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Efficacy and Safety of Methylnaltrexone for Opioid-Induced Constipation in Patients With Chronic Noncancer Pain

A Placebo Crossover Analysis

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Background and Objectives: In patients with chronic noncancer pain, subcutaneous methylnaltrexone for opioid-induced constipation (OIC) was examined in a randomized controlled trial (RCT) followed by an open-label extension (OLE). This study examined the reproducibility of RCT findings by analyzing data from placebo-treated patients who crossed over to methylnaltrexone.

Methods: Adults with less than 3 weekly rescue-free bowel movements (RFBMs), taking 50 mg or more of an oral morphine equivalent per day, were randomized to receive methylnaltrexone 12 mg or placebo for 4 weeks, followed by open-label methylnaltrexone 12 mg as needed for 8 weeks.

Results: A total of 134 placebo-treated patients (median morphine equivalent dose, 150 mg/d; mean of 1.1 RFBM per week) crossed over to methylnaltrexone in OLE. During the RCT, 9.7% of placebo-treated patients experienced an RFBM within 4 hours of first dose and 9.0% of all placebo injections resulted in an RFBM within 4 hours compared with 45.9% and 34.5%, respectively, with methylnaltrexone treatment in the OLE. When expressed as percentage of patients experiencing 3 or more RFBMs per week and a 1-RFBM increase over baseline, weekly values ranged from 35% to 40% during placebo treatment; at week 5 of OLE methylnaltrexone, this percentage increased to more than 70% and remained relatively stable throughout the OLE. The most common adverse events during methylnaltrexone treatment were abdominal pain (9.7% vs 1.5% for placebo) and nausea (5.2% vs 6.7%).

Conclusions: Findings during placebo treatment further establish the profile of OIC and support that little or no gastrointestinal tolerance develops across time. Findings under open-label conditions established the reproducibility and durability of methylnaltrexone for OIC.

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Opioid analgesics are commonly prescribed for the management of chronic noncancer pain but are associated with gastrointestinal (GI) adverse effects such as constipation, primarily mediated through μ-opioid receptors.[1,2] Opioids disrupt peristalsis, which also results in increased fluid absorption and drier stool and inhibition of GI secretions.[3] Many patients develop some degree of opioid-induced constipation (OIC),[4,5] and unlike other GI-related adverse effects (eg, nausea), patients typically do not develop tolerance to OIC across time, or they develop tolerance very slowly.[6,7] Severe OIC may result in opioid dose reduction or limitations on upward titration, potentially affecting adequate pain control.[4,8,9] Guidelines recommend that health care providers proactively manage opioid-associated adverse effects.[4]

Although randomized controlled data are generally lacking, stool softeners and stimulant laxatives may be prescribed at the initiation of opioid therapy.[1] However, these treatments are nonspecific and do not target the underlying pathophysiology of OIC,[10,11] including opioid inhibition of peristalsis. Methylnaltrexone bromide is a selective peripherally acting μ-opioid receptor antagonist that has restricted ability to cross the blood-brain barrier.[12–14] It antagonizes the negative opioid-induced effects on the GI tract, such as delayed gastric emptying[15] and prolongation of oral-cecal transit time.[16] Methylnaltrexone is indicated for the treatment of OIC in adults with chronic noncancer pain and for the treatment of OIC in patients with advanced illness receiving palliative care who have had an inadequate response to laxative therapy.[17] The efficacy and safety of methylnaltrexone in patients with chronic noncancer pain were demonstrated in a 4-week, randomized, placebo-controlled trial (RCT),[18] with efficacy and tolerability maintained for up to an additional 8 weeks in an open-label extension (OLE) phase. To assess the reproducibility of efficacy and safety findings from the RCT, data from placebo-treated patients who crossed over to methylnaltrexone treatment in the OLE phase were analyzed.

METHODS

Study Population

This study included adults with chronic noncancer pain (≥2 months' duration before screening) who had been taking opioids and had a stable medical status for at least 1 month (average daily dose ≥50 mg oral morphine equivalent for ≥2 weeks with no anticipated changes) and who had OIC (<3 rescue-free bowel movements [RFBMs] per week with ≥1 of the following signs or symptoms for ≥25% of bowel movements: hard or lumpy stools,[19] straining during bowel movements, or sensation of incomplete evacuation).[18] Patients were excluded if they had a history of inflammatory bowel disease, irritable bowel syndrome, or megacolon during the previous 6 months, were scheduled to undergo surgery during the study period, had evidence of bowel obstruction or fecal incontinence, history of rectal bleeding unrelated to hemorrhoids or fissures, or a history of chronic constipation before starting opioid therapy. Patients discontinued all laxative use before enrollment; rescue laxatives (bisacodyl tablets taken ≥4 hours after study drug administration, with only 1 dose allowed within a 24-hour period) were permitted if the patient had no bowel movements for 3 consecutive days during the RCT or OLE. The study was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice according to the Declaration of Helsinki, and all patients provided written informed consent.

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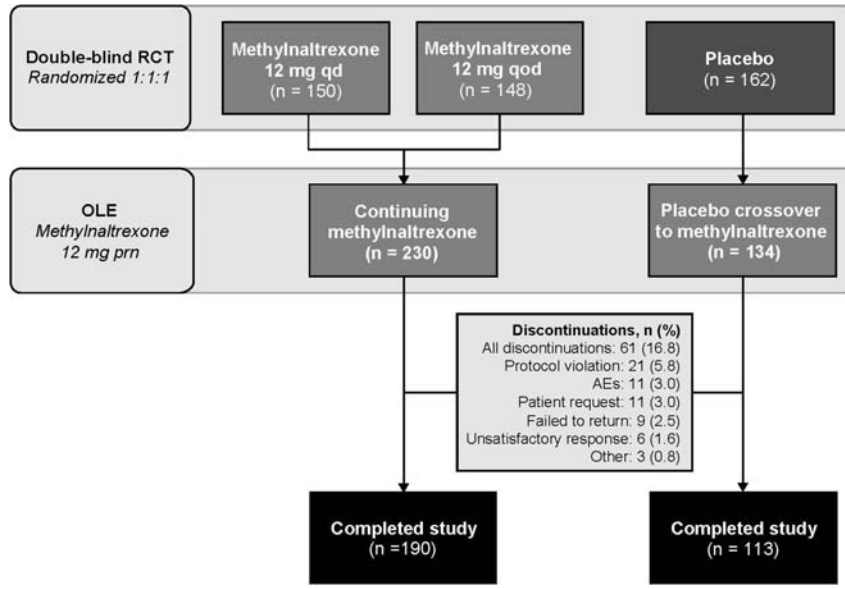

FIGURE 1. Patient disposition. AE indicates adverse event; OLE, open-label extension; prn, as needed; qd, once a day; qod, every other day; RCT, randomized controlled trial.

Study Design and Assessments

Details on the design of the RCT have been previously published.[18] Briefly, the RCT was a phase 3, double-blind, placebo-controlled, multicenter study (ClinicalTrials.gov identifier, NCT00529087) conducted at 91 sites in the United States and Canada. Patients were randomly assigned 1:1:1 to receive subcutaneous methylnaltrexone (Relistor; Salix Pharmaceuticals, Inc, Raleigh, North Carolina) 12 mg once daily (qd), methylnaltrexone 12 mg once every other day (qod), or placebo for 4 weeks. Patients who completed the RCT were eligible to enter an OLE phase and received subcutaneous methylnaltrexone 12 mg as needed (prn; maximum, qd) for 8 weeks, followed by a 14-day posttreatment follow-up period.

Efficacy outcomes were evaluated during the RCT and OLE using daily patient diaries, which included the number and time of bowel movements, stool consistency (Bristol Stool Form Scale[19]), straining during a bowel movement (0 = none to 4 = very severe), sense of complete evacuation (yes/no), and rescue laxative use. The coprimary efficacy end points in the RCT were the percentage of patients experiencing an RFBM within 4 hours of the first dose and the percentage of injections resulting in an RFBM within

TABLE 1. Patient Demographics and Baseline Characteristics*

Characteristics	Placebo Crossover (n = 134)	RCT Methylnaltrexone qd (n = 150)†	RCT Methylnaltrexone qod (n = 148)†
Mean age (SD), y	50.3 (10.8)	48.0 (10.7)	48.6 (11.0)
Range	25–83	24–78	23–73
Sex (male), %	64.2	62.0	57.4
Race, n (%)			
White	119 (88.8)	139 (92.7)	133 (89.9)
Black	12 (9.0)	7 (4.7)	10 (6.8)
Other	3 (2.2)	4 (2.6)	5 (3.4)
Mean BMI (SD), kg/m^2	30.2 (8.0)	30.3	28.9
Range	15.7–66.2	16.8–56.5	15.7–54.7
Primary pain condition, n (%)			
Back pain	78 (58.2)	96 (64.0)	83 (56.1)
Other	56 (41.8)	54 (36.0)	65 (43.9)
Mean oral morphine equivalents (SD), mg/d	214.6 (199.3)	214.4 (156.6)	225.2 (205.1)
Median	150.0	161.0	154.8
Mean OIC duration (SD), mo	78.3 (70.15)	76.4 (60.3)	76.1 (74.1)
Mean baseline bowel movements per week (SD)	1.1 (0.8)	1.0 (0.8)	0.9 (0.7)

*At baseline of RCT.

†Data from Michna et al.[18]

BMI indicates body mass index; OIC, opioid-induced constipation; qd, every day; qod, every other day; RCT, randomized controlled trial; SD, standard deviation.

4 hours of dose administration. Secondary efficacy end points included the percentage of patients experiencing 3 or more RFBMs per week and at least a 1-RFBM increase from baseline in the weekly RFBM rate ("responders"), the percentage of patients experiencing 3 or more RFBMs per week, the weekly RFBM rate, and the percentage of weekly injections resulting in an RFBM within 4 hours of dose administration. An RFBM was defined as a bowel movement not occurring within 24 hours of rescue laxative use. Safety assessments included monitoring of adverse events (AEs), clinical laboratory tests, vital signs, and concomitant medications.

Statistical Analyses

The RCT methylnaltrexone population included all patients randomized to treatment who received at least 1 dose of methylnaltrexone. The placebo crossover population included all patients who completed the RCT trial and received at least 1 dose of methylnaltrexone during the OLE. Data were analyzed using an observed case analysis. For between-group comparisons during the RCT, *P* values were calculated using the Wilcoxon rank sum test. Descriptive statistics were used for the placebo crossover population analyses.

RESULTS

A total of 460 patients received methylnaltrexone 12 mg qd (n = 150), methylnaltrexone 12 mg qod (n = 148), or placebo (n = 162) in the 4-week RCT (Fig. 1). Of the 162 patients who had received placebo in the RCT, 134 were enrolled in the OLE and crossed over to methylnaltrexone 12 mg prn treatment. The most common pain condition among the 134 patients in the placebo crossover population was back pain (58.2%), and the mean number of bowel movements per week at RCT baseline was 1.1 (Table 1).

A total of 13 (9.7%) of 134 patients had experienced an RFBM within 4 hours of the first placebo dose during the RCT; however, 61 (45.9%) of the 134 patients experienced an RFBM within 4 hours of the first methylnaltrexone dose in the OLE (Fig. 2). Similarly, on average, in the placebo crossover population, more injections with methylnaltrexone in the OLE resulted in an RFBM within 4 hours of dose versus injections with placebo in the RCT (Fig. 2). When response was expressed according to the percentage of patients experiencing 3 or more RFBMs per week and an increase of 1 or more RFBMs over baseline, weekly values ranged from 35% to 40% during placebo treatment in the RCT, suggesting a lack of tolerance development to OIC across time (Fig. 3A). However, when patients crossed over from placebo to methylnaltrexone treatment, the percentage increased to more than 70% within the first week (week 5) and remained relatively stable throughout the study. The percentage of patients experiencing 3 or more RFBMs per week and an increase of 1 or more RFBMs over baseline observed in the placebo crossover population during the OLE was consistent with data observed for those patients who had received methylnaltrexone qd or qod during the RCT and continued receiving methylnaltrexone during the OLE (Fig. 3B).

The number of RFBMs per week increased slightly but significantly during placebo treatment in the RCT, from 1.1 RFBMs per week to a range of 2.3 to 2.7 per week ($P < 0.001$); the results were significantly lower than data for patients who were treated with methylnaltrexone qd during the RCT (1.0 RFBM per week at baseline vs 4.3 to 4.6 during the RCT; $P < 0.05$ versus placebo at all weeks; Fig. 3B). When placebo-treated patients crossed over to receive methylnaltrexone prn in the OLE, weekly RFBMs increased to levels of approximately 4 within 1 week, remained stable through week 12, and the weekly data were consistent with results from patients who had received methylnaltrexone during both the RCT and the OLE (Fig. 3B). The trend in improvement observed with the placebo crossover population was also observed when the percentage of weekly injections resulting in an RFBM within 4 hours of dose administration was assessed (Fig. 3C). In the placebo group in the RCT, only approximately 10% of weekly injections resulted in an RFBM within 4 hours of dose administration; however, when patients crossed over to methylnaltrexone prn in the OLE, this percentage increased to 35% to 40%. Improvements observed in the placebo crossover population were consistent with results from patients who had received methylnaltrexone during both the RCT and OLE (Fig. 3C).

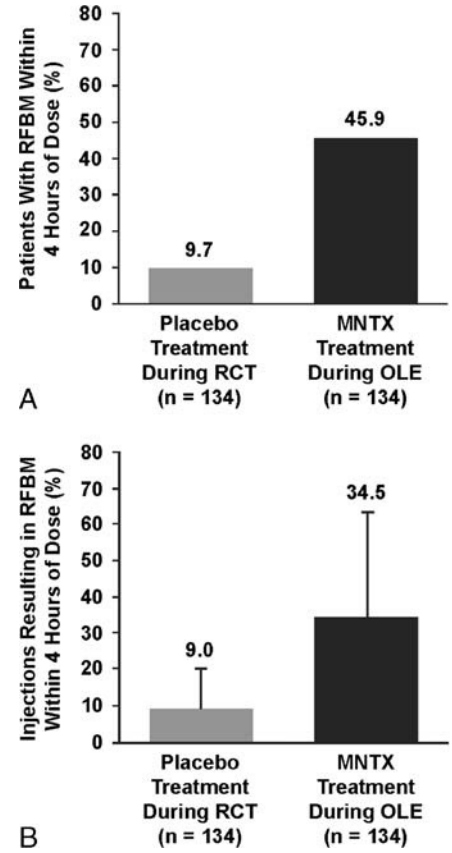

FIGURE 2. Rescue-free bowel movement (RFBM) within 4 hours of administration of the first dose of randomized controlled trial (RCT) placebo or open-label extension (OLE) methylnaltrexone (MNTX) (A) and percentage of injections that resulted in any RFBM within 4 hours of administration of either RCT placebo or OLE MNTX (B).

Overall, AEs were reported in 32.8% of 134 patients during placebo treatment in the 4-week RCT versus 43.3% of 134 patients during 8 weeks of methylnaltrexone treatment in the OLE (Table 2). Abdominal pain, nausea, and urinary tract infections were the most common AEs during the OLE. Serious AEs were reported in 1 patient (0.7%) during placebo treatment (musculoskeletal chest pain) in the RCT and 4 patients (3.0%) during methylnaltrexone treatment in the OLE (pneumonia in 2 patients; gastroenteritis and hypertension in 1 patient; and mental status change in 1 patient); none were considered by investigators to be drug related.

DISCUSSION

Methylnaltrexone is a peripherally acting μ-opioid receptor antagonist that targets the underlying pathophysiology of OIC: opioid agonism of μ-opioid receptors in the GI tract. Opioids

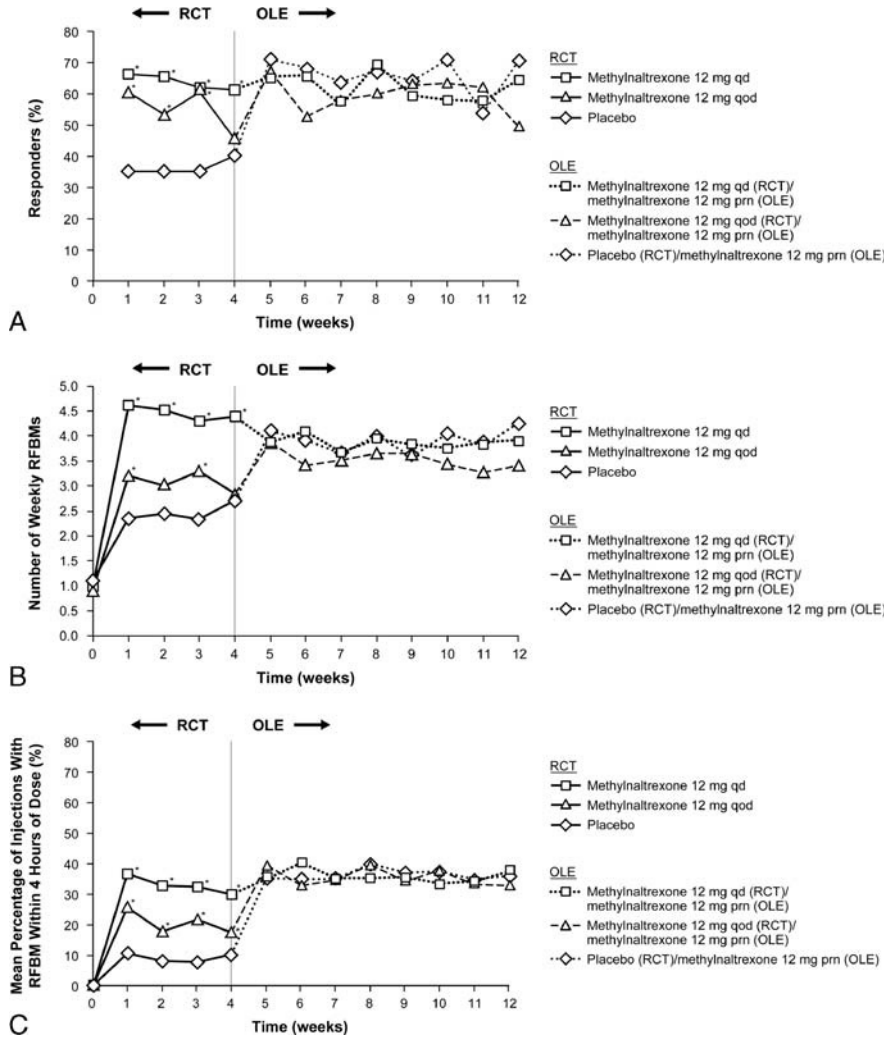

FIGURE 3. Percentage of patients with both a weekly number of rescue-free bowel movements (RFBMs) of 3 or more and an increase of 1 or more RFBMs from baseline by week (A); average weekly number of RFBMs by week (B); and percentage of weekly injections resulting in an RFBM within 4 hours of dose administration by week (C). *Statistically significant difference versus placebo ($P < 0.05$) during the randomized controlled trial (RCT). MNTX indicates methylnaltrexone; OLE, open-label extension; prn, as needed; qd, once a day; qod, every other day.

can interfere with normal GI motility, thereby reducing productive peristalsis, increasing fluid absorption from the GI tract, and decreasing intestinal secretions, which leads to drier harder stool.[3] Subcutaneous methylnaltrexone has been shown in an RCT to be well tolerated and to provide significant relief from OIC when administered once daily or every other day for the treatment of OIC in patients with chronic noncancer pain.[18] The current post hoc analysis examined the repeatability of these findings by evaluating the tolerability and response of patients who were initially treated with placebo during the RCT and crossed over to treatment with methylnaltrexone 12 mg prn for up to 12 weeks. This methodology minimized the risk of heterogeneity with the analyses by having each patient function as his or her own control.

The current analysis reaffirmed the data from the RCT and demonstrated that a higher percentage of patients achieved an RFBM within 4 hours of the first dose of methylnaltrexone during the OLE compared with their first dose of placebo in the RCT. As well, other efficacy analyses, including the percentage of weekly responders (≥3 RFBMs per week and ≥1 RFBM increase over baseline) and weekly number of RFBMs, improved when patients crossed over to receive methylnaltrexone prn compared with their experience with placebo treatment during the RCT. Furthermore, responder rates achieved when patients crossed over to methylnaltrexone treatment in the OLE (53.7%–70.9%) were consistent with results observed during the 4-week RCT for patients receiving methylnaltrexone qd (61.2%–66.4%) or qod (45.6%–60.5%) and results for the methylnaltrexone-treated patients who continued to receive methylnaltrexone in the OLE (56.3%–69.4% and 49.4%–67.5% for qd and qod dosing, respectively). This is the first OIC study to evaluate drug efficacy during an RCT and an OLE crossover period, and differences in "responder" definitions prevent comparisons with other studies; however, an RCT of oral μ-opioid receptor antagonist alvimopan that used a definition similar to the one used in the current study (ie, patients who had ≥3 spontaneous bowel movements per week and a mean increase from baseline of ≥1 spontaneous bowel movement per week) showed that responder rates with alvimopan 1 mg/d were only slightly higher (72%) than response rates in the current study.[20] A separate RCT of alvimopan using the identical definition of responder reported no significant difference with alvimopan 1 mg/d compared with placebo.[21] Lower response rates in patients with noncancer

TABLE 2. Summary of AEs (Placebo Crossover Population)

No. AEs (%)	Placebo Treatment During RCT (n = 134)	Methylnaltrexone Treatment During OLE (n = 134)
Any AEs	44 (32.8)	58 (43.3)
Serious AEs	1 (0.7)	4 (3.0)
Deaths	0	0
Most common AEs*		
Nausea	9 (6.7)	7 (5.2)
Abdominal pain	2 (1.5)	13 (9.7)
Diarrhea	4 (3.0)	6 (4.5)
Upper abdominal pain	5 (3.7)	4 (3.0)
Urinary tract infection	2 (1.5)	7 (5.2)
Hyperhidrosis	1 (0.7)	6 (4.5)
Back pain	1 (0.7)	4 (3.0)
Hypertension	0	5 (3.7)
Rhinorrhea	1 (0.7)	4 (3.0)
Influenza	0	4 (3.0)
Sinusitis	0	4 (3.0)

*Reported in 5% or more patients.

AE indicates adverse event; OLE, open-label extension; RCT, randomized controlled trial.

pain have been reported with naloxegol (a pegylated μ-opioid receptor antagonist; 34.9%–44.4%) and lubiprostone (a ClC-2 chloride channel agonist, 27.1%), but whether this reflects reduced efficacy or differences in study responder criteria is unknown.[22]

The tolerability profile of patients who crossed over to methylnaltrexone in the OLE was similar to their tolerability profile during exposure to placebo in the RCT. The most frequently reported AE during methylnaltrexone treatment was abdominal pain. The incidence of abdominal pain is considered related to an intentional propulsive effect of the GI tract during the normal course of a bowel movement. A post hoc analysis[23] of data from 2 placebo-controlled trials of methylnaltrexone for OIC in patients with advanced illness[24,25] characterized reports of abdominal pain as mostly mild to moderate in intensity; incidence decreased after the first dose while response to methylnaltrexone treatment was maintained.

Although only evaluated during a 4-week period in the RCT, the findings during placebo treatment further establish the nature of OIC. The data support that little or no GI tolerance to opioid therapy develops for the opioid-related adverse effect of constipation. This lack of tolerance differs from other adverse effects of opioid analgesics and could possibly be related to the actions associated with μ-opioid receptor subtypes (eg, tolerance develops for activities that are μ-1 dependent versus other subtypes).[26–28] Given the lack of tolerance development to OIC, it is important that OIC be anticipated and be treated as appropriate in patients receiving opioid analgesics.[4]

The strength of this placebo crossover analysis is that the design allowed patients to serve as their own controls when comparing the efficacy and safety of methylnaltrexone versus placebo. However, study limitations include the post hoc nature of the analysis, lack of statistical comparisons for placebo exposure and methylnaltrexone exposure data, and the unblinded administration of methylnaltrexone upon crossing over to the OLE. In conclusion, this study supports previous findings that subcutaneous methylnaltrexone is a tolerable and efficacious pharmacologic option for patients with OIC and chronic noncancer pain, and that administration does not result in the development of opioid tolerance across time.

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