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Cumulative Laxation Response with Methylnaltrexone: Implications for Hospitalized Patients with Advanced Illness and Opioid-Induced Constipation ☆,☆☆

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ABSTRACT

Background: Opioid-induced constipation (OIC) may increase the risk of fecal impaction and mortality in patients with advanced illness. Methylnaltrexone (MNTX) is efficacious for OIC.
Objective: The purpose of this analysis was to evaluate cumulative rescue-free laxation response with repeat MNTX dosing in patients with advanced illness who were refractory to current laxative regimens and to assess the influence, if any, of poor functional status on response to MNTX treatment.
Methods: This analysis included pooled data from patients with advanced illness and established OIC who were on a stable opioid regimen in a pivotal, randomized, placebo (PBO)-controlled clinical trial (study 302 [NCT00402038]) or a randomized, PBO-controlled Food and Drug Administration-required postmarketing study (study 4000 [NCT00672477]). Patients in study 302 received subcutaneous MNTX 0.15 mg/kg or PBO every other day, whereas those in study 4000 received MNTX 8 mg (body weight ≥38 to <62 kg), MNTX 12 mg (body weight ≥62 kg), or PBO every other day. Outcomes included cumulative rescue-free laxation rates at 4- and 24-hours postdose for the first 3 doses of study drug and time to rescue-free laxation. To assess if functional status influenced treatment outcomes, we performed a secondary analysis on the outcomes stratified by baseline World Health Organization/Eastern Cooperative Oncology Group performance status, pain scores, and safety.
Results: One hundred eighty-five patients received PBO and 179 patients received MNTX. The median age was 66.0 years, 51.5% were women, 56.5% had a baseline World Health Organization/Eastern Cooperative Oncology Group performance status score >2, and 63.4% had a primary diagnosis of cancer. Cumulative rescue-free laxation rates were significantly higher with MNTX than PBO 4- and 24-hours after doses 1, 2, and 3 ($P < 0.0001$), and between-treatment comparisons remained significant ($P < 0.0001$) regardless of performance status. The estimated time to first rescue-free laxation was shorter for patients receiving MNTX versus PBO. No new safety signals were identified.
Conclusions: Repeated use of MNTX represents a safe and effective treatment for OIC in patients with advanced illness regardless of baseline performance status. ClinicalTrials.gov identifier: NCT00672477. (*Curr Ther Res Clin Exp*. 2023; 84:XXX–XXX)

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Introduction

Constipation is a frequent complication in patients with advanced medical illnesses who receive opioids for pain management whether it be in the outpatient or inpatient setting.[1,2] There is no universally agreed-upon definition of opioid-induced constipation (OIC), but OIC is generally understood as a change from baseline bowel habits when initiating opioid therapy that is characterized by any of the following: reduced bowel movement (BM) frequency, development or worsening of straining to pass BMs, a sense of incomplete rectal evacuation, and harder stool consistency.[3] A survey conducted in the United States and Europe found that 81% of patients with chronic pain who received opioids experienced constipation, despite current laxative use.[4] Constipation prevalence in patients with advanced cancer has been reported to range from 40% to 90% and is more common among patients treated with opioids.[5–7] Opioid-related constipation may negatively influence health care utilization, including need for hospitalization, hospital length of stay, and need for emergency department visits, as well as patient comfort and pain severity.[1,2,8,9] Among cancer patients with OIC, significantly more experience nausea and vomiting, delirium, dyspnea, and urinary retention than those who were not constipated. These symptoms are considered to potentially prolong length of hospital stay and increase hospital costs.[10] Opioid analgesia also increases the risk for fecal impaction and colonic perforation, which are common among institutionalized elderly patients.[11–13] For example, a cross-sectional study in 687 nursing home residents found that the odds ratio for fecal impaction was 3.01 for patients routinely taking opioids (71% [impaction] vs 29% [no impaction]), translating to approximately 2.5 times greater risk of fecal impaction than in residents not taking opioids. Overall, 47% (73% in patients aged 81 years or older) had experienced at least 1 episode of fecal impaction during the past year.[14] Fecal impaction is associated with substantial risk; a retrospective review of patients who presented with fecal impaction to an emergency department found that 41% experienced serious related morbidities and 22% of patients died in the hospital.[11]

OIC is associated with substantial psychological distress in patients with serious medical illness. One study in advanced cancer patients showed that those with OIC experienced negative effects on cognition and mood.[15] Moreover, the clinical effects of constipation were frequently exacerbated by the failure to properly assess bowel function, especially in critical care situations,[16] as well as the tendency of providers to relegate constipation to secondary status with regard to treatment urgency compared with other concerns (eg, pain control).[17]

In a retrospective insurance database study of hospitalized patients, the use of oral or injectable opioid analgesics was associated with substantially increased use of laxative medications (relative risk = 1.96; 95% CI, 1.82–2.11).[18] However, in most patients with OIC, conventional laxatives fail to provide adequate symptom relief.[4,19] This may be attributable to the inability of conventional laxatives to address the distinctive underlying mechanism of OIC, namely opioid agonism of peripheral μ-opioid receptors throughout the lower gastrointestinal (GI) tract.[3,20,21] Activation of μ-opioid receptors reduces propulsive intestinal contractions and increases nonpropulsive contractions and water absorption during stool formation in the colon.[3,4,22] Unlike many other opioid side effects, OIC typically persists with continued opioid treatment, rather than receding in intensity. In the context of chronic noncancer pain, the continued influence of OIC in the absence of adequate relief may lead patients to reduce or discontinue their opioid medication, resulting in suboptimal analgesia and the attendant negative effects on quality of life.[3,4,17,22]

Methylnaltrexone (MNTX) (Relistor, Salix Pharmaceuticals, a division of Bausch Health US, LLC, Bridgewater, New Jersey), is a selective peripherally acting μ-opioid receptor antagonist (PAMORA) that decreases the constipating effect of opioid therapy without attenuating opioid analgesia.[23–26] MNTX tablets and subcutaneous injections have been approved by the Food and Drug Administration for treatment of OIC in adults with chronic noncancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent dose escalation. Subcutaneous MNTX is the only PAMORA indicated for treatment of OIC in adults with advanced illness or pain caused by active cancer who require opioid dose escalation for palliative care and the only injectable PAMORA indicated for OIC related to the treatment of chronic pain.[23]

The efficacy and safety of MNTX were evaluated in patients with advanced illness in a pivotal multicenter, double-blind, randomized, placebo (PBO)-controlled clinical trial and a randomized, PBO-controlled Food and Drug Administration-required postmarketing study.[25,27] Although these 2 studies are not the only PBO-controlled studies that have been conducted with MNTX,[28,29] they were selected and pooled for this post hoc analysis because both were conducted in patients with advanced illness using similar dosing and administration route of MNTX. In this post hoc analysis of results from these 2 studies, the objective was 2-fold: to determine cumulative response to repeat dosing with MNTX with respect to rescue-free laxation (RFL) in patients with advanced illness who were refractory to current laxative regimens and to assess the influence, if any, of poor functional status on response to MNTX treatment

Participants and Methods

Study design

This post hoc analysis was based on pooled data from 2 multicenter, double-blind, randomized, PBO-controlled clinical trials conducted in adults with OIC and advanced illness (study 302 [NCT00402038][25] and study 4000 [NCT00672477][27]). Each study had obtained institutional review board approvals from each study site and patients had provided written informed consent. Detailed methods of both studies have been previously described.[25,27]

In study 302, patients recruited from 26 study sites in the United States and Canada received MNTX 0.15 mg/kg SC or PBO every other day for 14 days. In study 4000, patients were recruited at 48 study sites (including outpatients and inpatients from home hospice, acute care, and skilled nursing, long-term care, or assisted living facilities) in the United States, United Kingdom, Canada, Europe, South America, and Australia. The study dose depended on patient body weight: ≥38 to <62 kg received MNTX 8 mg SC or PBO, and those weighing ≥62 kg received MNTX 12 mg SC or PBO; both groups were treated every other day for up to 14 days.

Study population

Male and female patients aged ≥18 years with OIC and a diagnosis of advanced illness (eg, incurable cancer, congestive heart failure, or chronic obstructive pulmonary disease) with a life expectancy ≥1 month were eligible for the study. OIC was defined as <3 BMs during the previous week and no clinically significant laxation during the 24 hours preceding the first dose of study drug or no clinically significant laxation within 48 hours before the first dose of study drug. In addition, patients must have been receiving chronic opioid therapy for ≥2 weeks in a stable opioid regimen (no dose reduction ≥50%) for ≥3 days before study drug initiation and must have been on a stable laxative regimen of any type (eg, stool softeners plus senna or equivalent) for ≥3 days before study drug initiation (only applied to standing-ordered laxatives, not as-needed). If a rescue laxative was given and resulted in laxation,

an additional 24 hours or 48 hours (depending on the definition of OIC) without laxation had to elapse for the patient to be eligible to start the study. Patients were permitted to continue use of baseline laxatives throughout the studies, except within 4 hours before or after the study dose. Potential enrollees were excluded if they had prior MNTX treatment (study 302) or prior MNTX treatment within 7 days of the study dose (study 4000), possible GI obstruction/fecal impaction, or possible nonopioid cause of bowel dysfunction contributing to constipation that, in the opinion of the investigator, was the primary cause of the constipation.

Study assessments

Baseline assessments included demographic characteristics and disease/treatment characteristics such as primary diagnosis, functional status, and daily opioid dose (morphine equivalents). Functional status was assessed using World Health Organization (WHO) performance status (study 302) and Eastern Cooperative Oncology Group (ECOG) performance status (study 4000).[30] For the current analysis, WHO performance status was mapped to the equivalent ECOG performance status categories.

Efficacy end points, based on pooled data, included achievement of RFL (ie, laxation without use of laxative, enema, or suppository) within 4 and 24 hours of initial study drug dose; cumulative laxation rates after the first and second study drug doses and after the first, second, and third study drug doses; median time to RFL; and RFL response rates stratified by WHO/ECOG performance status.

Safety assessments included pooled mean changes from baseline in pain intensity (to evaluated study drug effects on opioid analgesia) assessed on an 11-point scale (0 = no pain to 10 = worst imaginable pain), and the incidence of treatment-emergent adverse events (TEAEs). All serious TEAEs that occurred in study 302 have been published[25]; all serious TEAEs in study 4000 are available on the clinical trial registration website, www.ClinicalTrials.gov.[31]

Statistical Analysis

Efficacy assessments and pain scores were analyzed based on the intent-to-treat (ITT) population, defined as all patients who received ≥1 dose of study medication, which also defined the safety population. RFL responses at 4 and 24 hours postdose were compared by treatment group and by WHO/ECOG performance status scores using the Cochran-Mantel-Haenszel test; P values were generated using χ^2 tests. Time to RFL was analyzed and plotted using Kaplan-Meier methods, and comparisons were made using log-rank tests. Comparison of mean change from baseline in pain scores was based on t tests. Summary statistics were used to describe TEAEs by treatment group. Nominal significance levels were set at $P < 0.05$, with no adjustments for multiplicity. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

Study population

This pooled analysis was based on an ITT population of 364 patients (PBO n = 185 and MNTX n = 179). Median age was 66 years in each treatment group, and the study population was approximately 52% women and 94% White; study population demographic and baseline characteristics are summarized by treatment group in Table 1. Across the pooled study population, the most common primary diagnoses were cancer (63.4%), cardiovascular disorders (11.3%), and pulmonary disease (7.4%). Median baseline opioid consumption (morphine milligram equivalents per day) was

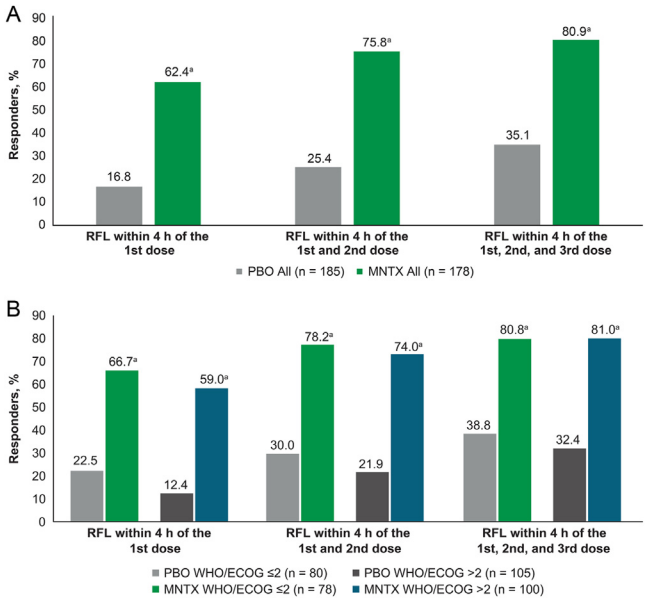

Figure 1. Cumulative rescue-free laxation (RFL) response within 4 hours of dosing. A. Cumulative proportion of patients treated with methylnaltrexone (MNTX) or placebo (PBO) in the overall population with RFL response within 4 hours (intent to treat [ITT] population). B. Cumulative proportions of patients treated with MNTX or PBO with RFL response within 4 hours (ITT population) based on World Health Organization/Eastern Cooperative Oncology Group performance status (≤2 or >2). [a]$P < 0.0001$ for MNTX vs PBO comparison.

higher in the MNTX group (156 mg; range = 0–4427 mg) than in the PBO group (130 mg; range = 0–10,160 mg). Baseline laxative use was extensive; more than 98% of patients across the pooled study population were using at least 1 laxative, indicating that this population was largely laxative refractory. In study 302, common baseline laxatives in each of the treatment groups included docusate with senna (41%), docusate (38.8%), senna (32.1%), bisacodyl (27.6%), magnesium hydroxide (22.4%), lactulose (22.4%), and enemas (13.4%). In study 4000, baseline laxatives comprised docusate sodium with senna (33.5%), bisacodyl (32%), lactulose (25.5%), Miralax (Bayer Consumer Health, Morristown, New Jersey) (25%), docusate sodium (20%), magnesium hydroxide (17.5%), senna (14.5%), and Fleet enema (C.B. Fleet, Lynchburg, Virginia) (10%). Overall, approximately 35% of patients with cancer and 40% without cancer were using 2 baseline laxatives. Despite these treatments, patients remained constipated and, therefore, qualified for study inclusion.

Efficacy

Treatment with MNTX compared with PBO significantly increased the proportion of patients with RFL response within 4 hours after the first dose and cumulatively within 4 hours after the first and second doses and after the first, second, and third doses ($P < 0.0001$ for all comparisons) (Figure 1A); cumulative RFL responses with MNTX increased from 62.4% within 4 hours of the first dose to 80.9% within 4 hours of the third dose compared with 16.8% and 35.1%, respectively, with PBO. Similar results were observed when cumulative RFL responses were analyzed by baseline WHO/ECOG performance status (≤2 or >2) (Figure 1B).

As shown in Figure 2A, Kaplan-Meier analysis demonstrated that the estimated time to RFL was much shorter in the MNTX group than the PBO group and >50% of MNTX-treated patients were likely to respond in under 2 hours, whereas <50% of PBO-treated patients were likely to respond by 24 hours. Median time to RFL was significantly shorter with MNTX than with PBO, at the 4- and 24-hour time points following initial dosing (4 hours:

Table 1
Baseline study population demographic characteristics, World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status, median opioid consumption, and primary diagnoses.

Characteristic	PBO (n = 185)	MNTX (n = 178)*	Total (N = 363)
Age, years†	66.0 (32–98)	66.0 (27–101)	66.0 (27–101)
Gender‡			
Male	89 (48.1)	87 (48.9)	176 (48.5)
Female	96 (51.9)	91 (51.1)	187 (51.5)
Race‡			
White	173 (93.5)	168 (94.4)	341 (93.9)
Black or African American	8 (4.3)	6 (3.4)	14 (3.9)
American Indian/Alaskan native	1 (0.5)	1 (0.6)	2 (0.6)
Asian	0	1 (0.6)	1 (0.3)
Other	3 (1.6)	2 (1.1)	5 (1.4)
Body weight, kg§	72.6 (24.0)	71.2 (19.7)	71.9 (22.0)
WHO/ECOG performance status score‡			
0	2 (1.1)	3 (1.7)	5 (1.4)
1	21 (11.4)	21 (11.8)	42 (11.6)
2	57 (30.8)	54 (30.3)	111 (30.6)
3	78 (42.2)	73 (41.0)	151 (41.6)
4	27 (14.6)	27 (15.2)	54 (14.9)
Daily opioid dose, morphine equivalents, mg/d†	130.0 (0–10,160)	156.0 (0–4,427)	145.7 (0–10,160)
Primary diagnosis‡			
Cancer	114 (61.6)	116 (65.2)	230 (63.4)
Cardiovascular disease	20 (10.8)	21 (11.8)	41 (11.3)
Pulmonary disease (nonmalignant)	13 (7.0)	14 (7.9)	27 (7.4)
COPD	5 (2.7)	9 (5.1)	14 (3.9)
Alzheimer's disease/dementia	4 (2.2)	4 (2.2)	8 (2.2)
Neurologic disease	3 (1.6)	4 (2.2)	7 (1.9)
Failure to thrive	3 (1.6)	0	3 (0.8)
ALS	1 (0.5)	1 (0.6)	2 (0.6)
Multiple sclerosis	2 (1.1)	0	2 (0.6)
Arthritis	0	1 (0.6)	1 (0.3)
Stroke	0	1 (0.6)	1 (0.3)
Other	20 (10.8)	7 (3.9)	27 (7.4)

ALS = amyotrophic lateral sclerosis; COPD = chronic obstructive pulmonary disease; MNTX = methylnaltrexone; PBO = placebo.

* One female patient from study 302 was excluded from this table and the efficacy analyses (but not the treatment-emergent adverse event summary statistics) because she received MNTX before being randomized to the MNTX group.

† Values are presented as median (range).

‡ Values are presented as n (%).

§ Values are presented as mean (SD).

1.11 vs >4 hours: median not achieved; 24 hours: 1.11 vs 23.58 hours; $P<0.0001$ for both comparisons). Similar results from the Kaplan-Meier analysis were observed when patients were stratified by baseline WHO/ECOG performance status (Figure 2B). Between-treatment differences remained highly significant at the 24-hour time point regardless of baseline WHO/ECOG performance status (performance status ≤2: 0.87 vs 17.79 hours; $P < 0.0001$; performance status >2: 1.46 vs >24 hours; $P < 0.0001$) (Figure 2B).

Safety

There was no evidence that MNTX treatment negatively affected the efficacy of opioid analgesia. Across the ITT population, mean changes from baseline in current and worst pain scores 1 day and 7 days after dosing were 0 or negative (indicating reduced pain) and similar between MNTX (current pain: −0.4 at 1 day and −0.5 at 7 days; worst pain: −0.7 at 1 day and −0.7 at 7 days) and PBO (current pain: −0.3 at 1 day and −0.2 at 7 days; worst pain: −0.6 at 1 day and −0.4 at 7 days). In addition, mean changes from baseline in pain scores were similar in patients receiving MNTX or PBO, regardless of WHO/ECOG baseline performance status ≤2 or >2.

The incidence of TEAEs was higher in the MNTX group compared with the PBO group. However, the most common TEAEs (and those most responsible for between-group differences) were, as expected, GI in nature, including abdominal pain, flatulence, nausea, and vomiting (Table 2). In addition, the incidence of TEAEs in the MNTX group collectively decreased from treatment day 1 to treatment day 2, as most notably observed with abdominal pain (where the incidence decreased from 12.8% on treatment day 1 to 8.1% on treatment day 2).

Discussion

Patients with OIC who are commonly refractory to other laxative regimens present several challenges to hospitalists. Without proper relief, patients with OIC have significant health care burdens and are at an increased risk of prolonged hospital stays.[1,2,8,9] In this pooled analysis of results from 2 studies in a diverse population of severely ill patients with intractable OIC despite laxative treatment, MNTX significantly increased RFL responses within 4 hours of initial dosing compared with PBO. Cumulative RFL responses to repeat MNTX dosing continued to increase after the second and third doses, reaching more than 80% and remaining more than 2-fold greater than RFL responses to PBO at all time points.

To our knowledge, there are few studies that have evaluated an OIC-specific treatment in patients with and without cancer and across a range of advanced medical illnesses, and this is the first analysis of cumulative treatment response in these patients. The most common diagnosis was cancer (~60%), followed by cardiovascular disease and pulmonary disease. More than half of patients in both studies were at WHO/ECOG baseline status >2, indicating severe functional impairment and typical of many patients seen in the hospital. MNTX demonstrated similar efficacy results, signifi-

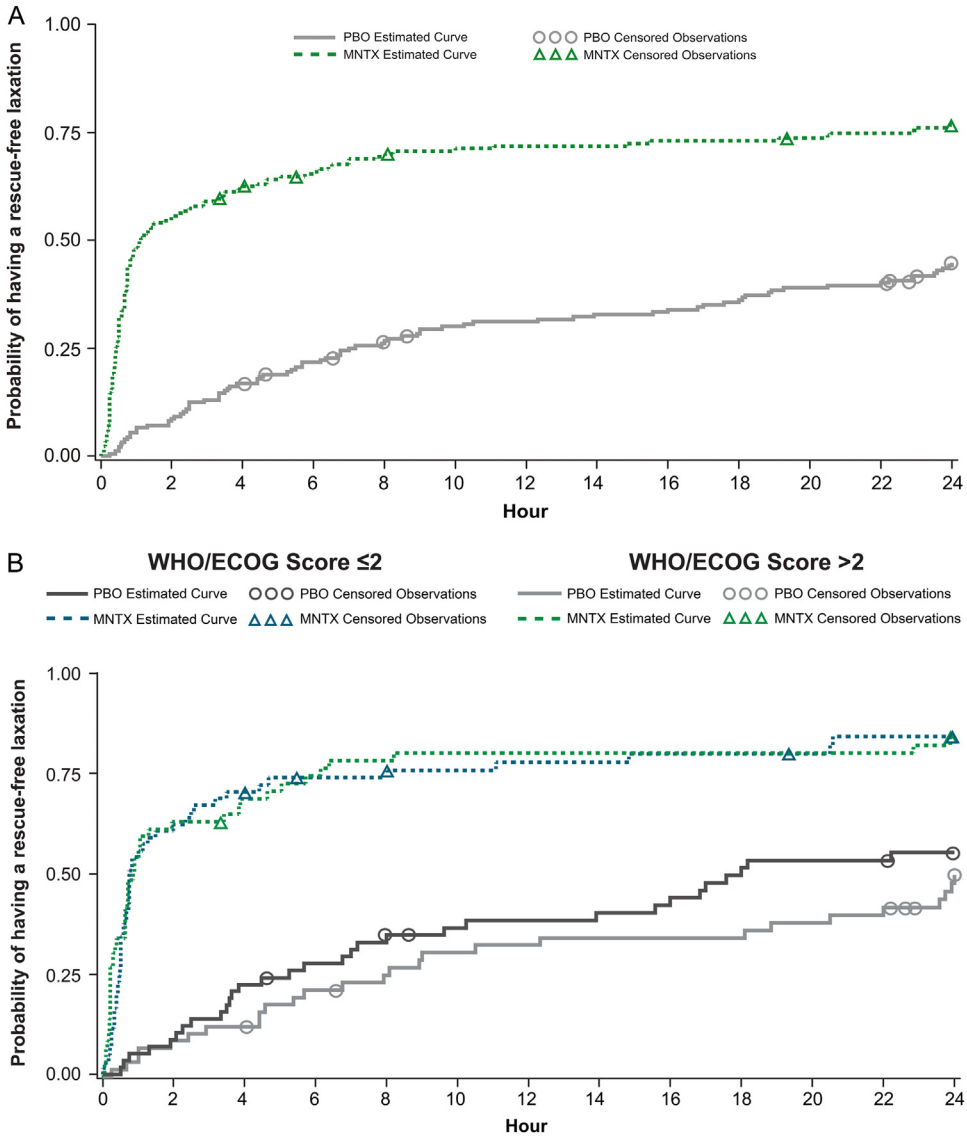

Figure 2. Kaplan-Meier analyses of cumulative rescue-free laxation (RFL) response (intent to treat [ITT] population). A. Cumulative RFL response by treatment following initial dosing. B. Cumulative RFL response by treatment and baseline World Health Organization/Eastern Cooperative Oncology Group performance status status (≤2 or >2). $P<0.0001$ for both methylnaltrexone (MNTX) vs placebo (PBO) comparisons.

Table 2
Treatment-emergent adverse events (TEAEs) reported by >2% of patients in any treatment group by treatment day (safety population).

	Treatment Day 1		Treatment Day 2	
System organ class preferred term*	PBO (n = 185)	MNTX (n = 179)	PBO (n = 170)	MNTX (n = 160)
Patients with ≥1 TEAE	27 (14.6)	47 (26.3)	24 (14.1)	36 (22.5)
Abdominal pain†	8 (4.3)	23 (12.8)	7 (4.1)	13 (8.1)
Flatulence	3 (1.6)	5 (2.8)	3 (1.8)	2 (1.3)
Nausea	4 (2.2)	5 (2.8)	3 (1.8)	3 (1.9)
Vomiting‡	1 (0.5)	4 (2.2)	1 (0.6)	2 (1.3)
Back pain	0	4 (2.2)	0	0

MNTX = methylnaltrexone; PBO = placebo.
* Values are presented as n (%).
† Includes the following system organ class preferred terms: abdominal pain and abdominal pain not otherwise specified.
‡ Includes the following system organ class preferred terms: vomiting and vomiting not otherwise specified.

cantly superior to PBO, regardless of baseline WHO/ECOG performance status (≤2 or >2) with respect to both cumulative RFL response and median time to RFL.

With respect to safety, a critical consideration in this fragile population, MNTX treatment did not influence the efficacy of opioid analgesia; mean pain scores remained constant or decreased similarly in both the MNTX and PBO groups. MNTX was generally well tolerated; the most common TEAEs were consistent with restoration of GI function and their incidence fell after treatment day 1. This is an important observation because adverse events associated with MNTX, most notably abdominal pain, have been associated with constipation relief. In a post hoc analysis of 2 MNTX trials, the incidence of abdominal pain was highest after the first dose and declined with subsequent dosing. The authors concluded

that abdominal pain may be attributed to the experience of a constipated patient having a BM.[32]

There are few studies that have evaluated MNTX use in the institutional setting. This pooled analysis is unique because it included laxative-refractory outpatients, acute care hospital patients, and inpatients from a mixture of settings, including home hospice, acute care, skilled nursing, long-term care, and assisted living facilities. In these various settings, it is of interest to see that whereas many patients with OIC responded to the first dose of MNTX, there was an additional laxation benefit from a second and third dose compared with PBO. There are important clinical and economic implications to this finding. It is established that patients with OIC due to the treatment of chronic noncancer pain have double the risk of all-cause inpatient hospitalizations, emergency department visits, and office or other outpatient visits relative to those who do not have constipation.[33] This equates to yearly increases in overall health care costs of more than $12,000 per patient with OIC.[33] These results have been echoed in other economic studies that have shown significant increases in hospital admissions, inpatient length of stays, total costs, and emergency department visits, as well as other increases in health care resource utilization, among patients with OIC.[2,10,34] Therefore, recognizing the need to treat OIC effectively may significantly reduce health care burden.

Limitations to the current analysis include its post hoc nature, and the slightly different study designs and populations used in the 2 studies; however, the study heterogeneity may also make the analysis findings applicable to a wider patient set. Another potential limitation stems from the 2 forms (subcutaneous and oral) now available with MNTX. Because both included studies evaluated only subcutaneous administration of MNTX, this analysis may not be fully generalizable to the use of oral MNTX. This suggests the need to conduct additional studies of the oral formulation in a similar population.

Conclusions

MNTX treatment is a highly effective treatment for OIC that can be safely administered in inpatient and outpatient settings to patients with advanced medical illness, regardless of deficits in performance status or prior failure on laxative therapy. In a patient population typical of those observed in the modern hospital environment with respect to comorbidities and performance status, MNTX produced highly significant improvements in RFL response and time to RFL, without negatively influencing opioid analgesia or increasing the burden of TEAEs other than those associated with GI functional restoration. MNTX represents a safe and effective OIC-specific therapy that should be considered for any patient with advanced illness receiving opioid analgesic therapy who fails to respond adequately to conventional laxatives.

Conflicts of Interest

Dr. Slatkin is an employee of Salix Pharmaceuticals, a subsidiary of Bausch Health US, LLC, Bridgewater, New Jersey; Dr. Stambler is a full-time employee and shareholder of Progenics Pharmaceuticals, Inc., a subsidiary of Lantheus Holdings, Inc, North Billerica, Massachusetts; and Dr. Israel is an employee of Bausch Health US, LLC, Bridgewater, New Jersey. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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Author contributions

Study design was conducted by Dr. Israel and Dr. Slatkin. Collection and assembly of data was conducted by Dr. Israel and Dr. Slatkin. Data analysis, data interpretation, manuscript preparation, manuscript review and revisions, and final approval of manuscript were conducted by all authors.

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