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Reductions in All-Cause Mortality Associated with the Use of Methylnaltrexone for Opioid-Induced Bowel Disorders: A Pooled Analysis

Lynn R. Webster, MD,* Darren Brenner, MD,† Robert J. Israel, MD,‡ Nancy Stambler, DrPH,§ and Neal E. Slatkin, MD¶,|

*PRA Health Sciences, Salt Lake City, Utah, USA; †Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; ‡Bausch Health US, LLC, Bridgewater, New Jersey, USA; §Progenics Pharmaceuticals, Inc., a subsidiary of Lantheus Holdings Inc., North Billerica, Massachusetts, USA; ¶University of California Riverside, School of Medicine, Riverside, California, USA; and |Salix Pharmaceuticals, a Division of Bausch Health US, LLC, Bridgewater, New Jersey, USA

Correspondence to: Lynn R. Webster, MD, PRA Health Sciences, 1255 East 3900 South, Salt Lake City, UT 84124, USA. Tel: 801-892-5140; E-mail: lrwebstermd@gmail.com.

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Abstract

Objective. Preclinical and clinical studies suggest that activation of the μ-opioid receptor may reduce overall survival and increase the risk for all-cause mortality in patients with cancer and noncancer pain. Methylnaltrexone, a selective, peripherally acting μ-opioid receptor antagonist, has demonstrated efficacy for the treatment of opioid-induced constipation. This retrospective analysis of 12 randomized, double-blind, placebo-controlled studies of methylnaltrexone evaluated the treatment of opioid-induced bowel disorders in patients with advanced illness or noncancer pain. **Methods**. The risk of all-cause mortality within 30 days after the last dose of study medication during the double-blind phase was compared between methylnaltrexone and placebo groups. The data were further stratified by cancer vs noncancer, age, gender, and acute vs chronic diagnoses. **Results**. Pooled data included 2,526 methylnaltrexone-treated patients of which 33 died, and 1,192 placebo-treated patients of which 35 died. The mortality rate was 17.8 deaths/100 person-years of exposure in the methylnaltrexone group and 49.5 deaths/100 person-years of exposure for the placebo group. The all-cause mortality risk was significantly lower among patients receiving methylnaltrexone compared with placebo (hazard ratio: 0.399, 95% confidence interval: 0.25, 0.64; $P = .0002$), corresponding to a 60% risk reduction. Significant risk reductions were observed for those receiving methylnaltrexone who had cancer or chronic diagnoses. Methylnaltrexone-treated patients had a significantly reduced mortality risk compared with placebo regardless of age or gender. **Conclusions**. Methylnaltrexone reduced all-cause mortality vs placebo treatment across multiple trials, suggesting methylnaltrexone may confer survival benefits in patients with opioid-induced bowel disorders taking opioids for cancer-related or chronic noncancer pain.

Key Words: Methylnaltrexone; Opioid Analgesia; Mortality; Survival

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Introduction

Evidence has emerged that people with cancer and noncancer pain who are treated with opioid analgesics may have an increased mortality risk beyond that attributable to opioid overdose alone [1]. This finding has been exemplified in analyses of commercial, Medicare, and Medicaid claims databases, which suggested that patients using opioids for noncancer pain over extended periods have an elevated risk of all-cause mortality compared with the general population or with patients receiving other analgesics, even when deaths from accidental overdose are excluded [1–3]. Preclinical and clinical studies have implied that activation of the μ-opioid receptor (MOR) may influence clinical parameters of overall survival (OS) in patients with cancer and noncancer syndromes [1, 4–7]. In patients with newly diagnosed advanced cancer, higher MOR expression and greater opioid requirements were associated with reductions in OS and shorter progression-free survival [8].

Opioid-induced constipation (OIC) is a prevalent side effect of chronic opioid therapy for noncancer and cancer pain [9–12]. Unlike other opioid-related side effects, OIC typically persists over time, and conventional laxatives often fail to provide sufficient relief from OIC symptoms [13, 14]. Opioid-induced bowel disorders (OIBD), including OIC and postoperative ileus, arise from the binding of exogenous or endogenous opioids to MORs in the gastrointestinal (GI) tract. Once the MORs are activated, increased intestinal fluid absorption and decreased luminal secretions and peristaltic activity occur, leading to increases in intestinal transit time [14–16].

In both cancer and noncancer settings, opioid therapy may extend for prolonged periods. In addition, OIC may extend throughout the duration of opioid therapy, necessitating equally prolonged use of agents used to treat OIC. Therefore, understanding the long-term safety of opioids and OIC treatments is important.

Methylnaltrexone (MNTX; Relistor®, Salix Pharmaceuticals, a division of Bausch Health US, LLC, Bridgewater, NJ, USA) is a selective, peripherally acting μ-opioid receptor antagonist (PAMORA) that has restricted diffusion across the blood-brain barrier. It is US Food & Drug Administration approved 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 opioid dose escalation or those with advanced illness or pain caused by active cancer who require opioid dose escalation for palliative care [17–19]. In a study of long-term MNTX use for OIC in patients receiving opioids for chronic noncancer pain, MNTX maintained efficacy throughout 1 year. No new safety signals were identified, and the overall pattern of adverse events was consistent with that observed in shorter-term studies [20]. Moreover, a post hoc analysis of two placebo (PBO)- controlled studies of MNTX treatment of patients with advanced illness and OIC found that patients with advanced cancer who received MNTX had significantly improved OS compared with those receiving PBO. The improvement in OS was even more pronounced among MNTX-treated patients who had responded to MNTX (ie, those who had a laxative response within 4 hours of at least two of the first four doses) [4].

To further evaluate all-cause mortality risk among patients treated with MNTX for OIBD, we conducted a post hoc pooled analysis of 12 PBO-controlled clinical trials.

Methods

Study Design

The study population included patients with noncancer pain or advanced illness who received subcutaneous, intravenous, or oral MNTX or matching PBO in 12 phase 2 to 4, randomized, double-blind, PBO-controlled studies. Studies included patients with OIC (MNTX 2101, MNTX 301, MNTX 302, MNTX 3356, MNTX 3201, MNTX 4000), OIBD (MOA-728 0200, MOA-728 2201, MOA-728 2202), and postoperative ileus (MOA-728 300, MNTX 3301, MOA-728 301). The characteristics of the studies (duration, dosage, patient disposition, development phase) are summarized in Table 1. Study protocols were approved by an institutional review board or an independent ethics committee for each individual study. Written informed consent was obtained from patients before entering each study. Adherence to Good Clinical Practice and the Declaration of Helsinki were practiced. Each clinical trial was registered in clinicaltrials.gov (NCT00387309 [MNTX 300], NCT00401375 [MNTX 3301], NCT00672477 [MNTX 4000], NCT00547586 [MOA-728 2201], NCT00605644 [MOA-728 2202], NCT00402038 [MNTX 302], NCT00401362 [MNTX 301], NCT01186770 [MNTX 3201], NCT00529087 [MNTX 3356], NCT00640146 [MNTX 2101], NCT00366431 [MOA-728 0200], NCT00528970 [MOA-728 301]).

Assessments and Analyses

Demographics and baseline characteristics were pooled and described descriptively for age, gender, body mass index (BMI), and daily opioid consumption based on oral morphine equivalents (OME) for the pooled overall population and for the cohort of patients who died (mortality cohort). The presence of cardiovascular risk factors was also collected. All-cause mortality was defined as the number of patients who died $\leq$ 30 days after the final dose of study medication during the double-blind phase of each study.

To calculate the person-years of exposure (PYE) for those who died, the sum of exposure days before death was divided by 365.25 and then multiplied by 100. To calculate the PYE for those who survived, the sum of exposure days before last study visit was divided by 365.25 and

Table 1. Randomized, double-blind, PBO-controlled studies of MNTX included in pooled analysis

Study	Phase	Patient Population	Group Ns*		MNTX Dosage	Deaths	
			MNTX	PBO		MNTX	PBO
MNTX 2101 [43]	2	Acute OIC after orthopedic surgery	18	15	12 mg SC MNTX once daily for 4–7 days	0	0
MOA-728 0200	2	OIBD and chronic noncancer pain	192	44	10, 50, 150, 300, or 450 mg oral MNTX once daily for 4 weeks	0	0
MOA-728 2201	2	OIBD and chronic noncancer pain	89	33	150, 300, 450, or 600 mg oral MNTX once daily for 4 weeks	0	0
MOA-728 2202	2	OIBD and chronic noncancer pain	99	29	150, 300, 450, or 600 mg oral MNTX once daily for 4 weeks	1	0
MOA-728 300 [44]†	3	Postoperative ileus	357	176	12 or 24 mg IV MNTX every 6 hours for up to 10 days	2	1
MNTX 3301 [44]†	3	Postoperative ileus	344	171	12 or 24 mg IV MNTX every 6 hours for up to 10 days	7	2
MOA-728 301	3	Postoperative ileus	249	124	12 or 24 mg IV MNTX every 6 hours for up to 10 days	0	1
MNTX 301 [18]	3	OIC and advanced illness	102	52	Single dose 0.15 or 0.30 mg/kg SC MNTX	2	1
MNTX 302 [45]	3	OIC and advanced illness	62	71	0.15 mg/kg SC MNTX every other day for 2 weeks (optional increase to 0.30 mg/kg for week 2)	10	16
MNTX 3356 [46]	3	OIC and chronic noncancer pain	298	162	12 mg SC MNTX once daily or every other day for 4 weeks	0	0
MNTX 3201 [47]	3	OIC and chronic noncancer pain	602	201	150, 300, or 450 mg oral MNTX once daily for 12 weeks	0	0
MNTX 4000	4	OIC and advanced illness	116	114	8 or 12 mg SC MNTX every other day for 14 days	11	14

*Intent-to-treat population.

†Studies MOA-728 300 and MNTX 3301 were phase 3 studies of identical design, described in a single publication [44].

IV = intravenous; MNTX = methylnaltrexone; OIBD = opioid-induced bowel dysfunction (defined as < 3 spontaneous bowel movements per week and hard or lumpy stools, a sensation of incomplete evacuation and/or straining, in ≥ 25% of bowel movements); OIC = opioid-induced constipation; PBO = placebo; SC = subcutaneous.

then multiplied by 100. The mortality rate per 100 PYE was calculated as (number of deaths/PYE) × 100. It should be noted that each study was of different duration ranging from 1 day to 12 weeks. Therefore, the duration of mortality follow-up ranged from approximately 1 to 4 months. Mortality risk for each treatment group was calculated for the overall population and for subgroups stratified by cancer vs noncancer, age <60 years vs ≥60 years, men vs women, and acute vs chronic diagnosis.

Mortality risks (*P* values, hazard ratios [HR] and 95% confidence intervals [CI]) for patients receiving MNTX or PBO were compared using a Cox proportional hazards regression model, with only treatment as the effect variable in the model, not adjusting for other factors. The model was also analyzed with the following covariates: cancer status (cancer vs noncancer), age (< 60 years vs ≥ 60 years) and gender (male vs female). *P* values had a two-sided nominal significance level of .05 without adjustment for multiplicity. The pattern of deaths over time among patients in the MNTX and PBO groups was also evaluated by Kaplan-Meier analysis.

Results

This analysis included 2,526 patients receiving MNTX and 1,192 receiving PBO. Table 2 describes the disposition of patients in the overall population as well as in each of the stratified subgroups analyzed (cancer vs noncancer; age < 60 or ≥ 60 years; men vs women; acute vs chronic diagnosis). Compared with the overall population, a greater proportion of patients in the mortality cohort had cancer, were at least 60 years old, and had a chronic diagnosis.

Baseline demographics and cardiovascular risk factors for the overall and mortality populations are summarized in Table 3. Compared with the overall population, the mortality cohort had an older mean age, a greater proportion of patients with a BMI < 30 kg/m^2, and a greater proportion of patients had hyperlipidemia/hypercholesterolemia, diabetes mellitus, myocardial infarction (MI), and stroke. The mortality cohort had a lower rate of hypertension and less obesity than the overall population, likely due to the high prevalence of advanced illnesses, including cancer, in this group. In the overall population, patients receiving MNTX had a higher median OME dose at baseline (MNTX: 174.0 mg/day vs PBO: 134.8 mg/day), whereas the reverse was observed in the mortality cohort (MNTX: 125.0 mg/day vs PBO: 200.0 mg/day). However, it should be noted that the mortality cohort OME values were only available from studies MNTX 301, MNTX 302, and MNTX 4000, all of which included patients with advanced illness,

Table 2. Baseline disposition for the overall population and by subgroup

	Overall Population		Mortality Cohort	
	MNTX (n = 2,526)	PBO (n = 1,192)	MNTX (n = 33)	PBO (n = 35)
Subgroups, n (%)				
Cancer	537 (21.3)	324 (27.2)	22 (66.7)	27 (77.1)
Noncancer	1,989 (78.7)	868 (72.8)	11 (33.3)	8 (22.9)
Age < 60 years	1,631 (64.6)	701 (58.8)	6 (18.2)	11 (31.4)
Age ≥ 60 years	895 (35.4)	491 (41.2)	27 (81.8)	24 (68.6)
Men	1,152 (45.6)	549 (46.1)	18 (54.5)	16 (45.7)
Women	1,374 (54.4)	643 (53.9)	15 (45.5)	19 (54.3)
Acute diagnosis (postoperative ileus)	966 (38.2)	486 (40.8)	9 (27.3)	4 (11.4)
Chronic diagnosis (advanced illness and chronic noncancer pain)	1,560 (61.8)	706 (59.2)	24 (72.7)	31 (88.6)

MNTX = methylnaltrexone; PBO = placebo.

including cancer. We also assessed the OME dose for the cancer only cohort and found that the median OME dose was similar in the MNTX group (192.5 mg/day) compared with the PBO group (200.0 mg/day). The median OME dose among cancer patients was higher than that observed in noncancer patients (MNTX = 120.0 mg/day; PBO = 80.0 mg/day).

Mortality Risk for the Overall Population

In the overall population, there were 33 deaths among 2,526 patients who received MNTX and 35 deaths among 1,192 patients who received PBO; deaths in each individual study are summarized by treatment group in Table 1. This equated to a significant 60% reduction in all-cause mortality risk among patients treated with MNTX compared with PBO (univariable HR: 0.399, 95% CI: 0.248, 0.643, $P = .0002$) The mortality rate was 17.8 and 49.5 deaths/100 PYE for MNTX and PBO, respectively. A Kaplan-Meier analysis of study deaths over time is presented in Figure 1. The curve temporally illustrates that deaths for patients receiving MNTX and PBO diverge early, with between-group differences emerging around day 15 before flattening due to the limited duration of studies and follow-up periods. Adjustments for cancer status, age group, and gender, resulted in a persistently significant attenuation of risk (HR: 0.508, 95% CI 0.314, 0.820, $P = .0056$).

Mortality Risk by Subgroup Stratification

A summary comparing mortality risk reduction with MNTX vs PBO based on HRs (95% CI) for the overall population and the stratified cohorts (cancer vs noncancer, age < 60 years vs ≥ 60 years, men vs women, acute diagnosis vs chronic diagnosis) is presented in Figure 2. In the stratified subgroups, each cohort except patients without cancer and those with an acute diagnosis had a significant mortality risk reduction when receiving MNTX. Univariable and multivariable HRs for MNTX use in each group are presented in Table 4.

Cancer vs Noncancer Diagnosis

Patients with cancer receiving PBO had a significant increase in all-cause mortality compared with those who received MNTX (HR: 0.470, 95% CI: 0.267, 0.827, $P = .0089$, Figure 3). There was no difference between treatment groups in mortality risk among those without cancer (HR: 0.541, 95% CI: 0.217, 1.347, $P = .1871$, Figure 3).

Age <60 Years vs ≥60 Years

Younger patients (< 60 years) who received MNTX had a 79% mortality risk reduction relative to those receiving PBO (HR: 0.210, 95% CI: 0.077, 0.567, $P = .0021$, Figure 4). For older patients (≥ 60 years), treatment with MNTX did not impact all-cause mortality to the same extent (HR: 0.555, 95% CI: 0.320, 0.963, $P = .0362$, Figure 4), but was still significant compared with PBO.

Women vs Men

Women who received MNTX had a 66% mortality risk reduction compared with those receiving PBO (HR: 0.340, 95% CI: 0.173, 0.670, $P = .0018$, Figure 5). This effect was not as pronounced among men, who had a 53% mortality risk reduction (HR: 0.467, 95% CI: 0.238, 0.918, $P = .0272$, Figure 5).

Acute Diagnosis vs Chronic Diagnosis

For patients with an acute diagnosis (postoperative ileus), there was no treatment effect on mortality risk (HR: 1.217, 95% CI: 0.373, 3.966, $P = .7446$, Figure 6). However, among those patients with a chronic diagnosis, which included patients with cancer and chronic noncancer pain, those receiving MNTX had a 68.5% reduction in mortality risk relative to those receiving PBO (HR: 0.315, 95% CI: 0.185, 0.537, $P < .0001$, Figure 6).

Discussion

In this post hoc analysis of all-cause mortality in patients receiving MNTX for OIBD, mortality risk was reduced by 60% compared with patients receiving PBO. This

Table 3. Demographics and baseline characteristics and cardiovascular risk factors for the pooled analysis population.

	Overall Population		Mortality Cohort	
Characteristic	MNTX (n = 2,526)	PBO (n = 1,192)	MNTX (n = 33)	PBO (n = 35)
Mean (range) age, years	55.0 (18, 101)	57.1 (19, 100)	69.6 (27, 93)	66.2 (39, 87)
Body mass index, kg/m^2, n (%)				
< 30	1,552 (61.4)	769 (64.5)	28 (84.8)	28 (80.0)
≥ 30	967 (38.3)	418 (35.1)	5 (15.2)	7 (20.0)
Missing	7 (0.3)	5 (0.4)	0	0
Cardiovascular risk factors, n (%)*, †				
Hypertension	1,094 (43.3)	509 (42.7)	6 (18.2)	2 (5.7)
Hyperlipidemia/hypercholesterolemia	1,033 (40.9)	527 (44.2)	19 (57.6)	18 (51.4)
Diabetes mellitus	695 (27.5)	398 (33.4)	19 (57.6)	19 (54.3)
Myocardial infarction	380 (15.0)	247 (20.7)	12 (36.4)	15 (42.9)
Stroke	393 (15.6)	256 (21.5)	11 (33.3)	17 (48.6)
Angina	278 (11.0)	150 (12.6)	2 (6.1)	2 (5.7)
Daily opioid consumption (OME), mg, median (range)‡	174.0 (4.5–33,120)§	134.8 (8.0, 10,160)	125.0 (12.0, 4,071)	200.0 (33.5, 10,160)

*Some patients had multiple cardiovascular risk factors.
†Risk factors affecting ≥10% of patients in either group.
‡Calculated for studies MNTX 301, MNTX 302 and MNTX 4000 only.
§There was an extreme outlier (122,560 mg/d) reported in the range for the MNTX group which was excluded.
MNTX = methylnaltrexone; OME = oral morphine equivalents; PBO = placebo.

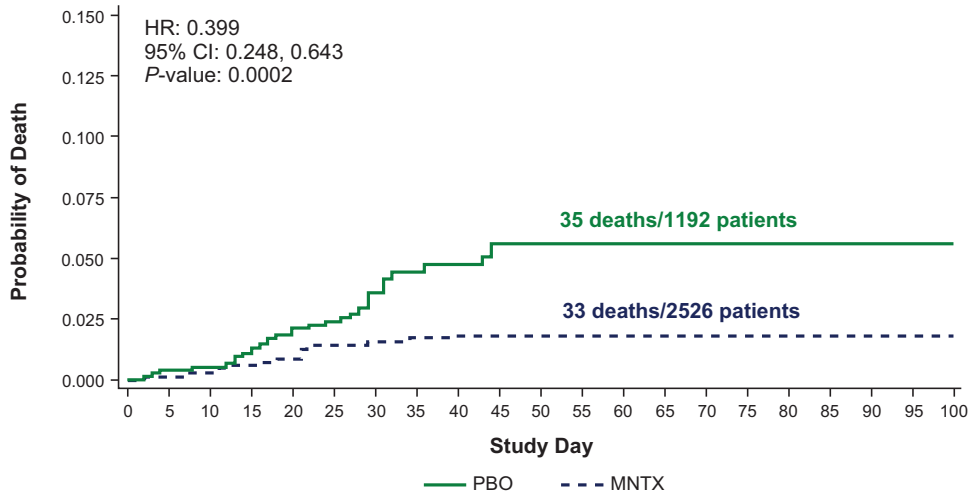

Figure 1. Kaplan-Meier analysis and plot of all-cause mortality over time in the pooled MNTX and PBO groups from phase 2 to phase 4 randomized, double-blind, PBO-controlled studies. CI = confidence interval; HR = hazard ratio; MNTX = methylnaltrexone; PBO = placebo.

reduction was substantial and statistically robust ($P = .0002$). When stratification variables were applied, patients receiving MNTX who had cancer or a chronic diagnosis also had significant reductions in all-cause mortality. Both age and gender stratifications identified significant reductions in mortality risk with MNTX. These were more robust in younger patients and women. These results support earlier findings from Janku and colleagues [4], which demonstrated that MNTX treatment was associated with significantly longer median OS than PBO in patients with advanced cancer and OIC; the effect being even more pronounced in the group of MNTX patients who had a laxation response within 4 hours of ≥two of the first four doses.

Preclinical evidence has suggested that MOR agonism may promote tumor progression and metastasis, and that some of these effects may be reduced by a MOR antagonist like MNTX. Evidence suggests that MOR is overexpressed in lung and prostate tumors, and that MOR overexpression is associated with reduced progression-free and OS [5]. Morphine and other MOR agonists have been found to promote angiogenesis, and in turn cell proliferation and migration, in human dermal and pulmonary endothelial cells [21]. For example, at clinically relevant levels, the angiogenic activity of morphine was 70% of that of vascular endothelial growth factor [5]. MOR agonists may also increase vascular permeability, further promoting migration and metastasis [22]. In

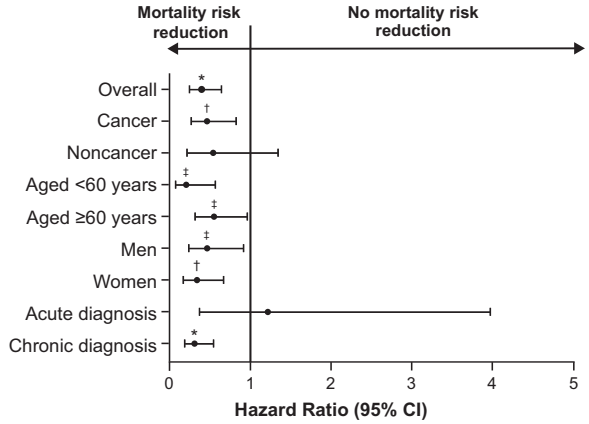

Figure 2. Comparison of mortality risk reduction with MNTX vs PBO based on hazard ratios (95% CI) for the overall population and for each subgroup. $^{*}P < .001$; $^{\dagger}P < .01$; $^{\ddagger}P < .05$. CI = confidence interval; MNTX = methylnaltrexone; PBO = placebo.

contrast, MNTX and other MOR antagonists can increase vascular barrier protection. MOR agonism may also promote the epithelial-mesenchymal transition, which paves the way to tumor cell metastasis [5]. In lung cancer cells, this transition involves interaction between MOR and growth factor receptors, and can be attenuated by MNTX [5, 6]. Although these collective preclinical findings are promising, the exact effects that MOR agonism may have on OS and cancer progression are unknown.

Clinical data also support the possible role of MOR agonism in cancer progression. The use of nonopioid-containing anesthesia/analgesia regimens has been shown to reduce the risk of recurrence or metastasis in breast cancer, and the risk of recurrence in prostate cancer, compared with opioid-based perisurgical analgesia [5, 7, 23]. In a large prospective cohort study of women with breast cancer, use of strongly immunosuppressive opioids, such as morphine, increased the rate of all-cause mortality fourfold [24]. Increased MOR expression has been associated with worse outcomes in prostate cancer, including reduced time to progression, progression-free survival, and OS. Increased opioid usage is also associated with worse outcomes and appears to be an independent contributor to progression risk [7]. Similarly, among patients with non-small cell lung cancer, pain severity and increased opioid requirements were found to be independent risk factors for reduced survival [25].

Activation of the MOR receptor itself may impact mortality risk. In a retrospective cohort study of critically ill patients, chronic opioid use was associated with a significant 2.20-fold increase in 90-day mortality [26]. The mortality risk was strongest among patients with cancer, which showed a 3.67-fold increase in 90-day mortality among chronic opioid users [26]. Interestingly, the 90-day mortality odds increased with an increase in morphine equivalent doses. In our analysis, the mortality cohort who received PBO had a greater median OME than those who received MNTX (200 mg/day vs 125 mg/day). Among cancer patients, the OME dose was 192.5 mg/day for MNTX and 200.0 mg/day for PBO; however, in noncancer patients the median OME dose was much lower (MNTX = 120.0 mg/d; PBO = 80.0 mg/day). The impact of mortality on opioid use was also depicted in a large 5-year analysis in patients using opioids chronically where mortality was significantly increased relative to nonopioid users (HR: 1.45, 95% CI: 1.28, 1.63, $P < .0001$). This effect was also evident when stratified by cancer and noncancer patients [27].

In noncancer disease states, MOR agonism may contribute to sepsis risk; sepsis rates have risen in tandem with the opioid abuse crisis [28]. Enteric glial cells, which possess MOR, are responsible for enhancing barrier function via their effects on intestinal epithelial cells. Morphine (and presumably other MOR agonists) disrupts this barrier enhancement, possibly via downregulation of glial-derived neurotrophic factor or through the disruption of epithelial tight junctions via upregulation of toll-like receptors, potentially increasing the risk of sepsis [28, 29]. Morphine is also involved with the suppression of natural killer cell activity, depression of antibody production, and inhibition of cell growth [30, 31]. Opioid use may also drive increased sepsis severity. A retrospective study of hospitalized sepsis patients found that in-hospital opioid use was associated with a sixfold greater risk of death compared with no opioid use (HR: 6.24, 95% CI, 4.41, 8.83, $P < .0001$) [32]. This study also observed that those treated with opioids compared with those not treated with opioids had significantly higher rates of gram-positive (39.3% vs 20.4%, $P < .0001$), gram-negative (31.3% vs 27.0%, $P = .0019$), and fungal infections (11.9% vs 2.2%, $P < .0001$) [32]. MOR agonists alter the gut microbiome as evidenced in a murine model of sepsis, that showed that morphine increased mortality and promoted overgrowth of gram-positive organisms more likely to disseminate beyond the intestine. These organisms upregulated the cytokine IL-17A, which induced inflammation and increased intestinal permeability, further facilitating bacterial dissemination. Opioid immunosuppression has also been studied in human immunodeficiency virus (HIV). Meng and colleagues reviewed opioid-induced mechanisms such as disruption of GI homeostasis and microbial translocation, which were found to accelerate HIV progression [33]. Conversely, in preclinical models, MNTX has been shown to reverse the enhancement of HIV infection of macrophages and block HIV replication [34]. These findings must be viewed with caution since not all potential confounders have been accounted for and it is unknown if it is the pain that necessitates opioid use or the opioid use itself that contributes to the increased risk in mortality [35].

It is also possible that the constipation relief provided by MNTX may itself be contributing to reduced mortality. In a 2019 study examining the impact of OIC on

Table 4. Univariable and multivariable adjusted hazard ratios for death with MNTX treatment vs. PBO

Group	Factors in Cox Model*	Hazard Ratio (MNTX/PBO)	95% CI for Hazard Ratio	*P* Value
Overall	Treatment	0.399	0.248, 0.643	.0002
	Treatment, cancer status, age group, and sex	0.508	0.314, 0.820	.0056
Cancer	Treatment	0.470	0.267, 0.827	.0089
	Treatment, age group, and sex	0.470	0.267, 0.829	.0090
Noncancer	Treatment	0.541	0.217, 1.347	.1871
	Treatment, age group, and sex	0.599	0.240, 1.493	.2715
Age <60 years	Treatment	0.210	0.077, 0.567	.0021
	Treatment, cancer status, and sex	0.237	0.087, 0.647	.0050
Age ≥60 years	Treatment	0.555	0.320, 0.963	.0362
	Treatment, cancer status, and sex	0.634	0.364, 1.104	.1071
Female	Treatment	0.340	0.173, 0.670	.0018
	Treatment, cancer status, and age group	0.396	0.201, 0.782	.0076
Male	Treatment	0.467	0.238, 0.918	.0272
	Treatment, cancer status, and age group	0.639	0.323, 1.265	.1989
Acute Diagnosis (Postoperative Ileus)	Treatment	1.217	0.373, 3.966	.7446
	Treatment, cancer status, age group, and sex	1.093	0.332, 3.591	.8840
Chronic Diagnosis (Advanced Illness/Chronic Noncancer Pain)	Treatment	0.315	0.185, 0.537	<.0001
	Treatment, cancer status, age group, and sex	0.617	0.358, 1.063	.0817

*Hazard ratios, 95% CIs, and *P* values based on Cox proportional regression models with treatment effect, unadjusted and adjusted for confounding factors.
MNTX = methylnaltrexone; PBO = placebo.

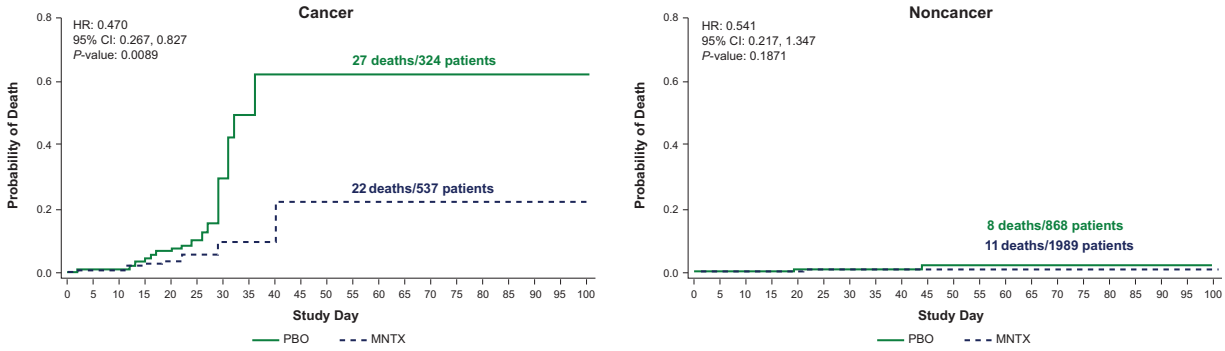

Figure 3. Kaplan-Meier plot of time to death by cancer and noncancer diagnosis. CI = confidence interval; HR = hazard ratio; MNTX = methylnaltrexone; PBO = placebo.

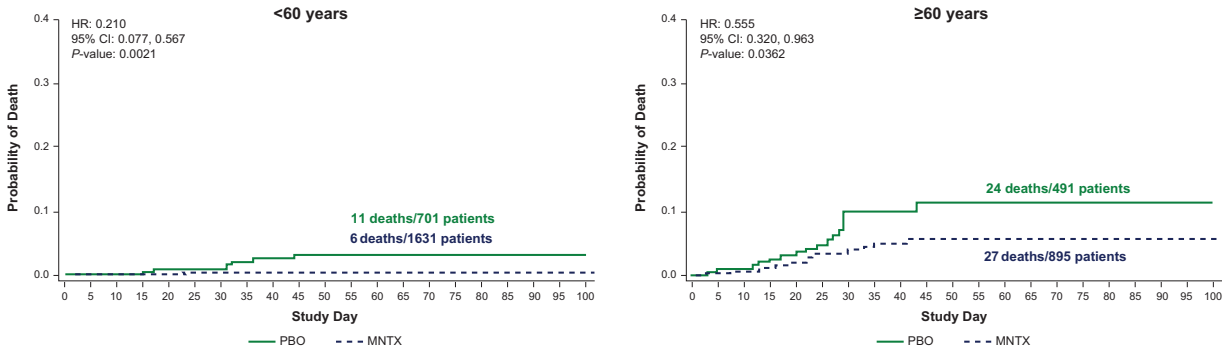

Figure 4. Kaplan-Meier plot of time to death by age. CI = confidence interval; HR = hazard ratio; MNTX = methylnaltrexone; PBO = placebo.

healthcare resource utilization, the risk of death within 12 months was significantly higher in opioid users with constipation than in those without constipation (OR 1.69: 95% CI 1.44, 1.98) [36]. Similar findings have been observed in other populations not necessarily receiving opioids. For example, a Japanese questionnaire-

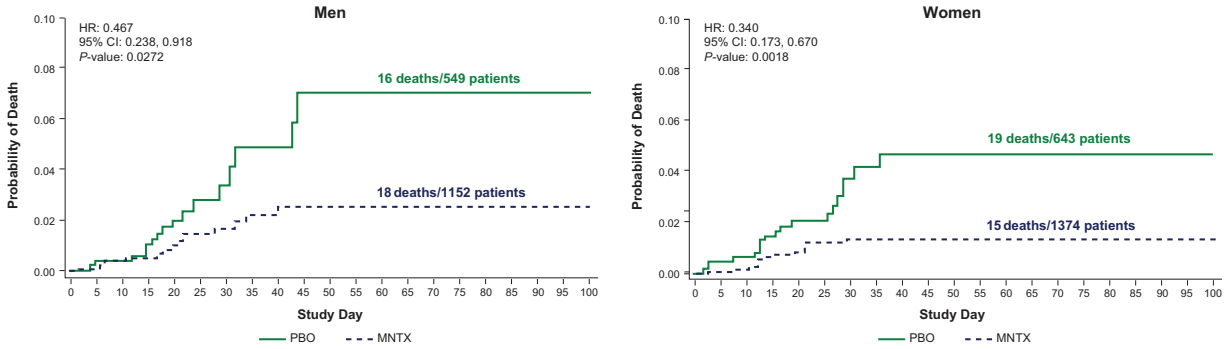

Figure 5. Kaplan-Meier plot of time to death by gender. CI = confidence interval; HR = hazard ratio; MNTX = methylnaltrexone; PBO = placebo.

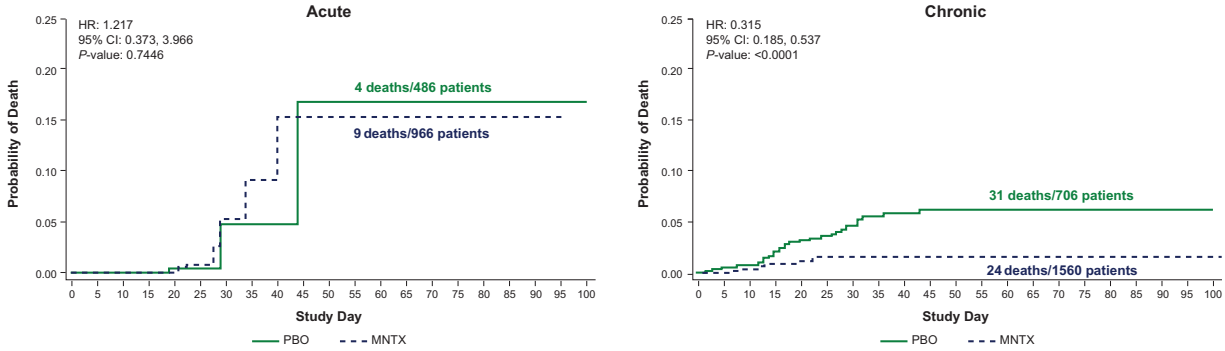

Figure 6. Kaplan-Meier analysis of mortality risk by diagnosis. CI = confidence interval; HR = hazard ratio; MNTX = methylnaltrexone; PBO = placebo.

based study found that, in comparison with daily (or more frequent) bowel movements (BMs), BM frequencies of 1 per 2 to 3 days and $\leq$ 1 per 4 days were associated with significantly increased cardiovascular disease mortality risk (multivariate-adjusted HR 1.21: 95% CI 1.08, 1.35; HR: 1.39, 95% CI: 1.06, 1.81; respectively) [37]. In another questionnaire-based study examining quality of life in palliative care patients in South Korea, patient-reported constipation was a significant prognostic factor for mortality (multivariate-adjusted HR 1.39: 95% CI 1.15, 1.68) [38]. A similar, albeit smaller effect was observed in a quality of life outcomes study among patients in a supportive care setting (HR: 1.02, $P = .0003$) [39]. Collectively these findings suggest that, regardless of opioid use, relief of constipation is associated with better survival outcomes, although the role of persistent constipation vis-à-vis mortality risk remains unclear and deserves further study.

It does not appear that the substantial reduction in mortality risk revealed in this analysis extends beyond MNTX to all PAMORAs. The PAMORA alvimopan, despite demonstrated efficacy in OIC treatment, was associated with a substantial increase in the risk for cardiovascular events compared with PBO (incidence rate for MI 1.30% vs 0%; for cardiovascular events 2.60% vs 1.12%, respectively). The observed elevation in cardiovascular risk led to restricting alvimopan to carefully controlled in-hospital use to prevent postoperative adverse events associated with opioids (ileus, delayed restoration of intestinal function) [40, 41]. MNTX has not been associated with an increase in risk of cardiovascular events [42].

Limitations of the current analysis include its retrospective nature, its variability between studies with respect to study drug dose, duration and route of administration, limited data collection on opioid requirements, and the inability to follow study subjects beyond prespecified time limits as these were short double-blind trials. In addition, the studies with the largest numbers of deaths had relatively small sample sizes that were roughly equal between treatment conditions. The studies with fewer deaths (or none) often had much larger numbers of MNTX patients than controls, which theoretically could create a confound. However, the encountered protective effect of MNTX was particularly driven by results in patients with advanced illness, such as cancer patients. The studies in patients with advanced illness (MNTX 301, MNTX 302, MNTX 4000) had mostly balanced patient numbers between the MNTX and PBO arms and actually more cancer patients received MNTX (n = 537) than PBO (n = 324). Importantly, the hazard ratio of MNTX vs PBO encountered in cancer patients (0.470) was comparable to the overall encountered survival benefit (0.399). These results suggest that substantial

confounding due to unequal allocation in the studies, including relatively healthier patients is unlikely. Furthermore, the relatively small number of mortality events precluded subgroup analysis with respect to the cause of death and relationship to the disease state requiring opioid therapy. However, the strong signal to all-cause mortality reduction with MNTX treatment, especially given the similarity between MNTX and PBO groups in demographic and cardiovascular risk variables, suggests that the observed effect is real and has a basis in opioid/MOR biology and its effects on underlying disease states.

The results of this study demonstrate a statistically and clinically significant reduction in all-cause mortality among patients receiving MNTX for treatment of OIC, with consistent effects observed in patients with cancer or chronic diagnoses, independent of age and gender. We hypothesize that MNTX may provide protective benefit against the additional mortality risk associated with opioid treatment in patients with chronic diagnoses and OIC. MNTX should be further considered and investigated regarding its role in, and the mechanisms underlying, reduction of mortality risk.

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Data Availability Statement

The data sets generated and/or analyzed during the current study are not publicly available at this time due to the proprietary nature of this information. Requests for additional information should be made to the corresponding author.

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