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The Influence of Age on Central Nervous System Effects of Methylnaltrexone in Patients With Opioid-Induced Constipation: A Pooled Analysis of 4 Clinical Trials

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OBJECTIVE

- To assess the impact of age on central nervous system safety of methylnaltrexone (MNTX) in patients with opioid-induced constipation (OIC)

INTRODUCTION

- Constipation, often noted as the most bothersome gastrointestinal (GI)-related side effect reported in patients taking opioid therapy,[1,2] increases with increased age[3]
  - OIC affects up to 86% of older patients who are receiving opioids for acute and chronic pain[4]
- The central effects of opioids, opioid antagonists, and other medications are often dependent upon the integrity of the blood-brain barrier (BBB)
  - Physiologic changes to the BBB that occur naturally with aging, such as loosening of tight junctions, may increase permeability of certain drugs across the BBB[5]
- MNTX, a peripherally acting μ-receptor antagonist approved for the treatment of OIC,[6] has restricted diffusion across the intact BBB and, therefore, has not been reported to impact opioid central analgesia
  - As a quaternary amine of the pure opioid antagonist naltrexone, MNTX exhibits lower lipid solubility and greater polarity than naltrexone, properties which impede diffusion across the BBB[7]
- It is unknown if potential age-related increases in BBB permeability influence the effect of MNTX on centrally mediated opioid effects, such as pain intensity, withdrawal effects, and safety
  - This post hoc analysis of 4 previously published placebo-controlled studies (study 302 [NCT00402038],[8] study 4000 [NCT00672477],[9] study 3356 [NCT00529087],[10] and study 3201 [NCT01186770][11]) compared MNTX use among those < and ≥65 years old with OIC to evaluate if opioid analgesia or symptoms of opioid withdrawal are compromised in the older population

METHODS

Key Inclusion Criteria

- Men and women aged ≥18 years with OIC defined as
  - For study 302 and 4000: <3 bowel movements during the previous week and no clinically significant laxation in the 24 hours before the first dose of study drug or no clinically significant laxation in the 48 hours before the first dose of the study drug
  - For study 3356 and 3201: <3 rescue-free bowel movements (RFBMs) per week that were associated with at least 1 of the following:
    - Study 3356: hard or lumpy stools, straining during bowel movements, a sensation of incomplete evacuation after bowel movements
    - Study 3201: ≥25% of RFBMs categorized as type 1 or 2 on the Bristol Stool Form Scale, straining during 25% of RFBMs, ≥25% of RFBMs with a sensation of incomplete evacuation
- Terminal diagnosis with a life expectancy ≥1 month and were receiving opioids for 2 weeks, of which 3 days were on a stable opioid dose (study 302, 4000) or chronic nonmalignant pain for ≥2 months and receiving ≥50 mg/day morphine equivalent doses for ≥14 days (studies 3201, 3356)
- If receiving a laxative, the regimen must have been stable for at least 3 days before the first dose of study drug (study 302, 4000). Rescue laxatives were permitted for studies 302, 4000, and 3356. All laxatives were discontinued before study entry in study 3201

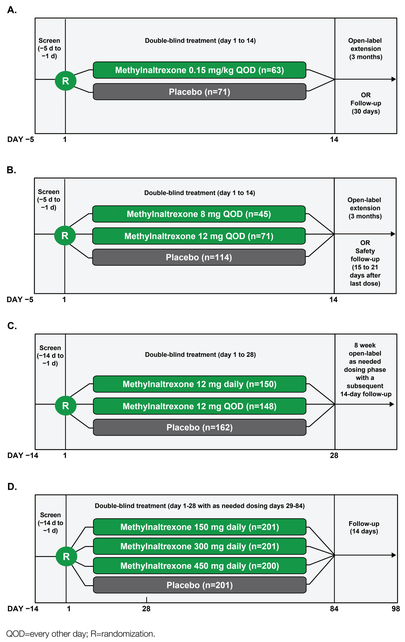
Key Exclusion Criteria

- History of MNTX treatment
- Bowel obstruction or impaction, which in the opinion of the investigator might have been primarily responsible for constipation
- Pregnant or breastfeeding

Study Design

- Patients from 4 randomized, double-blind trials were pooled and segregated by age (<65 years or ≥65 years)
- Study designs for each study are depicted in Figure 1A–D
  - Study 302: SC MNTX 0.15 mg/kg or placebo every other day for 2 weeks, which allowed dose escalation to 0.30 mg/kg or equivalent placebo volume during the second week
  - Study 4000: SC MNTX 8 or 12 mg in patients weighing 38 kg to <62 kg or ≥62 kg, respectively, or placebo every other day for 2 weeks
  - Study 3356: SC MNTX 12 mg once daily, 12 mg once every other day, or placebo for 4 weeks
  - Study 3201: oral MNTX 150, 300, or 450 mg or placebo daily for 4 weeks

Figure 1. Study Design for (A) Study 302, (B) Study 4000, (C) Study 3356, and (D) Study 3201



QOD=every other day; R=randomization.

Assessments

- All post hoc data were stratified by those aged < or ≥65 years
- Baseline demographics
- Pain intensity scales on a scale of 0 (no pain) to 10 (worst pain) for studies 302 and 4000 assessed pain predose and 4 hours postdose
- Symptoms of opioid withdrawal
  - Studies 3356/3201: Objective or Subjective Opiate Withdrawal Scales (OOWS and SOWS)
    - OOWS: clinicians assigned patients a score of 0 or 1 based on the absence or presence of 13 symptoms indicative of opioid withdrawal, with a total possible score of 13[12]
    - SOWS: patients rated their perceived severity of 19 opioid withdrawal symptoms on a scale from 0 (not at all) to 4 (extremely), with a total possible score of 76[12]
  - Study 302: modified Himmelsbach Opioid Withdrawal Scale, in which patients rated opioid withdrawal symptoms (rhinorrhea, tremor, piloerection, yawning, perspiration, restlessness, and lacrimation) on a 4-point scale (1, none; 2, mild; 3, moderate; 4, severe)
- Treatment-emergent adverse events (TEAEs) and TEAEs possibly related to opioid withdrawal on day 1 and day 2
- Rescue-free laxation (RFL) within 4 hours after the first dose

Statistical Analyses

- The pooled analysis consisted of the intent-to-treat population that included patients who received at least one dose of the study drug
- Demographics, baseline characteristics, and safety were summarized using descriptive statistics
- Symptoms of opioid withdrawal and pain scores were calculated as the mean (95% confidence interval) change from baseline based on an analysis of covariance model (ANCOVA) with treatment as effect and baseline as a covariate for comparing all MNTX groups to placebo
- TEAEs were reported as the number and percentage of patients reporting at least 1 TEAE in at least 2% of patients during the double-blind phase
- Efficacy was evaluated based on the percentage of patients with an RFL within 4 hours after the first dose and was analyzed using an ANCOVA model to compare treatments
  - *P* values comparing MNTX to placebo for RFL were based on chi-square tests
- Statistical significance was set at 0.05 and there were no adjustments for multiplicity

RESULTS

Patients

- Among the 1627 patients included in the 4 pooled trials, 1323 were <65 years (n=415 placebo; n=908 MNTX) and 304 were ≥65 years old (n=133, placebo; n=171, MNTX)
- The mean age was approximately 50 years in the younger cohort and 74 years in the older cohort. More men represented the older group versus the younger group; all groups were >85% white (Table 1)

Table 1. Baseline Demographics and Disease Characteristics

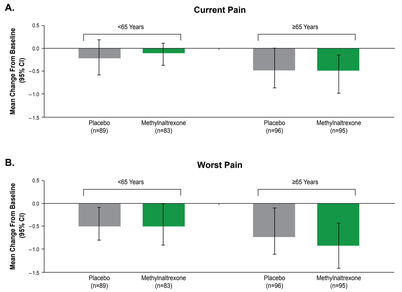
	Patients <65 Years		Patients ≥65 Years	
	Placebo (n=415)	All MNTX (n=908)	Placebo (n=133)	All MNTX (n=171)
Age, years Mean (95% CI)	50.2 (49.3, 51.0)	49.5 (49.0, 50.0)	75.2 (73.9, 76.6)	73.4 (72.3, 74.6)
Men, n (%)	132 (31.8)	277 (30.5)	84 (63.2)	93 (54.4)
Women, n (%)	283 (68.2)	631 (69.5)	49 (36.8)	78 (45.6)
Race, n (%)				
White	355 (85.5)	775 (85.4)	125 (94.0)	160 (93.6)
Black or African American	45 (10.8)	106 (11.7)	5 (3.8)	10 (5.8)
American Indian or Alaskan Native	3 (0.7)	4 (0.4)	1 (0.8)	1 (0.6)
Other	12 (2.9)	23 (2.5)	2 (1.5)	0
Ethnicity, n (%)				
Hispanic or Latino	21 (5.1)	62 (6.8)	7 (5.3)	11 (6.4)
Not Hispanic or Latino	394 (94.9)	845 (93.1)	126 (94.7)	160 (93.6)
Missing	0	1 (0.1)	0	0
Patients with cancer at baseline, n (%)	59 (14.2)	65 (7.2)	55 (41.4)	51 (29.8)
Baseline MED, mg/day Mean (95% CI)	301.6 (234.2, 368.9)	251.9 (229.5, 274.3)	168.5 (135.0, 202.1)	226.2 (166.8, 285.6)
Number of baseline laxatives Mean (95% CI)	0.8 (0.7, 0.9)	0.5 (0.5, 0.6)	1.8 (1.6, 2.1)	1.4 (1.2, 1.6)

CI = confidence interval; MED = morphine equivalent dose; MNTX = methylnaltrexone.

Pain Intensity

- At baseline, the mean current pain scores were 4.1 for placebo and 4.2 for MNTX in the younger cohort and 3.4 for placebo and 3.5 for MNTX in the older cohort
- At baseline, the mean worst pain scores were 5.7 for both the placebo- and MNTX-treated patients who were <65 years and 4.9 for both the placebo- and MNTX-treated patients ≥65 years
- Among patients either <65 or ≥ 65 years, there were no significant differences observed for MNTX or placebo groups with respect to the change from baseline in current and worst pain scores 4 hours after the first dose (Figure 2)

Figure 2. Current (A) and Worst (B) Pain Intensity Scores at Hour 4 Among Those <65 Years or ≥65 Years

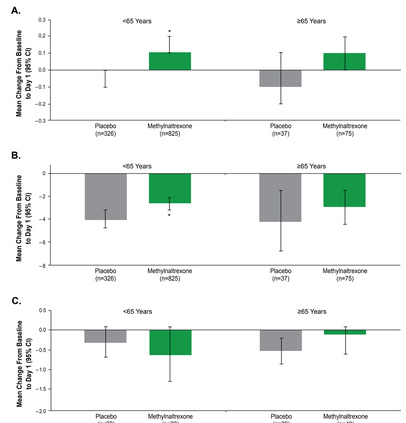


CI = confidence interval.

Symptoms of Opioid Withdrawal

- OOWS or SOWS
  - For those patients ≥65 years, there were no statistical differences between MNTX and placebo when assessing the mean change from baseline on the OOWS, SOWS, or modified Himmelsbach Opioid Withdrawal Scale (Figure 3)
  - On the OOWS and SOWS, use of MNTX had a small but significant difference from placebo among those <65 years (Figure 3A and 3B; *P*<0.05)
  - On the modified Himmelsbach Opioid Withdrawal Scale, no statistical differences were observed between MNTX and placebo regardless of age (Figure 3C)
  - Changes in the mean values on the opioid withdrawal scales did not appear to be clinically significant

Figure 3. Change in Scores Based on Age for the (A) OOWS (B) SOWS and (C) Modified Himmelsbach Opioid Withdrawal Scale



OOWS = Objective Opioid Withdrawal Scale; SOWS = Subjective Opioid Withdrawal Scale. *P<0.05

Treatment-Emergent Adverse Events

- In the double-blind phase, the most frequently reported TEAEs were abdominal pain, flatulence, and nausea (Table 2)

Table 2. TEAEs Occurring in at Least 2% of Patients Pooled From the Double-blind Phases of Each Study

	Patients <65 Years		Patients ≥65 Years	
	Placebo (n=415)	All MNTX (n=908)	Placebo (n=133)	All MNTX (n=171)
Patients with ≥1 TEAE	83 (20.0)	251 (27.6)	33 (24.8)	51 (29.8)
Abdominal pain	21 (5.1)	98 (10.8)	7 (5.3)	20 (11.7)
Flatulence	11 (2.7)	37 (4.1)	7 (5.3)	10 (5.8)
Nausea	14 (3.4)	55 (6.1)	4 (3.0)	10 (5.8)
Diarrhea	6 (1.4)	45 (5.0)	5 (3.8)	7 (4.1)
Dizziness	2 (0.5)	11 (1.2)	1 (0.8)	5 (2.9)
Hyperhidrosis	3 (0.7)	27 (3.0)	0	3 (1.8)
Abdominal distension	5 (1.2)	18 (2.0)	3 (2.3)	1 (0.6)
Abdominal pain upper	9 (2.2)	25 (2.8)	0	1 (0.6)

MNTX = methylnaltrexone; TEAE = treatment-emergent adverse event.
Data are presented as n (%) of patients.

- The only gastrointestinal TEAE possibly related to opioid withdrawal on day 1 occurring in >2% of patients ≥65 years was abdominal pain (MNTX, 5.8%; placebo, 2.3%; Table 3)
  - Gastrointestinal TEAEs possibly related to opioid withdrawal declined from day 1 to day 2 in the MNTX group, regardless of age
  - By day 2, gastrointestinal TEAEs among those ≥65 years were less than placebo

Table 3. Patients With at Least 1 Gastrointestinal TEAE on Day 1 and Day 2 Possibly Related to Opioid Withdrawal

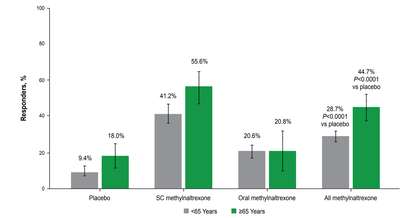
	Patients <65 Years				Patients ≥65 Years			
	Placebo (n=415)		All MNTX (n=908)		Placebo (n=133)		All MNTX (n=171)	
	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2
Patients with ≥1 GI TEAE	11 (2.7)	11 (2.7)	83 (9.1)	23 (2.5)	5 (3.8)	4 (3.0)	13 (7.6)	1 (0.6)
Abdominal pain	4 (1.0)	6 (1.4)	59 (6.5)	17 (1.9)	3 (2.3)	2 (1.5)	10 (5.8)	0
Nausea	5 (1.2)	3 (0.7)	33 (3.6)	8 (0.9)	2 (1.5)	0	2 (1.2)	1 (0.6)

GI = gastrointestinal; MNTX = methylnaltrexone; TEAE = treatment-emergent adverse event.
Data are presented as n (%) of patients.

Rescue-Free Laxation

- Among those <65 years, the percentage of RFL response within 4 hours after the first dose was 28.7% for MNTX and 9.4% for placebo (*P*<0.0001, Figure 4)
- Among those ≥65 years, the percentage of patients with RFL response within 4 hours after the first dose was double that of the younger cohort (44.7% for MNTX and 18.0% for placebo, *P*<0.0001, Figure 4)

Figure 4. Responders With Rescue-Free Laxation Within 4 Hours After the First Dose



CONCLUSIONS

- In this retrospective pooled analysis, MNTX use among those ≥65 years old did not impact immediate postdose opioid pain control, opioid withdrawal effects, or AEs
- Use of MNTX resulted in more patients reporting an RFL within 4 hours of study medication relative to placebo
- These preliminary results suggest that MNTX use for OIC is not impacted by possible age-related changes in the brain

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DISCLOSURES

Dr. Liao does not have anything to disclose. Dr. Slatkin received funding from Wyeth Pharmaceuticals for the methylnaltrexone study 302 referenced in this poster; has been employed by Salix Medical Affairs since July 2016; prior to that time, he worked on behalf of Salix as an unpaid consultant; and through February 2016 was also on the Salix speakers panel. Dr. Israel is an employee of Salix Pharmaceuticals. Dr. Stambler is a full-time employee and shareholder of Progenics Pharmaceuticals.

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