181

Efficacy and Safety of Methylnaltrexone for Opioid-Induced Constipation in Patients With Chronic Noncancer Pain: A Placebo Crossover Analysis

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INTRODUCTION

- Opioid-induced constipation (OIC) is a prevalent adverse effect of chronic opioid therapy and has been reported in 41% to 81% of patients with chronic noncancer pain taking long-term opioids[1,2]
  - OIC can be more distressing to patients receiving opioids than the underlying pain syndrome[3]
  - Unlike other adverse effects of opioid use (eg, nausea and vomiting), which usually resolve after continued therapy, patients develop little or no tolerance to OIC[4]
- Treatment of OIC with laxatives is inadequate in a substantial portion of patients, as these agents do not target the underlying pathophysiology of OIC,[5] which involves opioid activation of μ-opioid receptors in the gastrointestinal tract[6]
- Methylnaltrexone (MNTX; Relistor®, Salix Pharmaceuticals, Inc., Raleigh, NC, USA) is a selective, peripherally acting μ-opioid receptor antagonist that has restricted ability to cross the blood-brain barrier[7,8]
  - MNTX efficacy and safety in patients with chronic, nonmalignant pain and OIC has been demonstrated in a randomized, placebo-controlled, phase 3, 4-week study (RCT), with efficacy and tolerability maintained for up to an additional 8 weeks in an open-label extension (OLE) study[9,10]

OBJECTIVE

To examine the reproducibility of findings from the RCT, data from placebo-treated patients who crossed over to MNTX treatment in the OLE were analyzed

METHODS

Study Design

- Patients treated with placebo in the RCT and crossed over to receive MNTX in an OLE
  - In the RCT, patients received subcutaneous MNTX 12 mg once daily (QD), MNTX 12 mg once every other day (QOD), or placebo for 4 weeks[9] and, in the OLE, patients received subcutaneous MNTX 12 mg as needed (PRN; maximum, QD) for 8 weeks[10]

Study Population

- Patients eligible for RCT were ≥18 years of age with chronic pain (lasting ≥2 months prior to enrollment and taking opioids ≥1 month [average daily dose ≥50 mg oral morphine equivalents for ≥2 weeks]), caused by a noncancer condition, and OIC (<3 rescue-free bowel movements [RFBMs] per week with ≥1 of the following signs and symptoms: hard or lumpy stools, straining, or a sensation of incomplete evacuation)
  - Patients discontinued all laxatives taken prior to enrollment; rescue laxatives (bisacodyl tablets taken ≥4 hours after study drug administration and only 1 dose allowed within 24-hour period) were permitted if the patients had no bowel movements for 3 consecutive days during RCT or OLE

Assessments

- Efficacy outcomes evaluated during both phases using patient-reported diary information, which included number and time of bowel movements and rescue laxative use
  - Coprimary efficacy endpoints in RCT: percentage of patients with RFBMs within 4 hours of the first dose and percentage of injections resulting in any RFBM within 4 hours of dose administration
  - Secondary efficacy endpoint: percentage of patients experiencing ≥3 RFBMs/week and 1 RFBM increase over baseline

METHODS

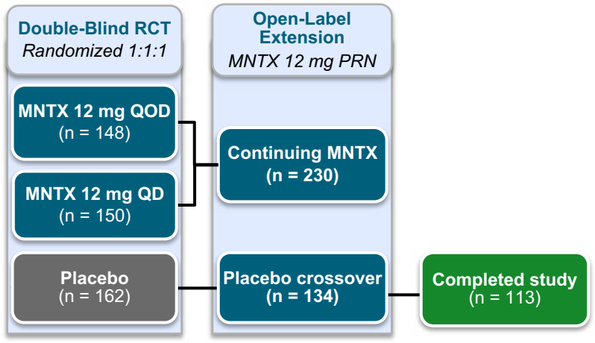
- Safety assessments included monitoring of adverse events (AEs), clinical laboratory tests, vital signs, and concomitant medications

RESULTS

Patient Disposition and Demographics

- 460 patients received MNTX 12 mg QD (n = 150), MNTX 12 mg QOD (n = 148), or placebo (n = 162) in the 4-week RCT
  - Of the 162 patients who had received placebo in the RCT, 134 patients crossed over to open-label MNTX treatment during the extension phase (Figure 1)

Figure 1. Patient Disposition



- The 134 patients in the crossover group were predominantly white (88.8%) and female (64.2%), with a mean (SD) age of 50.3 (10.8) years and back pain as the primary pain condition (Table 1)

Table 1. Baseline Characteristics

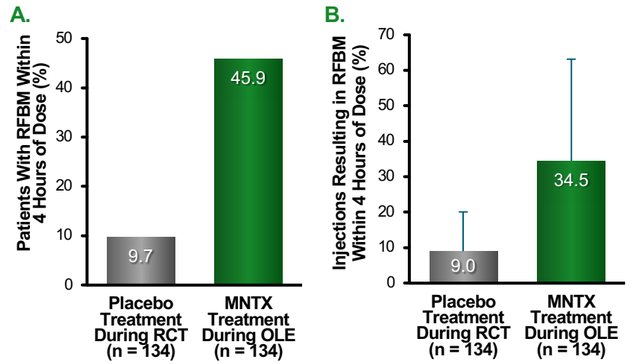
Characteristic		Placebo Crossover Patients (n = 134)
Primary pain condition, n (%)	Back pain Other	78 (58.2) 56 (41.8)
Baseline morphine equivalent dose, mg/day	Mean (SD) Median	214.6 (199.3) 150.0
Duration of OIC, mo, mean (SD)		78.3 (70.2)
Baseline average bowel movements per week, mean (SD)		1.1 (0.8)

Efficacy Outcomes

- 13 of 134 patients (9.7%) experienced a RFBM within 4 hours of first placebo dose during the RCT versus 61 (45.9%) who experienced a RFBM within 4 hours of first MNTX dose in the OLE (Figure 2)
  - Similarly, on average, more injections with MNTX in the OLE resulted in RFBM within 4 hours of dose versus injections with placebo in the RCT (34.5% and 9.0%, respectively)

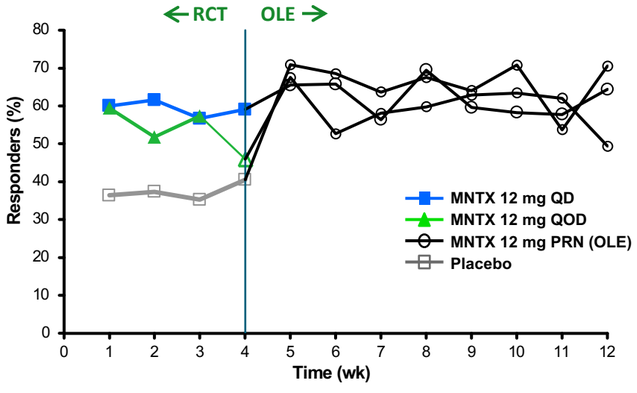
RESULTS

Figure 2. (A) RFBM Within 4 Hours of Administration of the First Dose of RCT Placebo or OLE MNTX; (B) Percentage of Injections That Resulted in Any RFBM Within 4 Hours of Administration of the Dose of RCT Placebo or OLE MNTX



- When expressed according to percentage of patients experiencing ≥3 RFBMs per week and ≥1 RFBM increase over baseline, weekly values ranged from 35% to 41% during placebo treatment in the RCT, suggesting a lack of tolerance development to OIC over time (Figure 3)
  - However, with MNTX treatment, this percentage increased to >70% within the first week (Week 5) and remained relatively stable throughout the study

Figure 3. Percentage of Patients With Weekly Number of RFBMs ≥3 and an Increase of ≥1 RFBM From Baseline



Solid symbols during the RCT phase indicate statistically significant difference versus placebo ($P < 0.05$).

RESULTS

Safety

- Overall incidence of AEs were reported in 32.8% of patients during placebo treatment in the RCT versus 43.3% of patients during 8 weeks of MNTX treatment in the OLE (Table 2)
  - Abdominal pain, nausea, and urinary tract infections were the most common AEs during the OLE

Table 2. Summary of Adverse Events

Adverse Events, n (%)		Placebo Treatment During RCT (n = 134)	MNTX Treatment During OLE (n = 134)
Any AEs		44 (32.8)	58 (43.3)
Most common AEs[a]	Abdominal pain	2 (1.5)	13 (9.7)
	Nausea	9 (6.7)	7 (5.2)
	Urinary tract infection	2 (1.5)	7 (5.2)
	Diarrhea	4 (3.0)	6 (4.5)
	Hyperhidrosis	1 (0.7)	6 (4.5)
	Hypertension	0	5 (3.7)
	Back pain	1 (0.7)	4 (3.0)
	Influenza	0	4 (3.0)
	Rhinorrhea	1 (0.7)	4 (3.0)
	Sinusitis	0	4 (3.0)
	Upper abdominal pain	5 (3.7)	4 (3.0)

[a]Reported in ≥5% of patients.

- Serious AEs were reported in 1 patient during placebo treatment (musculoskeletal chest pain) and 4 patients during MNTX treatment (pneumonia in 2 patients; gastroenteritis and hypertension in 1 patient; and mental status change in 1 patient); none were considered drug-related

CONCLUSIONS

- **This placebo-crossover study establishes the reproducibility and durability of MNTX for treatment of OIC in chronic noncancer pain**
- **Findings during placebo treatment in the RCT further establish the nature of OIC and support that little or no gastrointestinal tolerance develops over time**

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