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Attrition of Methylnaltrexone's Treatment-Emergent Adverse Events in Patients With Chronic Noncancer Pain and Opioid-Induced Constipation

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INTRODUCTION

- The use of opioids, often prescribed to treat chronic noncancer pain (CNCP), may be associated with gastrointestinal side effects such as nausea, abdominal pain, vomiting, and constipation[1-4]
- Opioid-induced constipation (OIC) occurs in as many as 80% of patients with noncancer pain treated with opioids,[5] and frequently leads to dose reductions or discontinuation of opioid therapy[1,2,4,6,7]
- Preventive measures and traditional constipation remedies, including lifestyle changes and over-the-counter or prescription laxatives, provide only limited relief from OIC,[6,8,9] and the development of tolerance to OIC is uncommon[1]
- Methylnaltrexone (Relistor®, Salix Pharmaceuticals, a division of Bausch Health US, LLC, Bridgewater, NJ) is a peripherally acting μ-opioid receptor antagonist that reverses opioid-induced effects in the gastrointestinal tract, such as delayed gastric emptying and prolonged oral-cecal transit time,[10,11] while maintaining centrally mediated opioid analgesia[12,13]
  - Methylnaltrexone is available in subcutaneous and oral formulations; both formulations are approved for the treatment of OIC in adults with CNCP, and the subcutaneous formulation is also indicated in patients with advanced illness or pain caused by active cancer[14]
- The majority of adverse events (AEs) that have occurred with methylnaltrexone treatment in clinical trials were gastrointestinal events (eg, abdominal pain, diarrhea, nausea).[13,15-17] Because these AEs are also common during laxation, it is plausible that gastrointestinal AEs reported in patients who receive methylnaltrexone are of short duration and may be linked to successful relief of OIC
- To test this hypothesis, we assessed changes in the frequencies of AEs after the second dose relative to the first dose of methylnaltrexone in adults with CNCP and OIC

METHODS

Study Design

- A post hoc analysis was performed using pooled data from 2 randomized, double-blind, placebo-controlled clinical trials that evaluated the efficacy and safety of subcutaneous or oral methylnaltrexone for the relief of OIC in patients with CNCP (NCT00529087, NCT01186770)[15,16]
  - Both studies received IRB approval
- Patients in the subcutaneous methylnaltrexone study were randomized 1:1:1 to receive treatment with methylnaltrexone 12 mg once daily, methylnaltrexone 12 mg every other day, or placebo for 4 weeks, then as needed for an additional 8 weeks during an open-label study phase[15]
- Patients participating in the oral methylnaltrexone study were randomized 1:1:1:1 to receive treatment with methylnaltrexone 150 mg, 300 mg, 450 mg, or placebo once daily for 4 weeks, then as needed for an additional 8 weeks during an open-label study phase[13,16]
- Rescue laxative use (1 dose of up to 3 or 4 bisacodyl tablets) was permitted if the patient had no bowel movements for 3 consecutive days and was limited to a single dose within a 24-hour period administered 4 hours or more after study drug administration

Study Patients

- Both studies enrolled adult patients who had CNCP for at least 2 months and OIC for at least 30 days
  - OIC was defined as fewer than 3 rescue-free bowel movements (RFBM; no laxative use within 24 hours prior to the bowel movement) per week on average and 1 or more of the following symptoms: hard or lumpy stools, straining during bowel movements, or a sensation of incomplete evacuation after bowel movements
- Patients were required to have been receiving an opioid for at least 1 month, with a daily dose of at least 50-mg oral morphine equivalents for 14 days prior to screening
- Patients with a history of clinically significant bowel or rectal disease, chronic constipation, or any other medical condition that might compromise the studies or put the patient at risk were excluded

Assessments

- The frequency and severity of treatment-emergent AEs were assessed on treatment days 1 and 2
- Methylnaltrexone efficacy was measured by the proportion of patients demonstrating a laxation response to treatment, defined as an RFBM within 4 hours of first study drug dose
- Opioid withdrawal was measured by the Subjective Opiate Withdrawal Scale [SOWS] and the Objective Opiate Withdrawal Scale [OOWS] at 1 hour postdose on day 1 and at weeks 2 and 4 during the double-blind treatment phases of the studies
  - For the SOWS, patients rated their perceived severity of 19 opioid withdrawal symptoms on a scale from 0 (not at all) to 4 (extremely), with a total possible score of 76
  - For the OOWS, clinicians assigned patients a score of 0 or 1 based on the absence or presence of 13 symptoms indicative of opioid withdrawal, with a total possible score of 13
- Maintenance of analgesia was assessed by changes in pain intensity scores at each study visit
  - Pain intensity scores were derived by asking patients to rate the intensity of their pain on a scale from 0 (no pain) to 10 (worst pain possible)

Statistical Analyses

- AEs were summarized using descriptive statistics
- Changes from baseline in SOWS and OOWS scores in the methylnaltrexone (all methylnaltrexone-treated patients) and placebo treatment groups were compared by analysis of covariance, with treatment as the main effect and the baseline value as a covariate
- Comparisons of the proportions of RFBM responders in the methylnaltrexone (all methylnaltrexone-treated patients) and placebo treatment groups were performed using chi-square tests
- Associations between individual AEs and the occurrence of an RFBM within 4 hours of the first study drug dose were evaluated using Fisher's exact test
- All *P*-values reported for between-group comparisons used a nominal value of 0.05 to denote statistical significance
- Corrections for multiplicity were not performed

RESULTS

Study Patients

- A total of 1263 patients were included in the pooled analysis: 900 were randomized to methylnaltrexone (subcutaneous, n=298; oral, n=602) and 363 were randomized to placebo
- Demographic and baseline characteristics were generally well balanced among treatment groups (**Table 1**)

Table 1. Patient Demographics and Baseline Characteristics

	Placebo (n=363)	Methylnaltrexone SC (n=298)	Methylnaltrexone Oral (n=602)	Methylnaltrexone All (n=900)	Total (N=1263)
Mean (range) age, years	51.3 (23, 83)	48.3 (23, 78)	51.3 (18, 82)	50.3 (18, 82)	50.6 (18, 83)
Gender, n (%)					
Men	134 (36.9)	120 (40.3)	227 (37.7)	347 (38.6)	481 (38.1)
Women	229 (63.1)	178 (59.7)	375 (62.3)	553 (61.4)	782 (61.9)
Race, n (%)					
White	307 (84.6)	272 (91.3)	494 (82.1)	766 (85.1)	1073 (85.0)
Black or African American	42 (11.6)	17 (5.7)	93 (15.4)	110 (12.2)	152 (12.0)
Other	14 (3.9)	9 (3.0)	15 (2.5)	24 (2.7)	38 (3.0)
Median (range) baseline MED, mg/day	145.3 (13.6, 1287)	160.0 (7.1, 1334)	151.0 (27.0, 2289)	152.5 (7.1, 2289)	150.0 (7.1, 2289)
Mean (SD) number of laxatives used	0.4 (0.6)	0.9 (0.5)	0.1 (0.4)	0.4 (0.5)	0.4 (0.6)
Mean (SD) RFBMs per week	1.3 (1.0)	1.0 (0.8)	1.4 (0.9)	1.3 (0.9)	1.3 (0.9)
Mean (SD) pain score	6.2 (1.9)	6.2 (1.9)	6.4 (1.9)	6.3 (1.9)	6.3 (1.9)

MED = morphine equivalent dose; RFBM = rescue-free bowel movements; SC = subcutaneous; SD = standard deviation.

Adverse Events

- The numbers of patients who experienced at least 1 AE decreased from day 1 to day 2 of treatment among all treatment groups with the greatest decrease occurring in the subcutaneous methylnaltrexone treatment group (**Table 2**)

Table 2. Adverse Events[a] Occurring on Treatment Day 1 and Day 2

Patients, n (%)

	Placebo		SC MNTX QD		SC MNTX QOD[b]		Oral MNTX		All MNTX	
	Day 1 (n=363)	Day 2 (n=354)	Day 1 (n=150)	Day 2 (n=145)	Day 1 (n=148)	Day 2 (n=138)	Day 1 (n=602)	Day 2 (n=571)	Day 1 (n=900)	Day 2 (n=854)
Patients with at least 1 AE	24 (6.6)	19 (5.4)	33 (22.0)	10 (6.9)	31 (20.9)	8 (5.8)	82 (13.6)	27 (4.7)	146 (16.2)	45 (5.3)
Abdominal pain	3 (0.8)	4 (1.1)	17 (11.3)	7 (4.8)	11 (7.4)	1 (0.7)	24 (4.0)	6 (1.1)	52 (5.8)	14 (1.6)
Nausea	3 (0.8)	3 (0.8)	8 (5.3)	4 (2.8)	11 (7.4)	0	11 (1.8)	4 (0.7)	30 (3.3)	8 (0.9)
Hyperhidrosis	1 (0.3)	1 (0.3)	8 (5.3)	1 (0.7)	7 (4.7)	1 (0.7)	5 (0.8)	1 (0.2)	20 (2.2)	3 (0.4)
Diarrhea	0	0	3 (2.0)	1 (0.7)	8 (5.4)	2 (1.4)	3 (0.5)	1 (0.2)	14 (1.6)	4 (0.5)
Abdominal pain, upper	3 (0.8)	1 (0.3)	1 (0.7)	0	6 (4.1)	1 (0.7)	4 (0.7)	1 (0.2)	11 (1.2)	2 (0.2)
Vomiting	0	1 (0.3)	0	0	7 (4.7)	1 (0.7)	3 (0.5)	1 (0.2)	10 (1.1)	2 (0.2)
Hot flush	3 (0.8)	1 (0.3)	3 (2.0)	0	3 (2.0)	2 (1.4)	1 (0.2)	0	7 (0.8)	2 (0.2)

[a]Reported by ≥2% patients in any treatment group.
[b]Treatment day 2 occurred on study day 3 for patients who received SC MNTX every other day.
AE = adverse event; MNTX = methylnaltrexone; QD = daily; QOD = every other day; SC = subcutaneous.

- Abdominal pain was the most common AE reported on treatment day 1 among patients who received methylnaltrexone or placebo
- On treatment day 2, the frequency of abdominal pain had decreased among patients treated with methylnaltrexone but was unchanged among patients who received placebo
- The frequency of AEs reported by methylnaltrexone-treated patients after treatment day 2 were comparable to or less than those reported after day 2 among patients who received placebo (**Table 3**)

Table 3. Adverse Events[a] Occurring After Treatment Day 2

Patients, n (%)

	Placebo (n=363)	SC MNTX (n=298)	Oral MNTX (n=602)	All MNTX (n=900)
Patients with at least 1 AE	203 (55.9)	152 (51.0)	309 (51.3)	461 (51.2)
Abdominal pain	28 (7.7)	28 (9.4)	21 (3.5)	49 (5.4)
Nausea	28 (7.7)	16 (5.4)	25 (4.2)	41 (4.6)
Diarrhea	19 (5.2)	18 (6.0)	32 (5.3)	50 (5.6)
Vomiting	18 (5.0)	5 (1.7)	12 (2.0)	17 (1.9)
Urinary tract infection	15 (4.1)	12 (4.0)	21 (3.5)	33 (3.7)
Upper respiratory tract infection	13 (3.6)	3 (1.0)	24 (4.0)	27 (3.0)
Flatulence	13 (3.6)	7 (2.3)	17 (2.8)	24 (2.7)
Back pain	12 (3.3)	8 (2.7)	21 (3.5)	29 (3.2)
Headache	12 (3.3)	12 (4.0)	15 (2.5)	27 (3.0)
Abdominal pain, upper	9 (2.5)	5 (1.7)	12 (2.0)	17 (1.9)
Influenza	8 (2.2)	3 (1.0)	12 (2.0)	15 (1.7)
Anxiety	7 (1.9)	1 (0.3)	16 (2.7)	17 (1.9)
Dizziness	3 (0.8)	7 (2.3)	5 (0.8)	12 (1.3)

[a]Reported by ≥2% patients in any treatment group.
AE = adverse event; MNTX = methylnaltrexone.

Opioid-Induced Constipation Relief

- The proportion of patients who were RFBM responders (ie, experienced an RFBM within 4 hours after the first dose of study treatment) was significantly greater among all patients who received methylnaltrexone (25.1%, n=226/900) compared with placebo (8.8%, n=32/363; *P*<0.0001)

Association Between AE Frequency and RFBM Response

- Among all methylnaltrexone-treated patients, abdominal pain, upper abdominal pain, diarrhea, and nausea on day 1 were reported by a significantly greater proportion of RFBM responders compared with nonresponders (**Table 4**)
- No statistically significant associations between the frequency of AEs and RFBM response were observed among patients who received placebo

Table 4. Association Between Adverse Events[a] Occurring After the First Dose of Study Drug and Rescue-Free Bowel Movements Within the First 4 Hours of Dosing

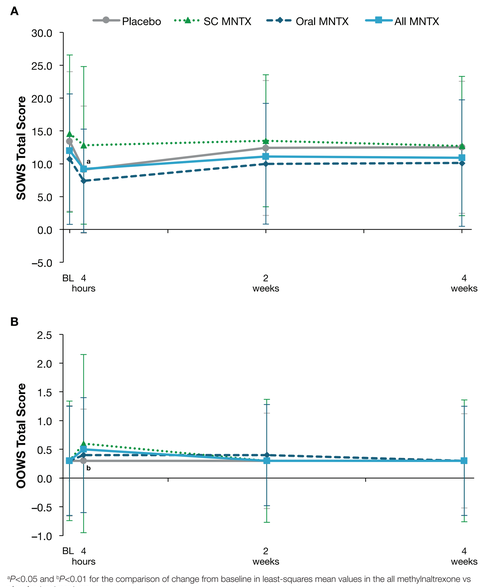
	Placebo, n (%)			Methylnaltrexone, n (%)		
	No RFBM within 4 hours of 1st dose (n=331)	RFBM within 4 hours of 1st dose (n=32)	*P*-Value	No RFBM within 4 hours of 1st dose (n=674)	RFBM within 4 hours of 1st dose (n=226)	*P*-Value
Abdominal pain	3 (0.9)	0	NS	28 (4.2)	24 (10.6)	0.0008
Abdominal pain, upper	3 (0.9)	0	NS	4 (0.6)	7 (3.1)	0.0074
Diarrhea	0	0	NS	6 (0.9)	8 (3.5)	0.0101
Nausea	3 (0.9)	0	NS	16 (2.4)	14 (6.2)	0.0092
Hyperhidrosis	1 (0.3)	0	NS	13 (1.9)	7 (3.1)	NS

[a]Reported by ≥2% patients in any treatment group.
AE = adverse event; MNTX = methylnaltrexone; NS = not significant, *P*>0.05; RFBM = rescue-free bowel movement.

Opioid Withdrawal and Maintenance of Analgesia

- In all treatment groups, slight decreases in SOWS total scores were observed between baseline and the day 1 postdose assessment (**Figure 1A**)
  - When changes from baseline in SOWS total scores were compared between the combined methylnaltrexone and placebo groups, a statistically significant difference was noted at day 1 (least-squares means, –3.6 and –2.6, respectively; *P*=0.01), but not at weeks 2 or 4
- The OOWS total scores increased slightly from baseline to the day 1 postdose assessment in all methylnaltrexone treatment groups, whereas the placebo score remained unchanged (**Figure 1B**)
  - The difference in changes from baseline values between the combined methylnaltrexone treatment group and placebo was statistically significant at day 1 (least-squares means, 0.13 and –0.02, respectively; *P*=0.001), but not at weeks 2 or 4

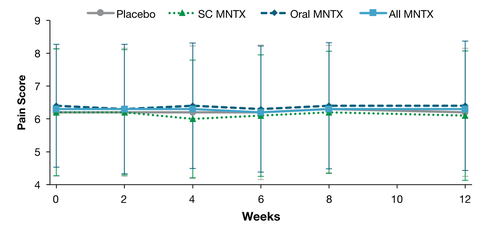
Figure 1. Effect of Study Treatment on (A) Subjective Opioid Withdrawal Scale (SOWS) Total Scores and (B) Objective Opioid Withdrawal Scale (OOWS) Total Scores



[a]*P*<0.05 and [b]*P*<0.01 for the comparison of change from baseline in least-squares mean values in the all methylnaltrexone vs placebo treatment groups.
Data are presented as means ± standard deviations.
BL = baseline; MNTX = methylnaltrexone; SC = subcutaneous.

- Pain intensity scores did not change significantly from baseline for any treatment group throughout the study (**Figure 2**)

Figure 2. Pain Scores During Treatment With Methylnaltrexone or Placebo



Data are presented as means ± standard deviations.
MNTX = methylnaltrexone; SC = subcutaneous.

CONCLUSIONS

- **The rates of AEs decreased considerably between the first and second methylnaltrexone treatment days and were comparable to placebo after the second dose**
- **The association between gastrointestinal AEs and laxation response support the hypothesis that early-onset AEs following methylnaltrexone treatment, particularly gastrointestinal AEs, are at least partially due to laxation**
- **Treatment with methylnaltrexone was shown to relieve OIC without inducing withdrawal symptoms or compromising analgesia**
- **For patients with chronic pain and OIC, methylnaltrexone offers a well-tolerated and effective treatment option for constipation relief**

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DISCLOSURES

Dr. Mehta has participated in several advisory boards for Salix Pharmaceuticals. Dr. Slatkin is an employee of Salix Pharmaceuticals, a subsidiary of Bausch Health US since July 2016; an unpaid consultant for Salix prior to July 2016; and a speaker for Salix through February 2016. Dr. Stambler is a full-time employee and shareholder of Progenics Pharmaceuticals. Dr. Israel is an employee of Bausch Health US, LLC.

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