n (%)				
White	139 (92.7)	133 (89.9)	141 (87.0)	927 (89.7)
Black	7 (4.7)	10 (6.8)	15 (9.3)	76 (7.4)
Other	4 (2.7)	5 (3.4)	6 (3.7)	31 (3.0)
Median MED, mg/d (range)	161.0 (45.5–831.2)	154.8 (7.2–1334.3)	160.8 (13.6–1286.5)	120.0 (1.2–2196.0)
Mean pain intensity score (SD)	6.2 (1.9)	6.3 (1.9)	6.3 (1.7)	6.1

SD = standard deviation.

- In the RCT, mean pain intensity scores for MNTX QD and QOD exhibited no significant changes from baseline versus placebo (Table 2); mean pain intensity scores also remained stable during the open-label MNTX phase (mean change from baseline at Week 12, -0.2; *P* = 0.1 vs baseline)

Table 2. Change From Baseline in Pain Intensity During RCT Double-Blind Phase

Treatment (n)	Mean Score (SD)	Change From Baseline (SD)	Change vs Placebo[a] (95% CI)	*P* value
Week 2				
MNTX 12 mg QD (n = 132)	6.2 (1.9)	0.0 (1.7)	0.1 (-0.3, 0.4)	0.7
MNTX 12 mg QOD (n = 132)	6.1 (1.9)	-0.1 (1.5)	0.0 (-0.3, 0.3)	0.97
Placebo (n = 153)	6.2 (2.0)	-0.1 (1.4)		
Week 4				
MNTX 12 mg QD (n = 122)	6.1 (1.9)	-0.2 (1.6)	-0.1 (-0.5, 0.3)	0.6
MNTX 12 mg QOD (n = 120)	5.9 (1.7)	-0.3 (1.5)	-0.3 (-0.7, 0.1)	0.1
Placebo (n = 143)	6.3 (2.0)	-0.1 (1.8)		

[a]Difference in adjusted change from baseline versus placebo.
CI = confidence interval; SD = standard deviation.

- Consistent with results observed during the RCT, mean pain intensity scores were unchanged from baseline during up to 48 weeks of treatment in the OLT (Table 3)

RESULTS

Table 3. Change From Baseline in Pain Intensity During OLT

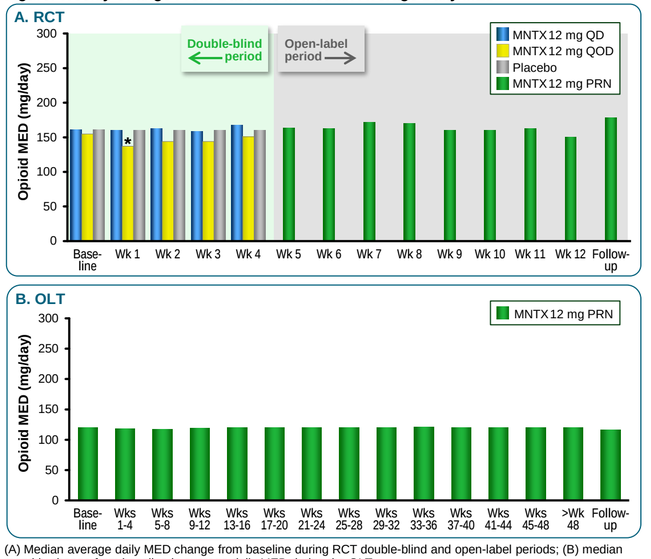
Assessment Timepoint	Patients, n[a]	Mean Score (SD)	Mean Change From Baseline (SD)
Week 4	898	6.0 (2.0)	-0.1 (1.8)
Week 8	789	6.0 (2.1)	0.0 (2.0)
Week 12	733	6.1 (2.1)	0.1 (1.9)
Week 16	689	6.1 (2.2)	0.0 (2.0)
Week 24	626	6.1 (2.2)	0.0 (2.0)
Week 32	582	6.1 (2.1)	0.0 (2.0)
Week 40	521	6.1 (2.1)	0.0 (2.0)
Week 48	435	6.1 (2.1)	0.0 (2.1)
Follow-up visit	286	6.2 (2.2)	0.1 (2.0)

[a]Data available for 1029 patients at baseline.
SD = standard deviation.

- In the RCT, the median of the average daily MED showed minimal fluctuations during both the double-blind (*P* ≥ 0.3 vs placebo) and open-label periods (Figure A)
  - A significant reduction from baseline in mean MED/day was observed at Week 1 for MNTX QOD (-8.0 mg; *P* = 0.005 vs placebo) versus an increase in MED/day with placebo (+1.9 mg); no significant difference was observed with MNTX QD (-4.8 mg; *P* = 0.05 vs placebo)
- In the OLT, median daily MED, assessed monthly, also remained unchanged from baseline (range, 117.3–121.1 mg/day; Figure B)

RESULTS

Figure. Weekly Change From Baseline in Median Average Daily MED



(A) Median average daily MED change from baseline during RCT double-blind and open-label periods; (B) median monthly change from baseline in average daily MED during the OLT.
*$P < 0.02$ vs baseline.

CONCLUSIONS

- **Results show no demonstrable effects of MNTX on centrally mediated opioid analgesia in patients with CNCP and OIC**
- **MNTX should be considered as an option for the treatment of OIC, without clinically significant concerns about compromising pain management strategies in patients with CNCP**

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