

OPIOIDS & SUBSTANCE USE DISORDERS SECTION

Original Research Article

Long-Term Safety and Efficacy of Subcutaneous Methylalntrexone in Patients with Opioid-Induced Constipation and Chronic Noncancer Pain: A Phase 3, Open-Label Trial

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Trial registration: ClinicalTrials.gov identifier: NCT00804141.

Abstract

Objective. Methylalntrexone, a peripherally acting μ -opioid receptor antagonist, alleviates opioid-induced constipation. Understanding its long-term safety and efficacy profile in patients with chronic noncancer pain is warranted given the persistence of opioid-induced constipation.

Methods. In this phase 3, multicenter, open-label trial, adults with chronic noncancer pain (N = 1034) received subcutaneous methylalntrexone 12 mg once daily for 48 weeks.

Results. The most common adverse events were gastrointestinal related (e.g., abdominal pain, diarrhea, nausea) and were mild to moderate in intensity. Only 15.2% of patients discontinued because of an adverse event. Serious cardiac-related adverse events occurred in nine patients. Of the seven instances of major adverse coronary events reported, three were adjudicated after external review; all instances occurred in patients with

cardiovascular risk factors. Methylnaltrexone elicited a bowel movement within four hours in 34.1% of the injections throughout the 48-week treatment period.

Conclusions. Change from baseline in mean weekly bowel movement rate, Bowel Movement Straining Scale score, Bristol Stool Scale score, and mean percentage of patients with complete evacuation from baseline to week 48 were significantly improved ($P < 0.001$ for all). Long-term subcutaneous methylnaltrexone was well tolerated, with no new safety concerns, and provided consistent opioid-induced constipation relief in patients with chronic noncancer pain.

Key Words. Cardiovascular; Constipation; Long-Term; Methylnaltrexone, Chronic Noncancer Pain; Opioids

Introduction

Opioids are recommended by the American Pain Society and American Academy of Pain Medicine for the treatment of patients with moderate to severe noncancer pain [1]. However, given the potential for abuse, opioids should only be prescribed to patients with a legitimate medical need (i.e., pain that cannot be effectively managed with nonopioid therapy) and who also do not have a history of substance abuse, misuse, or addiction [1]. In general, opioids should be utilized in cases where the potential harms (i.e., gastrointestinal effects) are balanced with the effectiveness of pain management [1]. Opioid use may lead to substantial gastrointestinal (GI)-related adverse events (AEs), including nausea, vomiting, and constipation [2,3]. Opioid-induced constipation (OIC) occurs as a result of stimulation of μ -opioid receptors within the GI tract that leads to nonpropulsive contractions within the small intestine, decreased gastric motility and emptying, increased sphincter tone, and reductions in gastric secretions [4]. In contrast with other GI opioid-related AEs (e.g., nausea), patients typically do not acquire tolerance to OIC [5]. Because of the adverse effects of OIC (e.g., bloating, heartburn and gastroesophageal reflux, aspiration) [6], some patients modify or discontinue their opioid dose regimen [7–9], which can lead to suboptimal pain management [9]. Stool softeners and laxatives may aid in and are often recommended for the relief of OIC [1], but they do not address the underlying physiologic cause of OIC.

Methylnaltrexone is a peripherally acting μ -opioid receptor antagonist (PAMORA) that is approved in the United States in subcutaneous and oral formulations. Both formulations are approved for the treatment of OIC in adults with chronic noncancer pain; the subcutaneous formulation is indicated for treatment of OIC in adults with advanced illness who are unresponsive to laxatives [10]. For patients with OIC and chronic noncancer pain,

the recommended dosage of methylnaltrexone is 450 mg once daily for the oral tablets and 12 mg once daily for subcutaneous injection. It is recommended that the dosage be reduced in patients with chronic noncancer pain who have renal or hepatic impairment (oral tablets: 150 mg once daily; subcutaneous injection: 6 mg once daily [renal impairment] and weight-based dosing [hepatic impairment]). The efficacy and safety of methylnaltrexone in patients with chronic noncancer pain were demonstrated for up to 12 weeks in a randomized, placebo-controlled trial with an open-label extension [11,12]. During the four-week randomized, placebo-controlled period, 34.2% of patients who received methylnaltrexone experienced a rescue-free bowel movement (RFBM) within four hours of dosing, compared with 9.9% of patients who received placebo ($P < 0.001$; number needed to treat = 4) [11]. Similar results were observed during the entire eight-week open-label phase [12]. Longer-term (i.e., >12 weeks) effects of methylnaltrexone have not been previously evaluated and are important given the potential safety concerns (e.g., cardiac-related AEs) with other PAMORAs.

Concerns about adverse cardiac events were raised after an increased number of myocardial infarctions (MIs) and severe cardiovascular (CV) events was observed in patients with chronic noncancer pain and OIC who received twice-daily alvimopan vs placebo for 12 months [13,14]. This prompted questions on the possible cardiac effects of other drugs within the μ -opioid receptor antagonist class. Stimulation of μ -opioid receptors by opioids causes contraction of smooth muscle in the intestine [15]. Receptor antagonism reverses this process [16] and may have a similar effect in cardiac smooth muscle. Short-term (≤ 3 months) data have not indicated any adverse cardiac safety concerns with methylnaltrexone in patients with chronic noncancer pain [11,17] or in patients with advanced illness [18–21]; however, long-term data would be beneficial to help identify any potential safety concerns not observed during short-term exposure. In this phase 3, open-label study, the safety (primary objective) and efficacy (secondary objective) of subcutaneous methylnaltrexone were evaluated for 48 weeks.

Methods

Clinical Study Design

This was a multicenter phase 3 study (ClinicalTrials.gov identifier: NCT00804141) conducted between December 03, 2008, and September 20, 2010, in six countries. Patients were 18 years of age or older and had chronic, nonmalignant pain for two or more months, were receiving opioids for one or more months, and had OIC for one month prior to screening. A diagnosis of OIC was confirmed if patients met two or more of the following criteria: experienced hard or lumpy stool for 25% or more of bowel movements (BMs), had straining during 25% or more of BMs, experienced a sensation of incomplete evacuation after 25% or more of BMs, required use of manual maneuvers to facilitate 25% or more of

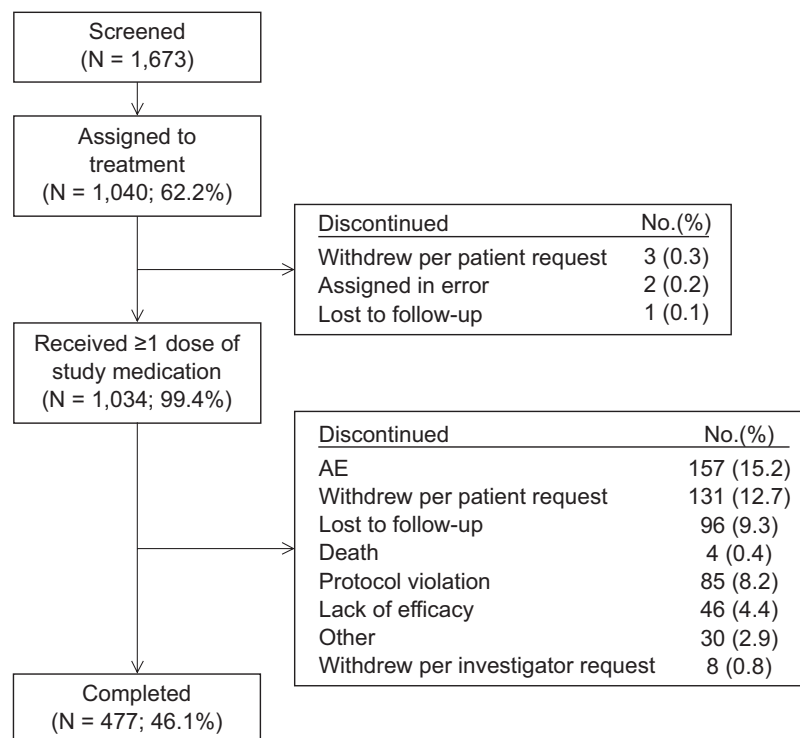


Figure 1 Patient disposition. AE = adverse event.

BMs, or had three or fewer BMs per week. All patients received open-label subcutaneous methylnaltrexone 12 mg once daily for 48 weeks. Methylnaltrexone dose could be adjusted as needed to a maximum of one dose per day and a minimum of one dose per week.

Patients were excluded if they had a history of chronic constipation before opioid treatment, had a diagnosis of bowel obstruction, fecal incontinence, rectal prolapse, or other significant GI disorder, had experienced inflammatory bowel disease, irritable bowel syndrome, or megacolon six months before screening, had a history of rectal bleeding not associated with fissures or hemorrhoids, or had a history of cancer within five years before study entry. Patients with CV conditions (e.g., uncontrolled hypertension) that might put the patient at greater risk and those with electrocardiogram (ECG) or laboratory abnormalities were not eligible for participation. Patients who had unstable hepatic, renal, pulmonary, psychiatric, or other medical conditions that might increase their risks during the study (e.g., uncontrolled hypertension) were also excluded. Use of lubiprostone, tegaserod, loperamide, partial opioid agonists, or a combination of opioid agonists/antagonists was not permitted; however, laxative use and nonpharmacologic treatment (manual disimpaction and pelvic floor retraining procedures) were allowed. Use of diphenoxylate and atropine was also permitted. The study was approved by independent ethics committees or institutional review boards at each participating site and was conducted in accordance with the Harmonisation Guidelines for Good

Clinic Practice and the Declaration of Helsinki. All patients provided written informed consent.

Assessments

Vital signs were measured at baseline, at weeks 4, 8, 12, 16, 24, 32, 40, and 48, and at follow-up visit or early discontinuation visit. Measurements of blood pressure and pulse rate were obtained before and approximately one hour postdose at each visit. Clinical laboratory parameters (e.g., blood chemistry, coagulation profile, urinalysis, and hematology) were measured at baseline, weeks 24 and 48, and follow-up visit, and a standard 12-lead ECG was performed at baseline within one hour after first dose and at additional time points at the investigators' discretion. Heart rate, changes from baseline in ECG results, rhythm type, and heart rate intervals PR, QRS, QT, and QTc corrected by Bazett's formula (QTcB) and Fridericia's formula (QTcF) were collected at screening, day 1, and throughout the study at the discretion of the investigator. AEs were assessed throughout the study. Withdrawal symptoms were assessed using Objective Opioid Withdrawal Scale and Subjective Opioid Withdrawal Scale scores at baseline (day 1) before and approximately one hour after administration of study medication. Pain was reported throughout the study using a pain intensity numeric rating scale [22], which asked patients to rate their pain over the previous 24 hours using an 11-point scale from 0 ("no pain") to 10 ("worst possible pain").

Efficacy assessments included weekly BM rate, the percentage of injections that resulted in a BM within four hours, weekly mean BM Bristol Stool Scale score (rated from 1 [separate hard lumps] to 7 [watery with no solid pieces]), average weekly BM straining scale score (rated from 0 [none] to 4 [very severe]), and the percentage of BMs with a sensation of complete evacuation. All were assessed from patient diary data reported daily via an interactive voice response system.

All safety and efficacy end points were evaluated in patients who received one or more doses of study medication. Changes from baseline were ascertained using two-sided paired *t* tests. No statistical power calculations were performed to determine sample size to obtain long-term safety and tolerability data, the primary objective of the study. It was anticipated that it would take 1,000 patients to result in 300 patients with six months of exposure and 100 patients with one year of exposure. All analyses were performed using SAS software version 9.1.3 (SAS Institute, Inc., Cary, NC, USA).

Results

A total of 1,034 patients received one or more doses of study medication (Figure 1). The most common reasons for study discontinuation were AEs (15.2%), patient request (12.7%), and loss to follow-up (9.3%). Most patients were white (89.7%), were female (64.7%), and reported back pain as their primary pain condition (53.8%) (Table 1). The daily median morphine equivalent dose (MED) of opioids at baseline was 120 mg (range = 1.22 mg to 2,196 mg) and remained similar throughout the treatment period. The majority of patients (42.4%) were receiving between 100 mg and less than 400 mg MED per day at baseline. The overall mean duration of methylnaltrexone treatment was 211.5 days. About half of the 1,034 patients (N=496; 48.0%) received 44 or more weeks of methylnaltrexone therapy. Concomitant laxative use was reported by 77.3% of patients. The most common laxatives were bisacodyl USP (Dulcolax, Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT, USA; 25.8%), docusate sodium (15.5%), and polyethylene glycol 3,350 (MiraLAX, Bayer Corporation, Whippany, NJ, USA; 15.9%). The median number of weekly methylnaltrexone injections was 5.98 (range = 0.05–7.14), with the greatest number of patients (49.6%) requiring more than six or seven doses per week (Figure 2).

Safety

Most AEs were GI or infection related, with abdominal pain, diarrhea, and nausea most frequently reported (Table 2). Approximately 11% of patients experienced a psychiatric disorder, predominantly anxiety (3.3%), depression (3.3%), and insomnia (2.5%). Only one patient reported drug dependence (0.1%). The majority of the AEs (72.7%) experienced by the 817 patients were mild to moderate in intensity. Overall, 15.2% of patients

Table 1 Demographic and baseline characteristics

Characteristic	Patients (N = 1,034)
Mean age (SD), y	51.7 (10.8)
Sex, No. (%)	
Female	669 (64.7)
Male	365 (35.3)
Race, No. (%)	
White	927 (89.7)
Black	76 (7.4)
Asian	12 (1.2)
Other	19 (1.8)
Primary pain condition, No. (%)	
Back pain	556 (53.8)
Osteoarthritis	112 (10.8)
Fibromyalgia	75 (7.3)
Cervical/neck pain	67 (6.5)
Neuropathic	51 (4.9)
Rheumatoid arthritis	22 (2.1)
Other	151 (14.6)
Median baseline MED (range), mg/d	120.0 (1.2–2,196.0)
Baseline MED category, mg/d	
<30	91 (8.8)
30–<60	185 (17.9)
60–<100	189 (18.3)
100–<400	438 (42.4)
≥400	131 (12.7)
Mean duration of OIC (SD), wk	341.4 (297.5)
Median (range)	262.9 (4.9–2,032.7)

MED = morphine equivalent dose; OIC = opioid-induced constipation; SD = standard deviation.

discontinued methylnaltrexone because of an AE. The most common AEs leading to discontinuation from the study were abdominal pain (4.7%), nausea (2.5%), and diarrhea (2.3%). The most common drug-related AEs that were severe in intensity were GI related (6.0%; N = 62), particularly abdominal pain (4.1%; N = 42).

Serious AEs (SAEs) were reported by 104 (10.1%) patients during the study. The most commonly reported SAEs were pneumonia (0.8%; N = 8), back pain (0.5%; N = 5), MI, abdominal pain, hypoesthesia, asthma, chronic obstructive pulmonary disease, diarrhea, and noncardiac chest pain (0.4%; N = 4 for each). Drug-related SAEs were reported in four patients: lower abdominal pain and depression occurred in one patient each, hypotension occurred in two patients, and one patient with hypertension also experienced an MI. Death occurred in four patients with SAEs. Three of these deaths were associated with major adverse coronary events and are discussed below. The fourth death occurred in a male with amyotrophic lateral sclerosis and low oxygen saturation. The

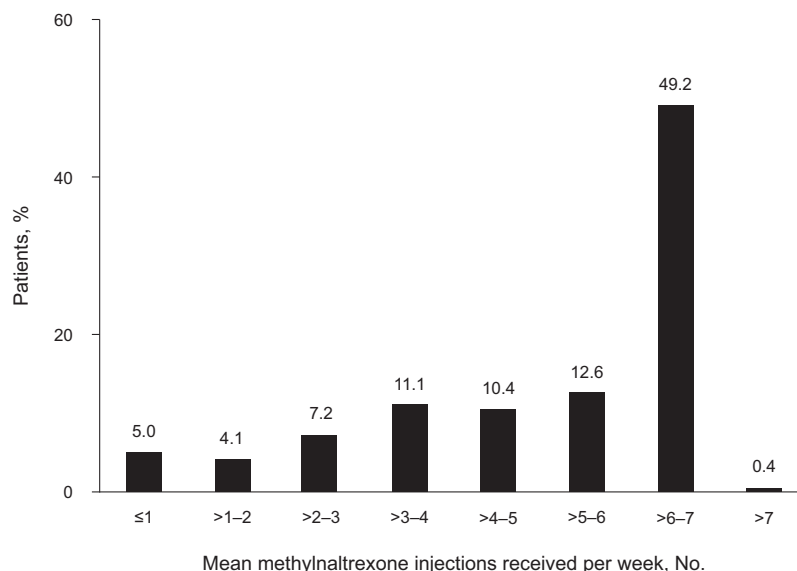


Figure 2 Distribution of mean weekly number of methylalntrexone injections.

Table 2 Adverse events

AE, No. (%)*	Methylalntrexone 12 mg QD (N = 1,034)
Any AE	817 (79.0)
Abdominal pain	248 (24.0)
Diarrhea	170 (16.4)
Nausea	156 (15.1)
Psychiatric disorders	111 (10.7)
Hyperhidrosis	92 (8.9)
Vomiting	74 (7.2)
Upper abdominal pain	69 (6.7)
Back pain	66 (6.4)
Influenza	64 (6.2)
Upper respiratory tract infection	60 (5.8)
Headache	58 (5.6)
Flatulence	57 (5.5)
Sinusitis	55 (5.3)
Dizziness	52 (5.0)
Bronchitis	49 (4.7)
Hot flush	49 (4.7)
Fatigue	36 (3.5)
Injection site pain	36 (3.5)
Anxiety	34 (3.3)
Depression	34 (3.3)
Urinary tract infection	34 (3.3)
Arthralgia	32 (3.1)

AE = adverse event; QD = once daily.

*Reported by more than 3% of patients.

patient died seven days after a methylalntrexone dose administration, and the death was considered by investigators to be unrelated to treatment.

Nine of the 1,034 (1.5 AE rate per 100 patient-years of exposure) patients experienced a cardiac-related SAE (Table 3). Of particular note was one patient (a 50-year-old female) who reported an SAE of vasospastic angina on day 81 of the long-term open-label study. This patient was admitted to the hospital with chest pain and difficulty breathing. SAE symptoms resolved eight days later and were not considered by the investigator to be related to methylalntrexone. Withdrawal from the study as a result of cardiac disorders occurred in six patients (0.6%).

Seven potential major adverse coronary events occurred during the study (nonfatal MI [N=3]; cardiac arrest [N=1]; cerebrovascular accident [N=1]; sudden death [N=1]; fatal MI [N=1]). A post hoc review of each event by a blinded external committee adjudicated three of the seven (42.9%) as major adverse coronary events. One of the three adjudicated events was an instance of MI occurring in a female with coronary artery disease and multiple cardiac risk factors (e.g., hyperlipidemia, smoking, chronic obstructive pulmonary disease, stenosis of coronary arteries) two days after a methylalntrexone dose administration. After stent placement, the patient resumed study medication without any further issues, and the incident was considered by investigators to be unrelated to treatment. The second was a 57-year-old male with an extensive history of cardiac symptoms. The patient was found deceased at home 13 days after a methylalntrexone dose administration. The presumed cause of death was MI or cardiac failure that was considered by investigators to be unrelated to study medication. The third event occurred in a 59-year-old male with cardiac risk factors who experienced an MI (study day 6), congestive heart failure (study day 43), and worsening hypertension (study day 57). The patient underwent coronary artery bypass grafting and

Table 3 Cardiac-related serious AEs

Cardiac Event*	Patients, No. (AE rate [†]) (N = 1,034; PY = 598.7)
Any cardiac disorder	9 (1.5)
Acute MI/MI	4 (0.7)
Cardiac arrest/cardiorespiratory arrest	1 (0.2)
Cardiac failure congestive	1 (0.2)
Cardiovascular disorder	0
Coronary artery disease	2 (0.3)
Cyanosis	0
Ischemic coronary artery disorders	3 (0.5)
Rate and rhythm disorders	0
Supraventricular arrhythmias	0

AE = adverse event; MI = myocardial infarction; PY = patient-years.

*Patients may have experienced one or more cardiac-related serious AEs.

[†]AE rate calculated as events per 100 patient-years of exposure.

continued methylnaltrexone through study day 274 without further issues.

Overall, there were no clinically meaningful alterations from baseline in laboratory values, vital sign measurements, or pain measurements, and no evidence of withdrawal. Of the 1,034 patients, 80.5% (N = 832) had an abnormal ECG measurement at one or more time points during the study; most of these instances occurred at baseline (69.7%) or within one hour after administration of methylnaltrexone on day 1 (69.9%) and were not considered to be clinically meaningful. Five patients discontinued from the study because of treatment-related prolongation of the QT interval or worsening prolongation. All of the QT prolongations resolved or returned to baseline values after discontinuation of methylnaltrexone.

Efficacy

Throughout the 48-week treatment period, 353 of the 1,034 methylnaltrexone injections (34.1%) elicited a BM within four hours postdose (Figure 3A). Mean weekly BM rate was increased at all time points during the study. A statistically significant increase in mean weekly BM rate from baseline (mean = 1.5 BM/wk) was observed throughout the entire 48-week period (mean = 5.3 BMs; mean change = 1.5 BM/wk; $P < 0.001$) (Figure 3B). A significant improvement in BM Straining Scale score was observed with methylnaltrexone treatment (mean = 2.3 at baseline vs 1.5 during the treatment period; mean change = -0.9; $P < 0.001$) (Figure 3C). Mean Bristol Stool Scale score significantly increased from 2.5 at baseline to 3.6 for the entire open-label period ($P < 0.001$) (Figure 3D). The mean percentage of BMs with a sensation of complete

evacuation significantly increased with methylnaltrexone, from 27.6% at baseline to 55.0% during the treatment period (mean change = 27.3%; $P < 0.001$).

Discussion

This open-label trial in patients with chronic noncancer pain demonstrated that a daily subcutaneous injection of methylnaltrexone was well tolerated and efficacious throughout 48 weeks of treatment for OIC. Similar to safety data reported for phase 3 trials of shorter duration [11,17–20], GI-related AEs were the most commonly reported AEs with long-term methylnaltrexone treatment. The percentage of patients reporting abdominal pain (24.0%) was only slightly higher than that observed during the pivotal four-week phase 3 trial (15.5% to 19.3%) [11]. No new tolerability issues, including cardiac-related concerns, were identified with long-term methylnaltrexone treatment during the current study.

Methylnaltrexone improved OIC symptoms throughout the 48-week treatment period, consistent with data reported in other clinical trials of shorter duration conducted in patients with chronic noncancer pain [11,17] or patients with advanced illness [18–20]. Opioid use augments the development of risk factors for CV events (e.g., artery hardening) [23,24] and increases the risk of CV events [25]. However, the issue of possible cardiac concerns with long-term use of PAMORAs was raised only after an increase in the number of MIs and severe CV AEs was observed during a 12-month double-blind, placebo-controlled trial in patients with chronic noncancer pain and OIC who received the PAMORA alvimopan [13]. Although CV-related AEs had been noted during short-term trials of alvimopan, no clinically significant differences vs placebo had been observed [26,27]. It is possible that central or peripheral opioid withdrawal symptoms related to PAMORAs could elicit physiologic stress, causing an increase in heart function and an elevated oxygen demand, which, especially in patients with CV disease (CVD), could lead to an adverse cardiac event. In patients with chronic noncancer pain, there has been no evidence of clinically meaningful opioid withdrawal symptoms and there were minimal changes in pain intensity with subcutaneous methylnaltrexone administration [11,28]. These data do not support the potential for opioid withdrawal, and thus increased cardiac demand, with ongoing methylnaltrexone exposure. The concern that PAMORAs could elicit contraction of the vasculature, thereby decreasing blood flow, seems unwarranted as no clinically significant changes in vital sign measurements were observed with methylnaltrexone during this 48-week study.

In contrast to data from a 12-week, randomized, placebo-controlled trial of subcutaneous methylnaltrexone 12 mg once daily in patients with chronic noncancer pain [11], several major adverse coronary events were reported in the current open-label 48-week study. However, all events occurred in patients with underlying

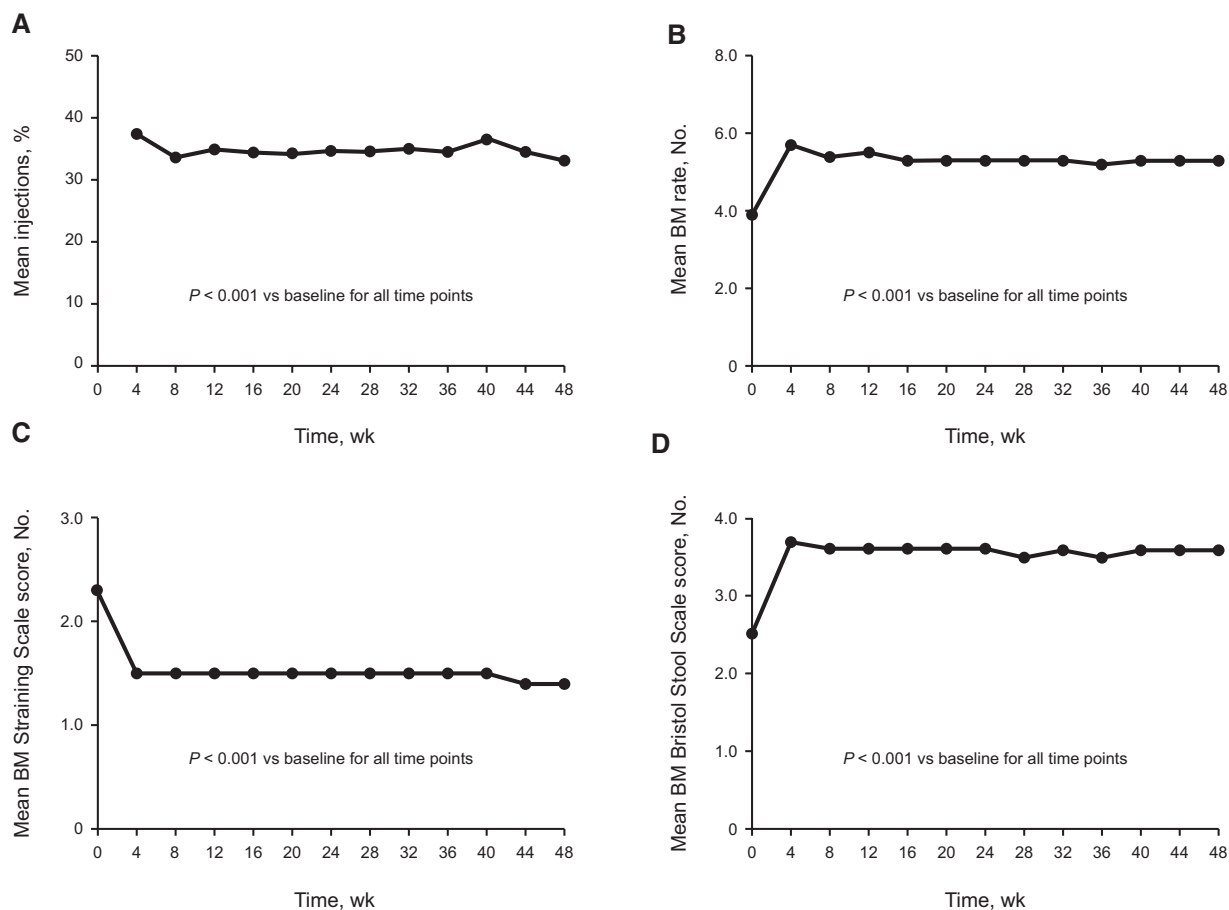


Figure 3 Improvement from baseline in the **(A)** percentage of injections resulting in a bowel movement (BM) within four hours; **(B)** weekly BM rate; **(C)** BM Straining Scale score; and **(D)** Bristol Stool Scale score during 48 weeks of treatment with methylnaltrexone. BM = bowel movement.

CVD or CV risk factors. Additionally, all patients who experienced a nonfatal adverse coronary event resumed treatment with methylnaltrexone. There was no clear pattern to the clinical presentation of the CV events; therefore, there is no evidence to suggest a causal relationship between these events and methylnaltrexone. Although a small number of patients in the current study had QT interval changes, all instances resolved or returned to baseline values after discontinuation of methylnaltrexone, and none of the changes were considered to be clinically significant. Thorough QT interval studies (ClinicalTrials.gov identifiers: NCT01363323 and NCT00434395) [10] have also demonstrated no clinically significant changes in the QT interval after subcutaneous or intravenous methylnaltrexone administration, even when administered at supratherapeutic doses.

The current study is limited by its open-label design, which may have impacted patient reporting of AEs, given that all patients knew they were receiving study medication. In addition, laxatives were allowed, which may have played a role in the development of some AEs. The study did not evaluate the possible influence

of demographic and baseline disease characteristics on the safety or efficacy of methylnaltrexone; therefore, additional studies are needed to assess the effects of methylnaltrexone on diverse patient populations (e.g., older patients, patients receiving both low and high opioid doses, patients receiving different types of opioids, etc.). In conclusion, methylnaltrexone administered subcutaneously daily for 48 weeks was well tolerated, with no new safety concerns identified, and treatment provided consistent and sustained improvement of OIC in patients with chronic noncancer pain.

Authors' Contributions

Category 1:

- (a) study concept and design;
- (b) acquisition of data;
- (c) analysis and interpretation of data.

Category 2:

- (a) drafting the manuscript;
- (b) revising the manuscript for important intellectual content.

Category 3:

- (a) approval of the final version to be published.

LRW: 1bc, 2ab, 3a;

EM: 1bc, 2ab, 3a;

AK: 1bc, 2ab, 3a;

RI: 1ab, 2ab, 3a;

JRH: 1c, 2ab, 3a.

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