Efficacy and Safety of Methylnaltrexone for the Treatment of Opioid-Induced Constipation: A Meta-analysis of Randomized Controlled Trials

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ABSTRACT

Introduction: Opioid-induced constipation (OIC) is a distressing side effect during opioid analgesia and is mainly mediated by gastrointestinal μ-opioid receptors. Methylnaltrexone, a peripheral μ-opioid receptor antagonist with restricted ability to cross the blood–brain barrier, may alleviate OIC without reversing analgesia. We performed a meta-analysis to assess the efficacy and safety of methylnaltrexone for the treatment of OIC.

Methods: This meta-analysis was registered in PROSPERO (CRD42020187290). We searched PubMed, Embase, and Cochrane Library for randomized controlled trials that compared methylnaltrexone with placebo for the treatment of OIC. Relative risks (RR) and 95% confidence interval (CI) were pooled using a random-effects model. We used the GRADE approach to assess the certainty of the evidence.

Results: Eight trials with 2034 participants were included. Compared with placebo, methylnaltrexone significantly increased rescue-free bowel movement (RFBM) within 4 h after the first dose (eight trials; 1833 participants; RR 3.74, 95% CI 3.02–4.62; high-certainty evidence), RFBM within 24 h after the first dose (two trials; 614 participants; RR 1.98, 95% CI 1.52–2.58; moderate-certainty evidence), and RFBM ≥ 3 times per week (three trials; 1,396 participants; RR 1.33, 95% CI 1.17–1.52; moderate-certainty evidence) and decreased need to take rescue laxatives (three trials; 807 participants; RR 0.73, 95% CI 0.63–0.85; moderate-certainty evidence). For safety outcomes, there was no difference in any adverse events between the two groups (eight trials; 2034 participants; RR 1.11, 95% CI 0.99–1.23; moderate-certainty evidence), including diarrhea, nausea, vomiting, and flatulence; but for the most commonly reported adverse events, the abdominal pain was higher in methylnaltrexone group than that in placebo group (six trials; 1813 participants; RR 2.30, 95% CI 1.29–4.08; moderate-certainty evidence).

Conclusion: Methylnaltrexone is an effective and safe drug for the treatment of OIC, but the safety of abdominal pain should be considered.

Keywords: Meta-analysis; Methylnaltrexone; Opioid-induced constipation

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Key Summary Points

Opioid-induced constipation (OIC) is a distressing side effect during opioid analgesia.

Methylnaltrexone is an effective and safe drug for the treatment of OIC.

The safety of abdominal pain should be considered.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13614500.

INTRODUCTION

Opioid-induced constipation (OIC) is the most common side effect during opioid analgesia in patients with advanced illness including incurable cancer or other terminal diseases. According to Rome IV, OIC is defined as new or deteriorating constipation when initiating, changing, or increasing opioid therapy, which must include two or more of the following: straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal blockage, use of manual maneuvers to facilitate defecation, and fewer than three spontaneous bowel movement per week [1]. Results showed that > 85% of cancer and > 40% of non-cancer patients treated with opioids experience symptoms of OIC [2]. Different from other complications of opioids such as nausea or vomiting, tolerance to constipation develops very slowly. In addition to increasing hospitalization and healthcare costs [3], OIC may cause patients to become intolerant to opioids, thus greatly compromising the analgesic effect of opioids and leading to a serious decline in quality of life

[4]. The first-line strategy to treat OIC is a prophylactic regimen that involves increased fluid and fiber intake, exercise, stool softeners, and laxatives. However, at present, there is a lack of high-quality evidence to confirm the effectiveness of these treatment regimens [5, 6]. The second-line treatment, which includes peripherally acting μ-opioid receptor antagonists, can be considered when patients have recalcitrant symptoms.

Methylnaltrexone, a pure peripheral μ-opioid receptor antagonist, is a quaternary compound created by adding a methyl group to the opioid antagonist naltrexone [7]. Since the methyl group restricts its ability to cross the blood–brain barrier, methylnaltrexone can alleviate OIC effectively without weakening centrally mediated analgesia. So far, trials reporting the effect of methylnaltrexone on the treatment of OIC have conveyed conflicting results. Furthermore, due to modest sample size, these individual trials were not adequately powered to detect the true effect.

The aim of this study was to investigate the efficacy and safety of methylnaltrexone for the treatment of OIC by performing a meta-analysis.

METHODS

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Protocol and Registration

The meta-analysis was performed in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* [8] and is reported in compliance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [9]. This meta-analysis was prospectively registered in PROSPERO (CRD42020187290).

Data Sources and Search Strategy

We searched PubMed, Embase, and Cochrane Library from inception to May 19, 2020, without any restrictions. Search terms included: methylnaltrexone, opioid*, opioid-induced constipation, intestinal dysfunction, bowel dysfunction, gut motility, and rescue-free bowel movement. The reference lists of included trials were scanned for potential eligible articles. Additionally, we reviewed conference abstracts for unpublished work.

Study Selection and Eligibility Criteria

Two authors (YYZ and WJG) independently carried out the study selection based on predefined inclusion and exclusion criteria. Disagreements were resolved by discussion. We included randomized controlled trials that compared the efficacy and safety of methylnaltrexone with placebo for the treatment of OIC in adults who received opioid therapy. We excluded trials with healthy volunteers as participants.

Data Extraction and Outcomes Assessment

We developed a data extraction sheet in standardized Excel (Microsoft Corporation, Redmond, WA, USA). Two authors (YYZ and WJG) independently extracted data from included trials. Discrepancies were handled by discussion. The following information was extracted from each trail: author, year, country, population, sample size, drug regimen (route and dosage), and outcome.

The primary efficacy outcome was rescue-free bowel movement (RFBM) within 4 h after first dose (RFBM was defined as a bowel movement without use of any rescue medication or procedure within 4 h before the bowel movement). The secondary efficacy outcomes included RFBM within 24 h after the first dose, RFBM $\geq$ 3 times per week, and need to take rescue laxatives. The primary safety outcome was any adverse events, which was defined as all treatment-related adverse events in individual trial. The secondary safety outcomes included abdominal pain, diarrhea, nausea, vomiting, and flatulence.

Quality Assessment and Certainty of Evidence

We used the Cochrane Collaboration's tool for assessing risk of bias [10]. We reviewed each trial and scored as high, low, or unclear the risk involving the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Thus, trials with high risk of bias for $\geq$ 1 key domains were considered to be at high risk of bias whereas trials with low risk of bias for all key domains were considered to be at low risk of bias; otherwise they were considered to be at unclear risk of bias.

We evaluated the certainty of evidence for primary and secondary outcomes according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for risk of bias, inconsistency, indirectness, imprecision, and publication bias, classified as very low, low, moderate, or high [11]. Summary tables were constructed using the GRADE Profiler (version 3.6, GRADE pro).

Statistical Analysis

We calculated relative risks (RRs) with 95% CIs for dichotomous outcomes. Meta-analyses were performed using a random-effects model accounting for clinical heterogeneity. All analyses were performed on an intention-to-treat basis. Statistical heterogeneity across trials was assessed by the Cochrane Q test (with $P < 0.1$ indicating significance) and quantified by the I^2 statistic ($I^2 > 50\%$ for a significant heterogeneity) [12, 13]. A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed using RevMan 5.3 (Nordic Cochrane Centre).

RESULTS

Trial Selection

A total of 630 articles were found from electronic databases. After duplicates were removed, 419 articles had been screened for titles and abstracts. Then, 27 articles were identified for full-text review. Of these, 18 articles were excluded: seven articles were excluded because their participants were healthy volunteers; two articles were excluded because there was no relevant data; six articles were excluded because they did not use a placebo as a control group; four articles were excluded because of duplicate data. Finally, eight trials (seven full texts and one abstract) were included (Fig. 1) [14–21].
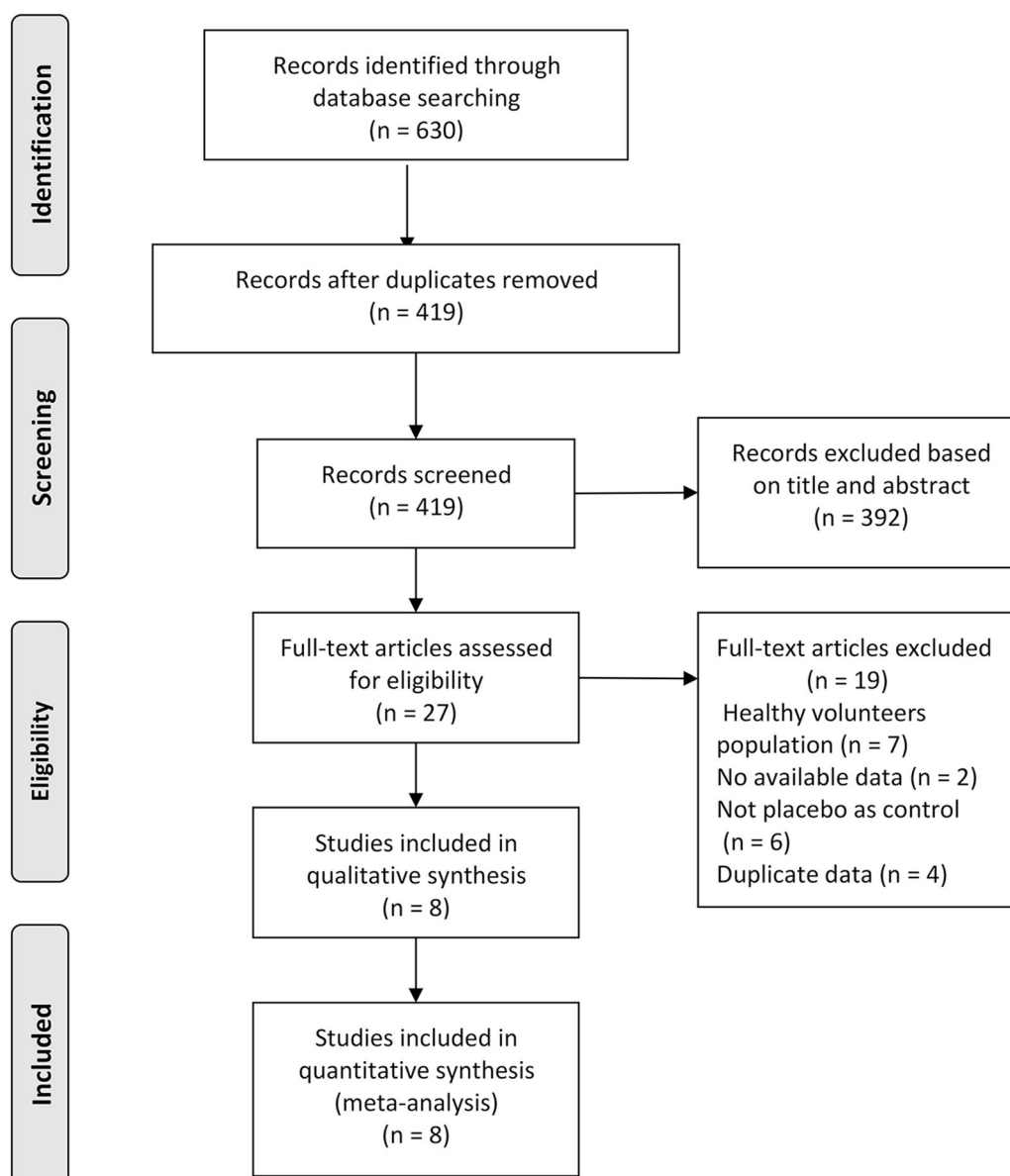
Fig. 1 PRISMA flow diagram

Table 1 Characteristics of the included trials

Trial	Country	Population	Sample size (methylnaltrexone/placebo)	Drug regimen		Outcomes	
				Route	Dosage	Efficacy	Safety
Thomas 2008 [14]	USA	Adult patients with advanced illness (a life expectancy ≥ 1 month)	133 (62/71)	Subcutaneous	0.15 mg/kg qod for 2 weeks	①③	⑤⑥⑦⑧⑨⑩
Slatkin 2009 [15]	USA	Adult patients with advanced illness (a life expectancy of 1–6 months)	154 (47[0.15 mg/kg]/ 55[0.30 mg/kg]/52)	Subcutaneous	0.15 mg/kg or 0.30 mg/ kg with a single injection	①②	⑤⑥⑦⑨⑩
Michna 2011 [16]	USA	Adult patients with chronic noncancer pain	460 (148[qod]/150[qd]/ 162)	Subcutaneous	12 mg qd or12 mg qod for 4 weeks	①②③④	⑤⑥⑦⑧⑨
Anissian 2012 [17]	USA	Adult patients undergoing orthopedic procedure	33 (18/15)	Subcutaneous	12 mg qd for up to 4 or 7 days	①④	⑤⑥⑦⑧⑩
Bull 2015 [18]	USA	Adult patients with advanced illness (a life expectancy ≥ 1 month)	230 (116/114)	Subcutaneous	8 mg or 12 mg qod for 2 weeks	①④	⑤⑥⑦⑧⑨⑩
Rauck 2017 [19]	USA	Adult patients with chronic noncancer pain	803 (200[450 mg]/ 201[300 mg]/ 201[150 mg]/201)	Oral	150 mg or 300 mg or 450 mg qd for 4 weeks	①③	⑤⑥⑦⑧⑩
Dimitroulis 2017 [20]	Greece	Adult patients with advanced NSCLC (a life expectancy ≥ 3 months)	137 (68/69)	Subcutaneous	12 mg qod for 4 weeks	①	⑤
Patel 2020 [21]	UK	Adult patients undergoing mechanical ventilation in ICU receiving opioids	84 (41/43)	Intravenous	8 or 12 mg via intravenous catheter over 15 min	①④	⑤

ICU intensive care unit, *qd* every day, *qod* every other day, *NSCLC* non-small cell lung cancer; ① Rescue-free bowel movement (RFBM) within 4 hours after the first dose, ② RFBM within 24 hours after the first dose, ③ patients with ≥3 RFBM per week, ④ use of rescue laxations, ⑤ any adverse events, ⑥ abdominal pain, ⑦ nausea, ⑧ diarrhea, ⑨ vomiting, ⑩ flatulence

Trial Characteristics

The characteristics of the included trials are presented in Table 1. These trials were published between 2008 and 2020. The sample size of the individual trial ranges from 33 to 803. The population mainly involved patients with advanced illness (incurable cancer or other terminal diseases) and chronic noncancer pain. The administrated route in all trials is subcutaneous except oral in one trail and intravenous one trail. All trials reported the efficacy and safety outcomes. The details of risk-of-bias assessment for each included trial are

summarized in Fig. 2. Overall, two trials were categorized as being at low risk of bias and six as being unclear risk of bias.

Efficacy of Methylnaltrexone for the Treatment of OIC

Primary Efficacy Outcome: RFBM Within 4 h After the First Dose

Eight trials with 1833 participants reported the primary efficacy outcome. Methylnaltrexone significantly increased RFBM within 4 h after the first dose compared with placebo (RR 3.74, 95% CI 3.02–4.62; $I^2 = 0\%$; Fig. 3).

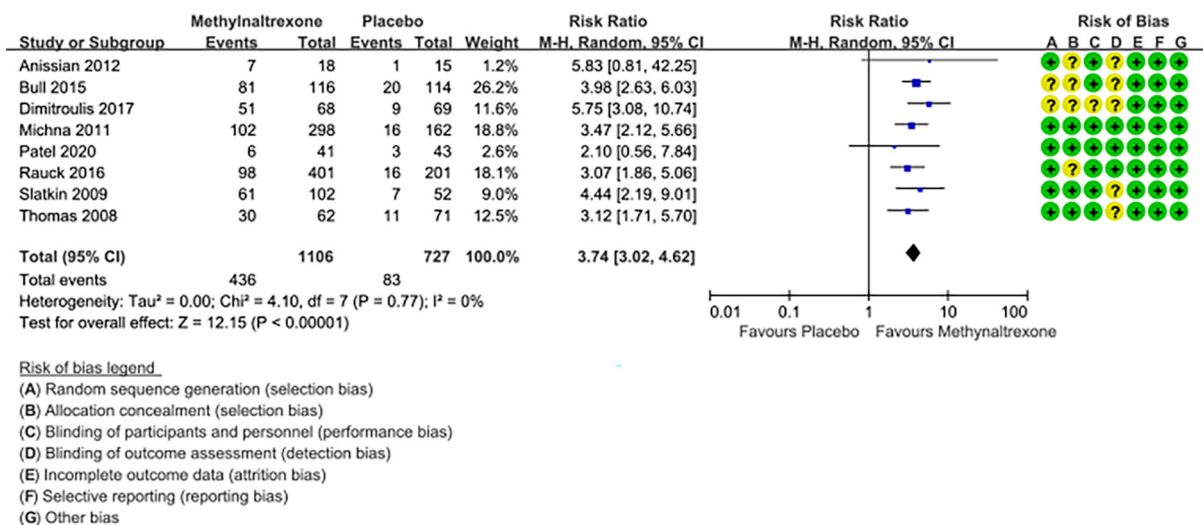**Fig. 2** Risk-of-bias summary. + = low risk; ? = uncertain risk

Fig. 3 Forest plot for RFBM within 4 h after first dose

Secondary Efficacy Outcomes: RFBM Within 24 h After the First Dose, RFBM ≥ 3 Times per Week, and Need to Take Rescue Laxatives

Compared with placebo, methylnaltrexone significantly increased RFBM within 24 h after the first dose (two trials; 614 participants; RR 1.98, 95% CI 1.52–2.58; $I^2 = 9\%$; Fig. 4) and RFBM ≥ 3 times per week (three trials; 1396 participants; RR 1.33, 95% CI 1.17–1.52; $I^2 = 0\%$; Fig. 4) and decreased need to take rescue laxatives (three trials; 807 participants; RR 0.73, 95% CI 0.63–0.85; $I^2 = 0\%$; Fig. 4).

Safety of Methylnaltrexone for the Treatment of OIC

Primary Safety Outcome: Any Adverse Events
Eight trials with 2033 participants reported the primary safety outcome. There was no difference in any adverse events between the methylnaltrexone and placebo groups (RR 1.11, 95% CI 0.99–1.23; $I^2 = 34\%$; Fig. 5).

Secondary Safety Outcomes: Abdominal Pain, Diarrhea, Nausea, Vomiting, and Flatulence
There were no differences in diarrhea (six trials; 1743 participants; RR 1.16, 95% CI 0.69–1.96; $I^2 = 32\%$), nausea (six trials; 1813 participants; RR 1.15, 95% CI 0.74–1.79; $I^2 = 23\%$), vomiting (four trials; 977 participants; RR 0.86, 95% CI

0.45–1.62; $I^2 = 25\%$), and flatulence (five trials; 1353 participants; RR 1.41, 95% CI 0.86–2.32; $I^2 = 0\%$) between the methylnaltrexone and placebo groups (Fig. 6). For the most commonly reported adverse events, the abdominal pain was higher in the methylnaltrexone group than that in placebo group (six trials; 1813 participants; RR 2.30, 95% CI 1.29–4.08; $I^2 = 62\%$; Fig. 6).
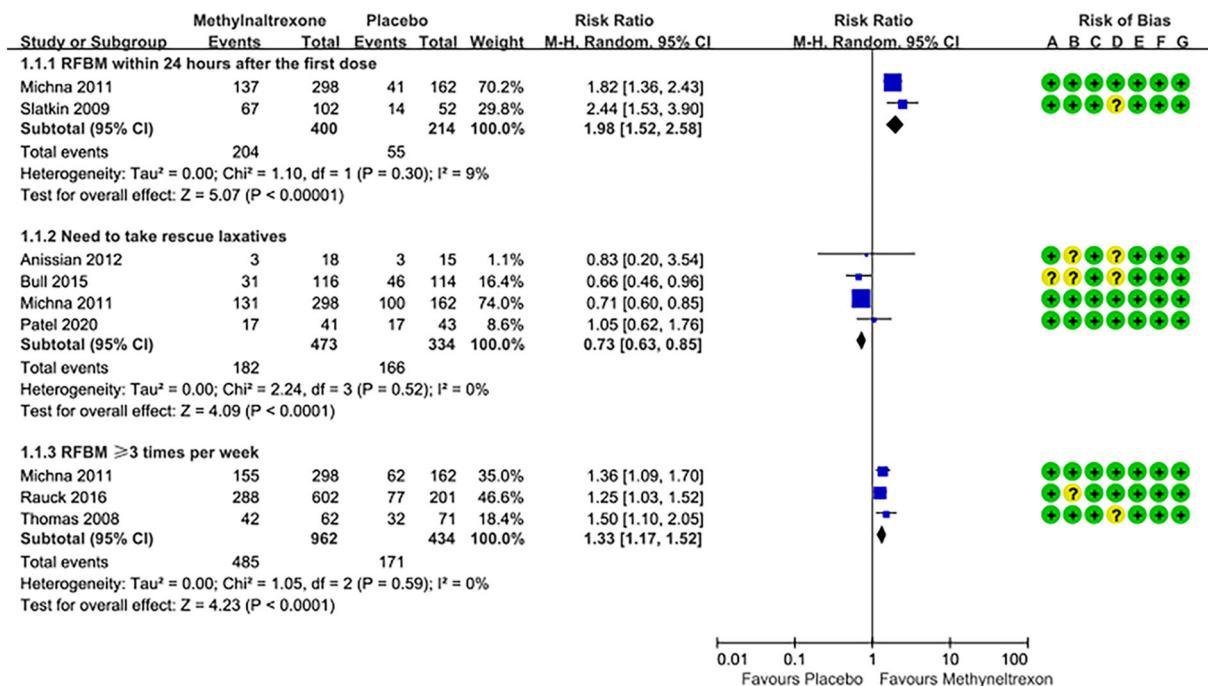
GRADE Certainty of Evidence

GRADE evidence profiles for the primary and secondary outcomes are shown in Table 2. The certainty of evidence is high for RFBM within 4 h after the first dose, moderate for RFBM within 24 h after the first dose, RFBM ≥ 3 times per week, need to take rescue laxatives, any adverse events, abdominal pain, diarrhea, nausea, vomiting, and flatulence.
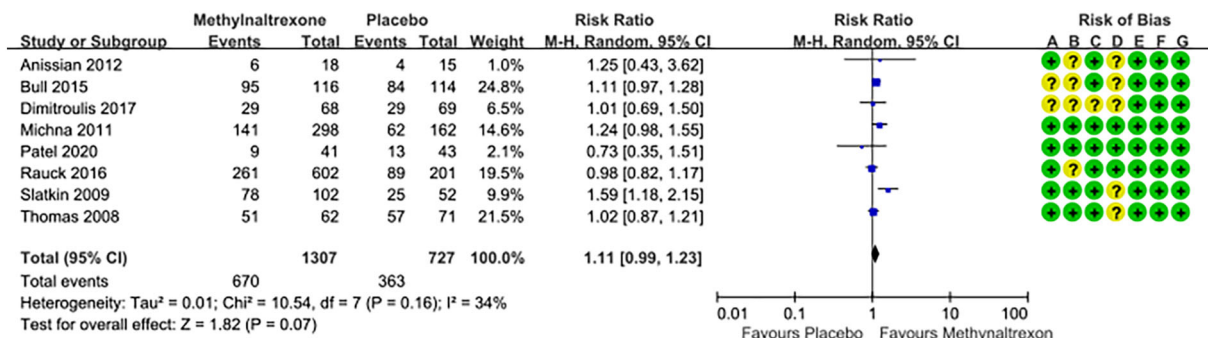
DISCUSSION

Main Findings

Our meta-analysis comprehensively and systematically reviewed the current available literature that compared methylnaltrexone with placebo for treating OIC. We found that

Fig. 4 Forest plot for secondary efficacy outcomes

Fig. 5 Forest plot for any adverse events

Fig. 6 Forest plot for secondary safety outcomes

Table 2 GRADE evidence profiles

Certainty assessment							Summary of findings			Anticipated absolute effects	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Risk with placebo	Risk difference with methylnaltrexone
							With placebo	With methylnaltrexone			
Primary efficacy outcome: RFBM within 4 h after the first dose											
1833 (8 RCTs)	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected Strong association [a]	⊕⊕⊕⊕ HIGH	83/727 (11.4%)	436/1106 (39.4%)	RR 3.74 (3.02 to 4.62)	114 per 1000	313 more per 1000 (from 231 to 413 more)
Secondary efficacy outcome: RFBM within 24 h after the first dose											
614 (2 RCTs)	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected [a]	⊕⊕⊕◯ MODERATE	55/214 (25.7%)	204/400 (51.0%)	RR 1.98 (1.52 to 2.58)	257 per 1000	252 more per 1000 (from 134 to 406 more)
Secondary efficacy outcome: RFBM ≥ 3 times per week											
1396 (3 RCTs)	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected [a]	⊕⊕⊕◯ MODERATE	171/434 (39.4%)	485/962 (50.4%)	RR 1.33 (1.17 to 1.52)	394 per 1000	130 more per 1000 (from 67 to 205 more)
Secondary efficacy outcome: need to take rescue laxatives											
807 (4 RCTs)	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected [a]	⊕⊕⊕◯ MODERATE	166/334 (49.7%)	182/473 (38.5%)	RR 0.73 (0.63 to 0.85)	497 per 1000	134 fewer per 1000 (from 184 to 75 fewer)

Table 2 continued

Certainty assessment							Summary of findings			Anticipated absolute effects	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Risk with placebo	Risk difference with methylnaltrexone
							With placebo	With methylnaltrexone			
Primary safety outcome: any adverse events											
2034 (8 RCTs)	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected [a]	⊕⊕⊕○ MODERATE	363/727 (49.9%)	670/1307 (51.3%)	RR 1.11 (0.99 to 1.23)	499 per 1000	55 more per 1000 (from 5 fewer to 115 more)
Secondary safety outcome: abdominal pain											
1813 (6 RCTs)	Not serious	Serious[b]	Not serious	Not serious	Publication bias strongly suspected strong association [a]	⊕⊕⊕○ MODERATE	48/615 (7.8%)	178/1198 (14.9%)	RR 2.30 (1.29 to 4.08)	78 per 1000	101 more per 1000 (from 23 to 240 more)
Secondary safety outcome: nausea											
1813 (6 RCTs)	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected [a]	⊕⊕⊕○ MODERATE	45/615 (7.3%)	89/1198 (7.4%)	RR 1.15 (0.74 to 1.79)	73 per 1000	11 more per 1000 (from 19 fewer to 58 more)
Secondary safety outcome: diarrhea											
1743 (6 RCTs)	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected [a]	⊕⊕⊕○ MODERATE	39/606 (6.4%)	68/1137 (6.0%)	RR 1.16 (0.69 to 1.96)	64 per 1000	10 more per 1000 (from 20 fewer to 62 more)
Secondary safety outcome: vomiting											
977 (4 RCTs)	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected [a]	⊕⊕⊕○ MODERATE	27/399 (6.8%)	33/578 (5.7%)	RR 0.86 (0.45 to 1.62)	68 per 1000	9 fewer per 1000 (from 37 fewer to 42 more)

Table 2 continued

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With methylnaltrexone		Risk with placebo	Risk difference with methylnaltrexone
Secondary safety outcome: flatulence											
1353 (5 RCTs)	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected[a]	⊕⊕⊕◯ MODERATE	21/453 (4.6%)	55/900 (6.1%)	RR 1.41 (0.86 to 2.32)	46 per 1000	19 more per 1000 (from 6 fewer to 61 more)

CI confidence interval, *RR* risk ratio

[a] It is hard to rule out the existence of publication bias since less than 10 trials were included

[b] $I^2 > 50\%$ indicates a significant heterogeneity

compared with placebo, methylnaltrexone significantly increased RFBM within 4 h after the first dose, RFBM within 24 h after the first dose, and RFBM ≥ 3 times per week and decreased need to take rescue laxatives; there was no difference in any adverse events (including diarrhea, nausea, vomiting, and flatulence) between the two groups except for abdominal pain.

Comparison with Existing Literature

Several previous reviews on the similar topic have been published [22–29]. Six of them evaluated the treatment of OIC with different pharmacological therapies, mainly μ-opioid receptor antagonists, including methylnaltrexone [22–27]. These meta-analyses consistently found that methylnaltrexone is effective and safe for the treatment of OIC. Two of them specifically evaluated the effect of methylnaltrexone on the treatment of OIC and found that methylnaltrexone increased RFBM within 4 h after the first dose [28, 29]. In line with these two reviews, our meta-analysis also found that methylnaltrexone increased RFBM within 4 h after the first dose. Besides, we found that methylnaltrexone increased RFBM within 24 h after the first dose and RFBM ≥ 3 times per week and decreased need to take rescue laxatives. For safety outcomes, we found that there was no difference in any adverse events (including diarrhea, nausea, vomiting, and flatulence) between the methylnaltrexone and placebo groups. Notably, the occurrence of abdominal pain is higher in the methylnaltrexone group than that in the placebo group. In summary, our meta-analysis further confirmed that methylnaltrexone is an effective and safe drug for the treatment OIC, but some differences also should be noted. First, previous meta-analyses included less than 1500 patients. In comparison, our meta-analysis identified another two recent trials and included more than 2000 patients. With added statistical power of at least 500 cases, our meta-analysis was the latest and the most comprehensive, which further reinforces earlier results of previous meta-analyses. Second, we used an intention-to-treat principle and pooled data with a random-effects model

accounting for clinical heterogeneity to ensure a more conservative estimate of the efficacy and safety of methylnaltrexone for the treatment of OIC. Third, we evaluated the certainty of evidence using GRADE approach to facilitate clinical decision-making.

Implication for Clinical Practice

The European expert consensus statement for the management of OIC recommended that peripheral μ-opioid receptor antagonists can be considered as second-line treatment when prophylactics and laxatives are not effective in relieving OIC [30]. The most well-known example is naloxone, commonly used as an intravenous reversal agent in the context of opioid over-dosing. Methylnaltrexone, a quaternary ammonium derivative of naltrexone, has been approved for the treatment of OIC as subcutaneous injection since 2008. In our meta-analysis, methylnaltrexone was administered as subcutaneous injection in most trials. The results suggested that methylnaltrexone is effective and safe for the treatment of OIC, but one important thing to note is that methylnaltrexone may increase the risk of abdominal pain. The possible explanations for abdominal pain are as follows: the abdominal pain may be perceived as related to intentional initiative of propulsive peristalsis during the normal process of laxation induced by methylnaltrexone; the abdominal pain may represent localized gastrointestinal withdrawal effects. Although the abdominal pain was mild to moderate and may be dose-dependent, methylnaltrexone still should be used cautiously, especially, in patients with preexisting gastrointestinal disorders. The serious complication of gastrointestinal perforation associated with methylnaltrexone has been reported in some cases [31, 32].

Strengths and Limitations

The strength of this meta-analysis lies in compliance with the PRISMA statement, registration on PROSPERO with protocol, and applying GRADE approach to assess the certainty of the evidence. Our meta-analysis has some limitations that may affect the interpretation of the results. First, it is hard to rule out the existence of publication bias since only eight trials were included in our meta-analysis. Second, although no statistical heterogeneity was observed for main outcomes, differences in included population and drug regimen may introduce clinical heterogeneity and could affect the results.

CONCLUSIONS

Methylnaltrexone is an effective and safe drug for treating OIC, but the safety of abdominal pain should be considered.

ACKNOWLEDGEMENTS

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