Research Square

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

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Abstract

Background: 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: We searched PubMed, Embase, and Cochrane Library for randomized controlled trials that compared methylnaltrexone with placebo for the treatment of OIC. The primary efficacy outcome was rescue-free bowel movement (RFBM) within 4 hours after the first dose. Secondary efficacy outcomes included RFBM within 24 hours after the first dose, RFBM ≥3 times per week, and need take rescue laxatives. The primary safety outcome was any adverse events. Secondary safety outcomes included abdominal pain, diarrhea, nausea, vomiting, and flatulence. Relative risks (RR) and 95% confidence interval (CI) were pooled using random-effects model with the intention-to-treat principle. We used the GRADE approach to assess the certainty of the evidence.

Results: Eight trials with 2,034 participants were included. Compared with placebo, methylnaltrexone significantly increased RFBM within 4 hours after the first dose (8 trials; 1,833 participants; RR 3.74, 95% CI 3.02-4.62; I^2 = 0%; high-certainty evidence), RFBM within 24 hours after the first dose (2 trials; 614 participants; RR 1.98, 95% CI 1.52-2.58; I^2 = 9%; moderate-certainty evidence), and RFBM ≥3 times per week (3 trials; 1,396 participants; RR 1.33, 95% CI 1.17-1.52; I^2 = 0%; moderate-certainty evidence) and decreased need to take rescue laxatives (3 trials; 807 participants; RR 0.73, 95% CI 0.63-0.85; I^2 = 0%; moderate-certainty evidence). For safety outcomes, there was no difference in any adverse events between the two groups (8 trials; 2,034 participants; RR 1.11, 95% CI 0.99-1.23; I^2 = 34%; 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 (6 trials; 1,813 participants; RR 2.30, 95% CI 1.29-4.08; I^2 = 62%; moderate-certainty evidence).

Conclusions: Methylnaltrexone is an effective and safe drug for treating OIC. But the safety of abdominal pain should be considered.

Trial registration: PROSPERO (CRD42020187290).

Background

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, that 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]. >85% of cancer and > 40% of non-cancer patients treated with opioids experience symptoms of OIC [2]. Differ 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 with 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 trails were not adequately powered to detect the true effect. Therefore, we performed a meta-analysis to investigate the efficacy and safety of methylnaltrexone for the treatment of OIC.

Materials

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, 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 trails with healthy volunteers as participants.

Data extraction and outcomes assessment

We developed a data extraction sheet in standardized Excel (Microsoft Corporation). Two authors (YYZ and WJG) independently extracted data from included trails. 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 outcomes.

The primary efficacy outcome was rescue-free bowel movement (RFBM) within 4 hours after first dose (RFBM was defined as a bowel movement without use of any rescue medication or procedure within four hours before the bowel movement). The secondary efficacy outcomes included RFBM within 24 hours after the first dose, RFBM ≥ 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 ≥ 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 database. 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: 7 articles were excluded because their participants were healthy volunteers; 2 articles were excluded because there was no relevant data; 6 articles were excluded because they did not use a placebo as a control group; 4 articles were excluded because of duplicate data. Finally, 8 trials (7 full texts and 1 abstract) were included (Fig. 1) [14–21].

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 trails were categorized as being at low risk of bias and six as being unclear risk of bias.

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	□□	□□□□□□
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	□□	□□□□□
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	□□□□	□□□□□
Anissian 2012 [17]	USA	Adult patients undergoing orthopedic procedure	33 (18/15)	Subcutaneous	12 mg qd for up to 4 or 7 days	□□	□□□□□
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	□□	□□□□□□
Rauck 2017 [19]	USA	Adult patients with chronic noncancer pain	803 (200[450mg]/201[300mg]/201[150mg]/201)	Oral	150 mg or 300 mg or 450 mg qd for 4 weeks	□□	□□□□□
Dimitroulis 2017 [20]	Greece	Adult patients with advanced NSCLC (a life expectancy ≥ 3 months)	137 (68/69)	Subcutaneous	12 mg qod for 4 weeks	□	□
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	□□	□

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

Efficacy of methylnaltrexone for treating OIC

Primary efficacy outcome: RFBM within 4 hours after the first dose

Eight trials with 1,833 participants reported the primary efficacy outcome. Methylnaltrexone significantly increased RFBM within 4 hours after the first dose compared with placebo (RR 3.74, 95% CI 3.02–4.62; I^2 = 0%; Fig. 3).

Secondary efficacy outcomes: RFBM within 24 hours after the first dose, RFBM ≥ 3 times per week, and need to take rescue laxatives

Compared with placebo, methylnaltrexone significantly increased RFBM within 24 hours after the first dose (2 trials; 614 participants; RR 1.98, 95% CI 1.52–2.58; I^2 = 9%; Fig. 4) and RFBM ≥ 3 times per week (3 trials; 1,396 participants; RR 1.33, 95% CI 1.17–1.52; I^2 = 0%; Fig. 4) and decreased need to take rescue laxatives (3 trials; 807 participants; RR 0.73, 95% CI 0.63–0.85; I^2 = 0%; Fig. 4).

Safety of methylnaltrexone for treating OIC

Primary safety outcome: any adverse events

Eight trials with 2,033 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 (6 trials; 1,743 participants; RR 1.16, 95% CI 0.69–1.96; I^2 = 32%), nausea (6 trials; 1,813 participants; RR 1.15, 95% CI 0.74–1.79; I^2 = 23%), vomiting (4 trials; 977 participants; RR 0.86, 95% CI 0.45–1.62; I^2 = 25%), and flatulence (5 trials; 1,353 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 methylnaltrexone group than that in placebo group (6 trials; 1,813 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 hours after the first dose, moderate for RFBM within 24 hours after the first dose, RFBM ≥ 3 times per week, need to take rescue laxatives, any adverse events, abdominal pain, diarrhea, nausea, vomiting, and flatulence.

Table 2
GRADE evidence profiles

Certainty assessment							Summary of findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%) With placebo	Study event rates (%) With Methylnaltrexone	Relative effect (95% CI)	Anticipa Risk with placebo
Primary efficacy outcome: RFBM within 4 hours 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 1,000
Secondary efficacy outcome: RFBM within 24 hours 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 1,000
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 1,000
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 1,000
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 1,000
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 1,000
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 1,000
Secondary safety outcome: Diarrhea										

CI: Confidence interval; **RR**: Risk ratio

Explanations

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.

Certainty assessment							Summary of findings			
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 1,000
Secondary safety outcome: Vomitting										
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 1,000
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 1,000

CI: Confidence interval; **RR**: Risk ratio

Explanations

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.

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 compared with placebo, methylnaltrexone significantly increased RFBM within 4 hours after the first dose, RFBM within 24 hours 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 hours after the first dose [28, 29]. In line with these two reviews, our meta-analysis also found that methylnaltrexone increased RFBM within 4 hours after the first dose. Besides, we found that methylnaltrexone increased RFBM within 24 hours 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 methylnaltrexone group than that in 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 1,500 patients. In comparison, our meta-analysis identified another two recent trials and included more than 2,000 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 decisions 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 administrated 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. Thus, methylnaltrexone should be used cautiously, especially, in those patients with pre-existing gastrointestinal disorders.

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 8 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.

Abbreviations

CI = confidence interval;

GRADE = Grading of Recommendations Assessment, Development, and Evaluation;

OIC = opioid-induced constipation;

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses;

RFBM = rescue-free bowel movement;

RR = Relative risk.

Declarations

- **Ethics approval and consent to participate:** Not applicable
- **Consent for publication:** Not applicable
- **Availability of data and materials:** Not applicable
- **Competing interests:** The authors declare that they have no competing interests
- **Funding:** None
- **Authors' contributions:**

Ying-Ying Zhang: Conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be published.

Rong Zhou: Acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be published.

Wan-Jie Gu: Conception and design of the study, analysis and interpretation of data, drafting and revising the article, final approval of the version to be published.

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Figures

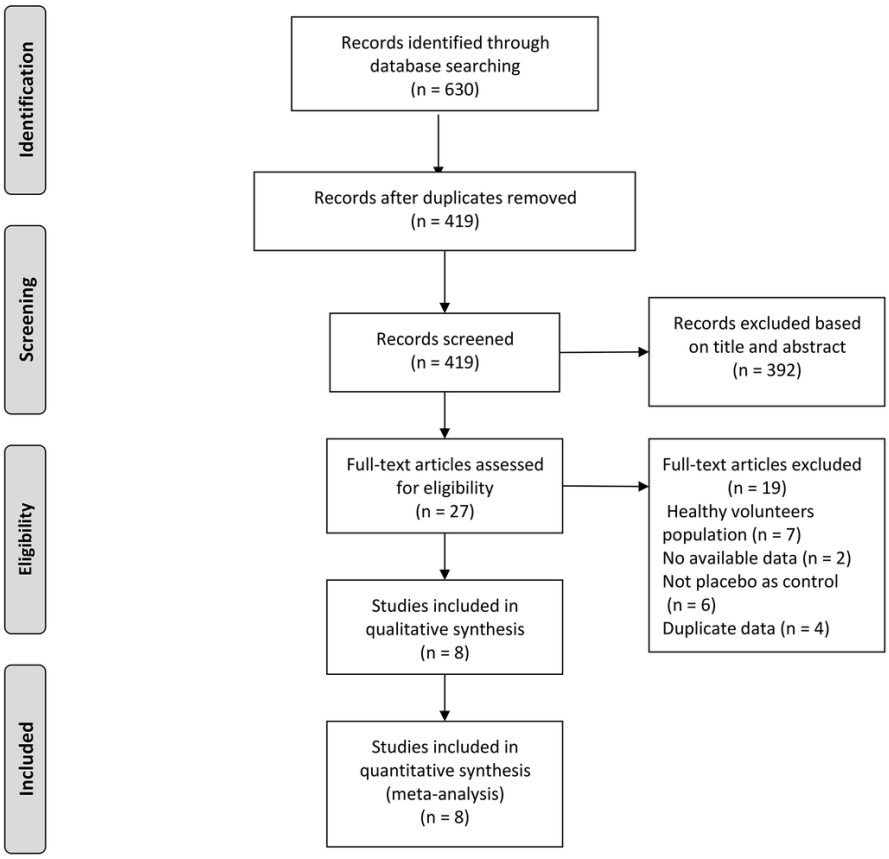

Figure 1

PRISMA flow diagram.

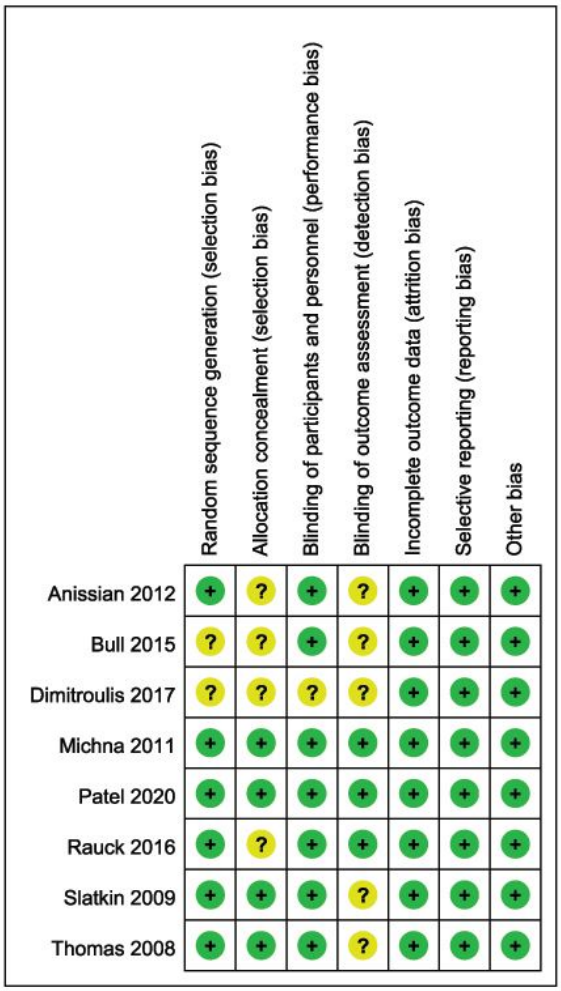

Figure 2

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

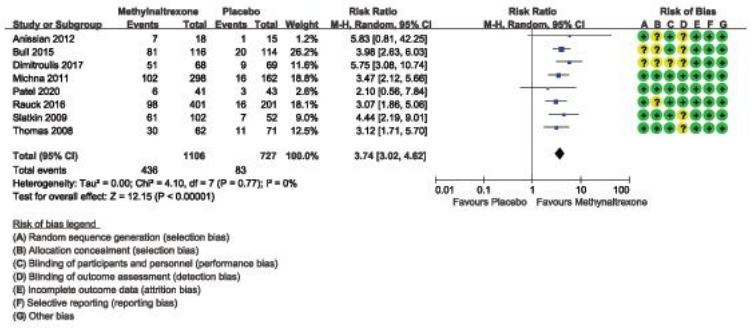

Figure 3

Forest plot for RFBM within 4 hours after first dose.

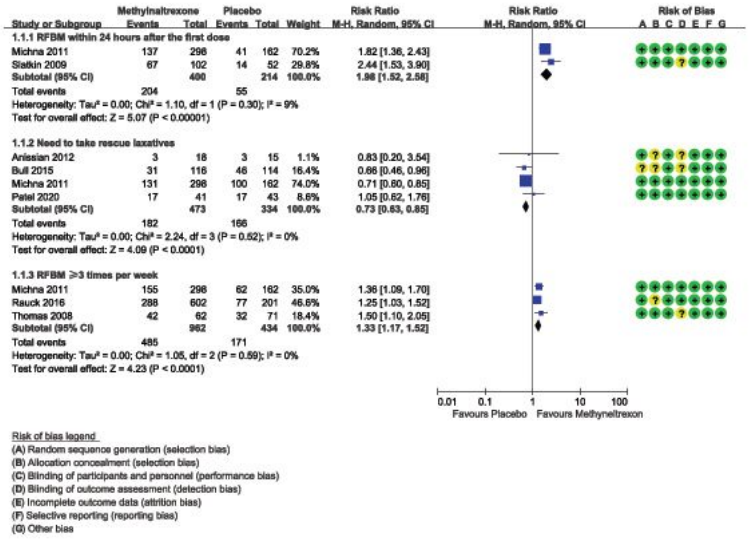

Figure 4

Forest plot for secondary efficacy outcomes.

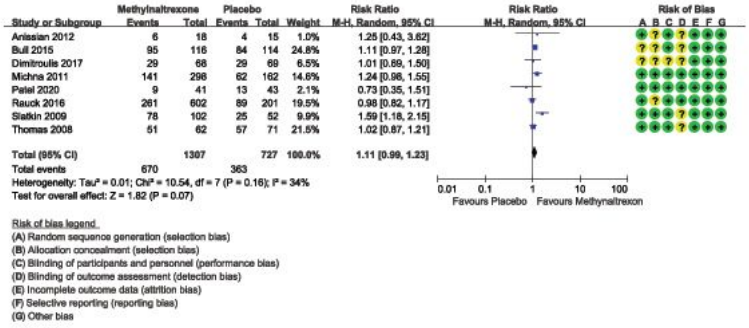

Figure 5

Forest plot for any adverse events.

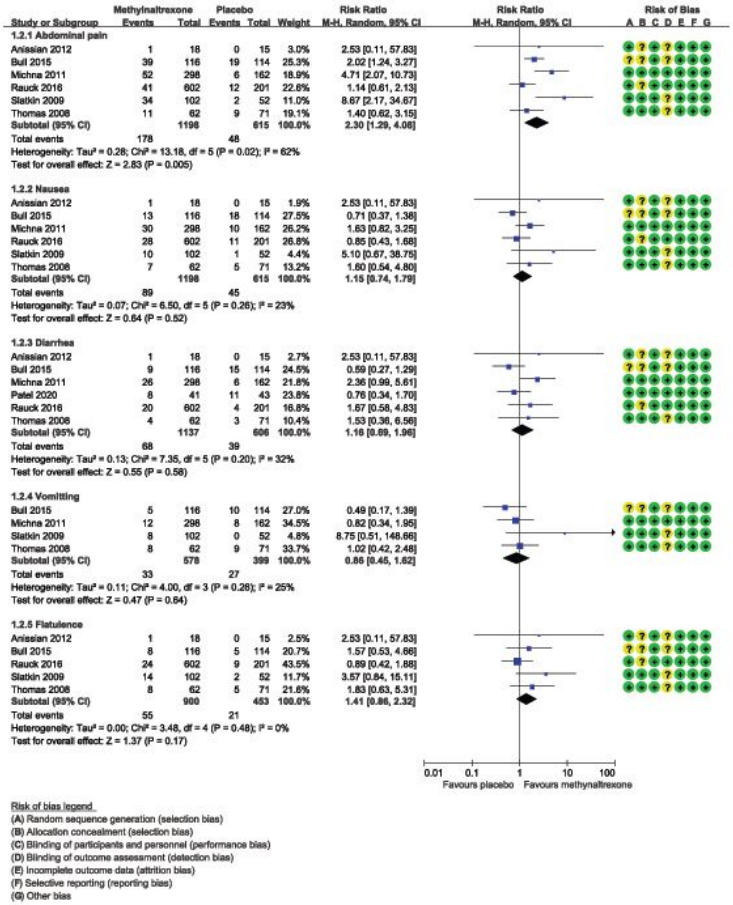

Figure 6

Forest plot for secondary safety outcomes.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- GraphicalAbstract.png