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META ANALYSIS AND SYSTEMATIC REVIEW

Peripherally acting μ-opioid antagonist for the treatment of opioid-induced constipation: Systematic review and meta-analysis

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Key words
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Abstract

Background and Aim: Opioid-induced constipation (OIC) is a frequent adverse event (AE) that impairs patients' quality of life (QOL). Peripherally acting μ-opioid receptor antagonists (PAMORAs) have been recognized as a treatment option for OIC, but the effect consistent across the studies has not been evaluated.

Methods: We conducted a quantitative meta-analysis to explore the efficacy of PAMORA for OIC (registered with PROSPERO: CRD42018085298). We systematically searched randomized controlled trials (RCTs) in Medline, Embase, and Central databases. Change from baseline in spontaneous bowel movements, pooled proportion of responders, QOL, and AEs were calculated and compared with results in placebo cases.

Results: We included 31 RCTs with 7849 patients. A meta-analysis revealed that patients under PAMORA therapy had considerably improved spontaneous bowel movement from baseline compared with those given placebo (20 RCTs; mean difference, 1.43; 95% confidence interval [CI], 1.18–1.68; $n = 5622$) and more responded (21 RCTs; risk ratio [RR], 1.81; 95% CI, 1.55–2.12; $n = 4821$). Moreover, QOL of patients receiving PAMORA was significantly better (8 RCTs; mean difference, −0.22; 95% CI, −0.28 to −0.17; $n = 2884$). AEs were increased significantly in the PAMORA group (26 RCTs; RR, 1.10; 95% CI, 1.06–1.15; $n = 7715$), especially in gastrointestinal disorders, whereas serious AEs were not significant (17 RCTs; RR, 1.04; 95% CI, 0.85–1.28; $n = 5890$).

Conclusion: Peripherally acting μ-opioid receptor antagonist has been shown to be effective and durable for patients with OIC and is the only drug with confirmed evidence in meta-analysis. The possibility of publication bias was the limitation of this study.

Introduction

Opioids are widely used for the treatment of pain syndromes.[1] Despite analgesic effectiveness, opioids cause gastrointestinal side effects, called opioid-induced bowel dysfunction (OIBD).[2,3] The most common syndrome of OIBD is opioid-induced constipation (OIC).[4,5] OIC occurs in approximately 10–15% of opioid-treated cancer patients, significantly impairs quality of life (QOL), and increases costs.[6,7] Furthermore, OIC is the most common reason to discontinue opioid use.[8] Laxatives have been traditionally used for patients with OIC. However, data indicate that OIC persists despite sufficient laxative use with little improvement in symptoms.[9,10]

Peripherally acting μ-opioid receptor antagonists (PAMORAs) are therapeutic agents that block μ-opioid receptors in the gastrointestinal tract and inhibit the action of opioids without central opioid activity. Three PAMORAs, methylnaltrexone bromide (Relistor), naloxegol (Movantik), and naldemedine (Symproic), have been approved by the Food and Drug Administration (FDA) for the treatment of patients with OIC.[11] In the latest guidelines of OIC, PAMORA is a treatment option alongside laxatives.[12]

However, to date, to our knowledge, the consistent effect of PAMORA across studies has not been systemically evaluated. In trials of PAMORA in patients with OIC, patient backgrounds were well balanced between randomized groups, but the groups showed differences in the prevalence of ethnicities, malignant or nonmalignant diseases, and opioid doses. Thus, the efficacy of PAMORA remains unclear in clinical settings. Evidence that supports the efficacy of PAMORA may provide a basis for developing a new management strategy for OIC. We conducted a systematic review of the literature to identify randomized controlled trials (RCTs) evaluating the role of PAMORA in patients with OIC, and we conducted a meta-analysis to estimate the effect and safety of PAMORA.

Methods

Search methods for identification of studies. This meta-analysis was registered with the PROSPERO database (number CRD42018085298) and was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis

statement.[13] The date of inception of this study was January 1, 2018. We searched RCTs in the PubMed (1946 to the date of search), Embase (1974 to the date of search), and Cochrane databases (from inception through February 12, 2018) to identify potentially relevant studies. The search strategy included a combination of free text words, words in titles/abstracts, and medical subject headings, including "bowel dysfunction" OR "constipation" AND "mu-opioid antagonist" OR "Naldemedine" OR "Rizmoic" OR "S-297995" OR "Symproic" OR "Methylnaltrexone" OR "Relistor" OR "MRZ-2663" OR "Naloxegol" OR "Movantik" OR "NKTR-118" OR "Bevenopran" OR "CB-5945" OR "Axelopran" OR "TD-1211." No language restrictions were applied. We manually searched the reference lists of the selected articles from Google Scholar, ClinicalTrials.gov., and relevant reviews.

Inclusion and exclusion criteria. We included all published and unpublished RCTs that evaluated the efficacy of PAMORA for patients with OIC in this review. The primary outcome was change from baseline in spontaneous bowel movement (SBM). The secondary outcomes included QOL, responder rate, and adverse events (AEs).

Studies were included if they met the following criteria: (i) RCTs, (ii) adults receiving opioid or opiate drugs, (iii) diagnosis of OIC or OIBD with constipation, (iv) comparison with placebo groups, and (v) study reported on any of the aforementioned outcomes. Crossover and cluster RCTs were excluded to avoid heterogeneity. We regarded SBM (defined as a bowel movement without a rescue laxative taken within the past 24 h[14–16]) as the same disease concept as a rescue-free bowel movement (defined as a bowel movement where no laxatives were used during the prior 24 h).

Data extraction. Data were extracted by two authors (K. N. and S. Y.) independently. The titles and abstracts of the studies retrieved using the search strategy and those from additional sources were screened independently. Then, the full texts of relevant articles were retrieved to assess eligibility. Any discrepancies were resolved through consultation with the third author (T. Y.) and discussion. Missing data were requested from study authors. We estimated data based on other available summary statistics or from data in published figures. Data were extracted as intention-to-treat analyses; if it was unavailable, per-protocol analyses was adopted. If there were outcomes measured at multiple time points, we selected the outcome measured by the longest duration in order to eliminate arbitrariness or double count. In case of multiple arms, we selected the arm used in the clinical setting or with an FDA-approved dose to reduce heterogeneity.

Assessment of risk of bias in the included studies. Two review authors (K. N. and S. Y.) independently assessed the risk of bias in the included studies and assessed the quality of each study with the risk of bias tool in the Cochrane Handbook for Systematic Reviews of Interventions.[17] The risk of bias was assessed based on the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Disagreements were resolved by discussion, with involvement of a third review author (T. Y.).

Meta-analysis and subgroup analysis. Participants were divided into two groups: the PAMORA and placebo groups. Subgroup analysis was conducted for each drug. All analyses were performed using Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration). When the change in standard deviation for each group was not available, it was reconstructed from the standard error with the RevMan calculator. As to the continuous outcomes, mean differences (MDs) and 95% confidence intervals (CIs) were estimated as the effect results (e.g. change from baseline SBM and QOL). The effect of each pharmacologic therapy was combined to estimate the pooled risk ratio (RR) and associated 95% CIs for dichotomous outcomes (e.g. proportion of responder and AEs).

Statistical heterogeneity in each meta-analysis was tested using τ^2, I^2, and χ^2 statistics following the Cochrane Handbook for Systematic Reviews of Interventions.[17] We regarded heterogeneity as insignificant when I^2 was greater than 50% and a fixed-effects model was used, whereas random-effects models were performed when heterogeneity existed ($P < 0.1$, $I^2 > 50\%$). To increase the validity of the results of the test, we performed a sensitivity analysis. All CIs had two-sided probability coverage of 95% using Mantel–Haenszel fixed-effects and DerSimonian–Laird random-effects models. A P value less than 0.05 was considered significant. When 10 or more studies were included in a meta-analysis, publication bias was evaluated by visually inspecting funnel plots.

Results

A total of 816 articles were identified and screened, and 31 RCTs (7849 patients) were included in the meta-analysis. The search strategy generated 808 citations. In addition, we found eight other articles manually. Of these 816 articles, we excluded 127 because they were duplicates, as well as 539 review articles and 18 case reports. We retrieved the full texts of the remaining 132 articles. Ultimately, 51 articles, including 31 RCTs, met our inclusion criteria.[14–16,18–40] Figure 1 shows the screening process and reasons for excluding studies.

Study characteristics. The characteristics of the included RCTs and participant information are presented in Table 1. A total of 7849 participants were included in the 31 RCTs.[14–16,18–40] Of these RCTs, seven[14–16,19,20,30] used naldemedine (n = 1399), seven[18,23,24,27,29,34,35] used methylnaltrexone (n = 605), four[21,28,31,32] used alvimopan (n = 518), six[22,33,40] used naloxegol (n = 547), five[25,36–38] used bevenopran (n = 776), and two[26,39] used axelopran (n = 69). All 29 RCTs gave a placebo to the control group (n = 3935). Three RCTs[16,22,33] were reported together in one publication.

Risk of bias in the included studies. We assessed the study quality following the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[17] The risk of bias for each study is summarized in Table 2. We excluded three trials because of serious risk of bias, in which over half of the patients were terminated early by the sponsor.[36,37]

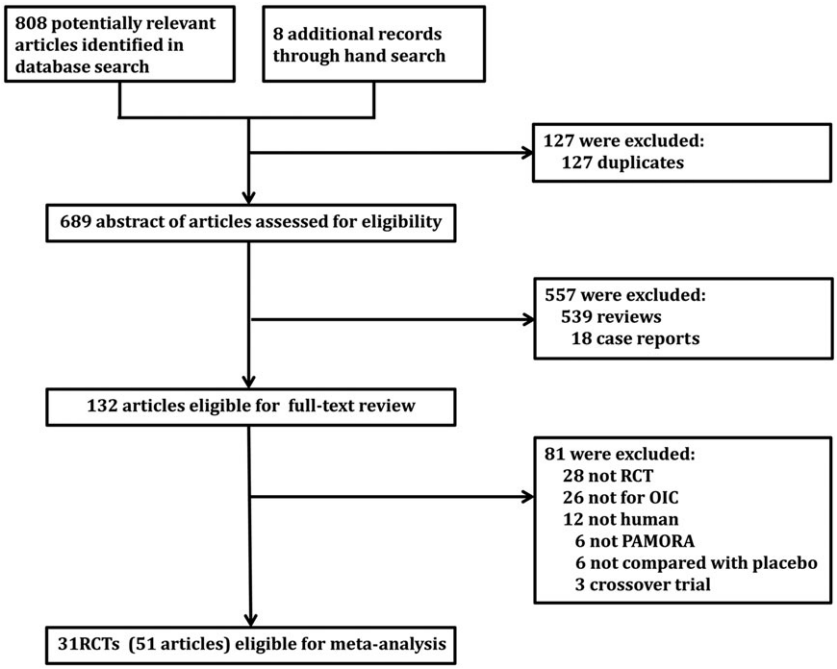


Figure 1 Literature search and study selection. OIC, opioid-induced constipation; PAMORA, peripherally acting μ-opioid receptor antagonist; RCT, randomized controlled trial.

Change from baseline of spontaneous bowel movements. A total of 20 RCTs[14–16,20–22,25,26,28–34,39] with 5622 patients were included in the analysis of change from baseline of SBM per week. The overall results showed a significant increase in this change among participants treated with PAMORA (MD, 1.43; 95% CI, 1.18–1.68; $P < 0.00001$; Fig. 2). In each subgroup analysis, naldemedine (6 RCTs; MD, 1.71; 95% CI, 1.13–2.28; $P < 0.00001$), methylnaltrexone (2 RCTs; MD, 1.49; 95% CI, 1.10–1.89; $P < 0.00001$), alvimopan (4 RCTs; MD, 1.17; 95% CI, 0.68–1.67; $P = 0.49$), naloxegol (5 RCTs; MD, 1.35; 95% CI, 0.71–1.98; $P < 0.00001$), bevenopran (1 RCTs; MD, 1.98; 95% CI, 0.88–3.08; $P = 0.00004$), and axelopran (2 RCTs; MD, 1.52; 95% CI, 0.72–2.33; $P = 0.0002$) were significantly improved. Moderate heterogeneity ($\chi^2 = 34.67$, $P = 0.02$, $I^2 = 45\%$) was observed. In sensitive analysis, when we excluded two trials (Webster 2013, 5 mg and Webster 2013, 50 mg) in which the dose of the drug was 10 times different, heterogeneity was reduced ($\chi^2 = 24.68$, $P = 0.10$, $I^2 = 31\%$), while the overall result was not changed (MD, 1.37; 95% CI, 1.15–1.59; $P < 0.00001$). Funnel plot asymmetry seemed to be observed for the impact of PAMORA and placebo (Fig. S1).

Quality of life. Eight RCTs[22,29,30,33,38] with 2284 subjects reported the Patient Assessment of Constipation of Quality of Life Scale. The overall results showed a significant improvement in QOL among participants treated with PAMORA (MD, −0.22; 95% CI, −0.28 to −0.17; $P < 0.00001$; Fig. 3). Little heterogeneity was observed ($\chi^2 = 7.13$, $P = 0.42$, $I^2 = 2\%$).

Proportion of responders. In total, 21 RCTs[14–16,18,20,21,23,24,26–29,31–35,39,40] of PAMORA recruited 4821 patients. PAMORA showed a greater response than placebo (RR, 1.81; 95% CI, 1.55–2.12; $P < 0.00001$). Considerable heterogeneity between studies ($\chi^2 = 85.52$, $P < 0.00001$, $I^2 = 77\%$) was observed; we applied a random-effects model (Fig. 4). In subgroup analysis, methylnaltrexone (7 RCTs; $\chi^2 = 59.21$, $P < 0.00001$, $I^2 = 90\%$) and alvimopan (4 RCTs; $\chi^2 = 16.04$, $P = 0.001$, $I^2 = 81\%$) had significant heterogeneity. On the other hand, naldemedine (5 RCTs; $\chi^2 = 7.08$, $P = 0.13$, $I^2 = 44\%$), naloxegol (3 RCTs; $\chi^2 = 0.42$, $P = 0.81$, $I^2 = 0\%$), and axelopran (2 RCTs; $\chi^2 = 0.97$, $P = 0.32$, $I^2 = 0\%$) did not demonstrate high heterogeneity.

Adverse events. A total of 7715 patients with 4100 AEs were reported in 26 RCTs.[14–16,19–35,38,40] Overall, there were significantly increased AEs in patients given PAMORA (RR, 1.10; 95% CI, 1.06–1.15; $P < 0.00001$; Fig. 5a), while the rate of serious AEs was not significant (17 RCTs; RR, 1.04; 95% CI, 0.85–1.28; $P = 0.68$; Fig. 5b). Gastrointestinal toxicity, diarrhea (25 RCTs; RR, 2.07; 95% CI, 2.14–4.65), abdominal pain (26 RCTs; RR, 2.22; 95% CI, 2.14–4.65), vomiting (22 RCTs; RR, 1.47; 95% CI, 1.17–1.84), and nausea (27 RCTs; RR, 1.39; 95% CI, 1.17–1.65) were significantly increased AEs (Fig. S2).

Discussion

To our knowledge, this is the first investigation specifically aimed to assess the effectiveness of PAMORA for OIC and that provides good quality evidence. The strengths of this review included two important clinical issues. The first issue is that PAMORA was favorable in multiple outcomes for patients with OIC, and AEs were increased in the PAMORA group.

In our comprehensive evaluation, PAMORA significantly improved change in baseline SBM, QOL, and responder rate. To our knowledge, this study included the largest number of patients from geographically diverse regions, different ethnicities, with malignant or nonmalignant diseases, and different opioid doses. The effect of OIBD on the subjects' QOL has not been studied

Table 1 Characteristics of the eligible studies

Study	Phase	Participants	Drug, dosage, and treatment period	Median age (years), gender (%), and race (%)	Available outcome
COMPOSE1	III	547 non-cancer patients with OIC	Naldemedine 0.2 mg or placebo for 12 weeks	53.4 (10.7) years Female 60.4 White 80.0, Asian 18.5, and others 1.5	Change SBM, responder rate, and AEs
COMPOSE2	III	533 non-cancer patients with OIC	Naldemedine 0.2 mg or placebo for 12 weeks	53.5 (11.0) years Female 60.5 White 81.6, African American 16.0, and others 2.3	Change SBM, responder rate, and AEs
COMPOSE3	III	1246 non-cancer patients with OIC	Naldemedine 0.2 mg or placebo for 52 weeks	53.4 (11.1) years Female 63.3 White 79.7, Black 18.4, and others 1.9	Change SBM, QOL, and AEs
Katakami 2017	II	226 cancer patients with OIC	Naldemedine 0.1, 0.2, or 0.4 mg or placebo for 2 weeks	Placebo: 64.2 (9.6) years; naldemedine: 63.4 (10.4) years Female 70.2 Asian 100	Change SBM, responder rate, and AEs
Webster 2017	II	244 non-cancer patients with OIC	Naldemedine 0.1, 0.2, or 0.4 mg or placebo for 4 weeks	51.9 (10.8) years Female 70.2 White 82.3, Black 16.0, and others 1.7	Change SBM, responder rate, and AEs
Webster 2016	II	72 non-cancer patients with OIC	Naldemedine 0.01, 0.03, 0.1, 0.3, 1, or 3 mg or placebo for 2 weeks	43.3 (10.3) years Female 52.8 White 97.2 and others 2.8	AEs
COMPOSE4	III	193 cancer patients with OIC	Naldemedine 0.2 mg or placebo for 2 weeks	Placebo: 64.6 (11.8) years; naldemedine: 63.8 (9.4) years Female 52.8 Asian 100	Change SBM, responder rate, and AEs
Yuam 2000	Unclear	22 patients with OIC	Intravenous injection of methylnaltrexone 0.015 up to 0.365 mg/kg or placebo for up to 2 days	No available	Responder rate
Thomas 2008	III	134 advanced illness (including cancer) patients with OIC	Subcutaneous injection of methylnaltrexone 12 mg or placebo for up to 4 or 7 days	Placebo: 70 (39–98) years; methylnaltrexone: 72 (34–93) years Female 56.7 White 94.0 and Black 6.0	Responder rate and AEs
Slatkin 2009	II	154 advanced illness patients with OIC	Subcutaneous injection of methylnaltrexone 0.15 or 0.3 mg/kg or placebo for 4 weeks	65.3 (14.9) years Female 45.5 Caucasian 82.5, Black 7.8, Hispanic 7.8, and others 1.9	Responder rate and AEs
Michna 2011	III	460 non-cancer patients with OIC	Subcutaneous injection of methylnaltrexone, 12 mg q.d. or 12 mg every other day or placebo for 4 weeks	48.79 (10.9) years Female 60.2 White 89.8, Black 7.0, and others 1.9	Change SBM, QOL, and AEs
Anissian 2012	II	33 non-cancer patients after surgical procedure with OIC	Subcutaneous injection of methylnaltrexone 0.15 mg/kg or placebo for 2 weeks	Placebo: 65.2 (11.6) years; methylnaltrexone: 65.2 (11.6) years Female 66.7 White 72.7 and Black 29.3	Responder rate and AEs
Bull 2015	IV	230 advanced illness patients with OIC	Subcutaneous injection of methylnaltrexone 8 or 12 mg every other day compared with placebo for 2 weeks	Placebo: 65.7 (13.0) years; methylnaltrexone: 65.3 (12.9) years Female 48.7 White 93.9 and others 6.1	Change SBM, responder rate, and AEs

(Continues)

Table 1. (Continued)

Study	Phase	Participants	Drug, dosage, and treatment period	Median age (years), gender (%), and race (%)	Available outcome
Rauck 2017	III	803 non-cancer patients with OIC	Oral methylnaltrexone 150, 300, or 450 mg or placebo for 4 weeks	Placebo: 52.6 (10.3) years; ethylnaltrexone: 51.4 (10.5) years Female 39.4 White 84.3, Black 3.0, and others 2.7	Responder rate and AEs
Paulson 2005	II	168 non-cancer patients with OIC	Alvimopan 0.5 or 1.0 mg or placebo for 3 weeks	Placebo: 48 (31–72) years; alvimopan: 51 (30–77) years Female 69.0 White 78.2, African American 16.4, and Black 5.4	Responder rate and AEs
Webster 2008	II	522 non-cancer patients with OIC	Alvimopan 0.5 or 1.0 mg b.i.d. or 1.0 mg q.i.d. or placebo for 6 weeks	Placebo: 51.3 (11.2) years; alvimopan: 49.7 (10.5) years Female 64.1 White 94.5 and others 5.5	Change SBM, responder rate, and AEs
Jansen 2011	III	518 non-cancer patients with OIC	Alvimopan 0.5 mg q.i.d. or 0.5 mg b.i.d. or placebo for 12 weeks	51.7 (11.3) years Female 63.0 White 91.0, Black 8.0, and others 1.0	Change SBM, responder rate, and AEs
Irving 2011	III	485 non-cancer patients with OIC	Alvimopan 0.5 mg q.i.d. or 0.5 mg b.i.d. or placebo for 12 weeks	52.1 (11.6) years Female 64.0 White 91.0, Black 7.0, and others 2.0	Change SBM, responder rate, and AEs
Webster 2013	II	207 patients with OIC	Naloxegol 5, 25, or 50 mg or placebo for 4 weeks (3 RCT)	49.7 (11.7) years Female 62.2	Change SBM, QOL, and AEs
KODIAC-04	III	652 non-cancer patients with OIC	Naloxegol 12.5 or 25 mg or placebo for 12 weeks	Placebo: 52.9 (10.0) years; naloxegol: 52.2 (20.3) years Female 60.3 White 77.8, Black 19.2, and others 3.0	Change SBM, responder rate, QOL, and AEs
KODIAC-05	III	700 non-cancer patients with OIC	Naloxegol 12.5 or 25 mg or placebo for 12 weeks	Placebo: 52.3 (11.6) years; naloxegol: 51.9 (12.1) years Female 62.9 White 80.2, Black 18.1, and others 1.7	Change SBM, responder rate, QOL, and AEs
KODIAC-06	III	9 non-cancer patients with OIC	Naloxegol 12.5 or 25 mg or placebo for 4 weeks	Placebo: 52.5 (4.93) years; naloxegol: 53.8 (11.69) years Female 77.8 White 66.7 and others 33.3	Responder rate and AEs
NCT01696643	III	1403 non-cancer patients with OIC	Bevenopran 0.25 mg b.i.d. or placebo for 52 weeks	54.2 (10.11) years Female 60.9 White 79.7, Black 17.0, and others 3.2	QOL and AEs
Singla 2012	II	131 non-cancer patients with OIC	Bevenopran 0.1 or 0.25 mg b.i.d. or placebo for 4 weeks	18–65 (94.7) years; over 65 years (5.3) Female 48.0	Change SBM and AEs
NCT01901302	III	61 non-cancer patients with OIC	Bevenopran 0.25 mg b.i.d. or placebo for 12 weeks	18–65 (95.0) years; over 65 (5.0) years Female 75.4	AEs
NCT01901341	III	44 non-cancer patients with OIC	Bevenopran 0.25 mg b.i.d. or placebo for 12 weeks	18–65 (95.5) years; over 65 (4.5) years Female 65.9	AEs
NCT01901328	III	49 non-cancer patients with OIC	Bevenopran 0.25 mg b.i.d. or placebo for 12 weeks	18–65 (95.9) years; over 65 years (4.1) Female 75.5	AEs

(Continues)

Table 1. (Continued)

Study	Phase	Participants	Drug, dosage, and treatment period	Median age (years), gender (%), and race (%)	Available outcome
Vickey 2011	II	70 non-cancer	Axelopran 0.25, 0.75, 2, 5, or 10 mg or placebo for 4 weeks	NA	Change SBM, responder rate, and AEs
Vickey 2012	II	217 non-cancer patients with OIC	Axelopran 5, 10, or 15 mg or placebo for 4 weeks	49 (21–65) years Female 59	Change SBM, responder rate, and AEs

AEs, adverse events; b.i.d., bis in die; change SBM, change from baseline of spontaneous bowel movement; NA, not applicable; OIC, opioid-induced constipation; q.d., quaque die; q.i.d., quater in die; QOL, quality of life.

Table 2 Risk of bias

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
COMPOSE1	+	+	+	+	+	+	+
COMPOSE2	+	+	+	+	+	+	+
COMPOSE3	?	?	+	+	+	+	+
Katakami 2017	+	+	+	?	+	+	+
Webster 2017	?	+	+	+	+	+	+
Webster 2016	?	+	+	–	+	+	+
COMPOSE4	+	+	+	+	+	+	+
Yuan 2000	–	+	?	+	+	?	–
Thomas 2008	+	+	+	+	+	+	+
Slatkin 2009	+	+	+	+	+	+	+
Michna 2011	+	+	+	+	?	?	+
Anissian 2012	+	–	+	?	+	+	+
Bull 2015	?	?	+	+	+	+	+
Rauck 2017	?	?	+	+	?	–	?
Paulson 2005	+	+	+	+	–	?	+
Webster 2008	–	?	?	+	+	–	+
Jansen 2011	+	+	?	+	–	+	+
Irving 2011	–	+	?	+	–	+	+
Webster 2013 5 mg	?	?	+	+	–	+	+
Webster 2013 25 mg	?	?	+	+	–	+	+
Webster 2013	?	?	+	+	–	+	+
KODIAC-04	+	+	+	+	+	+	+
KODIAC-05	+	+	+	+	+	+	+
KODIAC-06	?	+	+	+	–	–	–
NCT01696643	?	?	+	+	–	+	–
Singla 2012	?	?	+	+	+	+	+
NCT01901302	?	?	+	+	–	+	–
NCT01901341	?	?	+	+	–	+	–
NCT01901328	?	?	+	+	–	+	–
Vickey 2012	?	?	?	+	–	–	+

+, low risk of bias; –, high risk of bias; ?, unclear.

extensively.[41] Among patients receiving long-term opioid therapy, OIC is known to be associated with significant increases in physician visits and significantly lower QOL.[7] It was clinically meaningful that PAMORA improved not only the surrogate endpoint (e.g. change in SBM and responder rate) but also the QOL as the true endpoint. Furthermore, some reports suggested the anticancer effect of PAMORA.[42] In the *post hoc* analysis of two methylnaltrexone studies, PAMORA group showed a significantly longer overall survival ($P = 0.033$).[43]

The second clinical implication of this study was that PAMORA significantly increased AEs compared with placebo, while many RCTs reported no significant differences. The most frequently reported AE was gastrointestinal toxicity. Diarrhea, abdominal pain, vomiting, and nausea were significantly increased in the PAMORA group. The most common gastrointestinal toxicity was diarrhea, and QOL scores are improved despite the fact that toxicity was significantly higher. Diarrhea might be controlled by reducing the laxative administered with PAMORA. In addition,

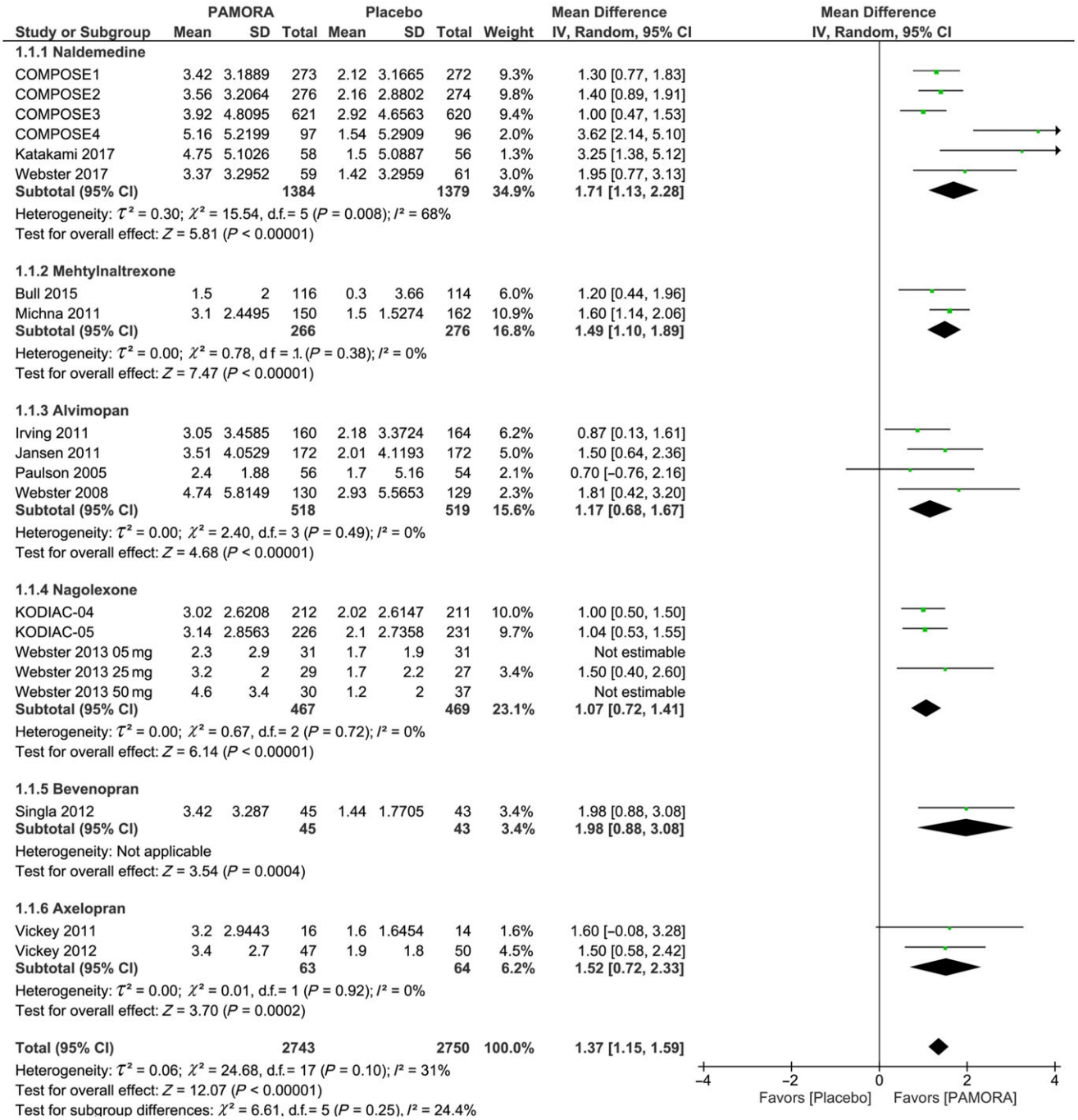


Figure 2 Change in spontaneous bowel movement. CI, confidence interval; PAMORA, peripherally acting μ-opioid receptor antagonist. [Color figure can be viewed at wileyonlinelibrary.com]

the detail profile of AEs was clearly different among the drugs administered (Fig. S2). Diarrhea was not significant with alvimopan and axelopran, while abdominal pain was not significant with methylnaltrexone, alvimopan, and axelopran. Only naloxegol was associated with a significantly higher incidence of nausea and vomiting. The difference in AEs may be a reference for choosing a PAMORA. Although serious AEs were not significant and the QOL score was superior in the PAMORA group, PAMORA treatment was durable.

Despite side effects being a major contributor to the phenomenon of undertreatment of opioids, diagnosis and treatment of OIC remain insufficient among medical staff. The absence of a standard protocol for treatment of OIC was thought to be a reason for this insufficiency. A precise evaluation of the therapeutic effect

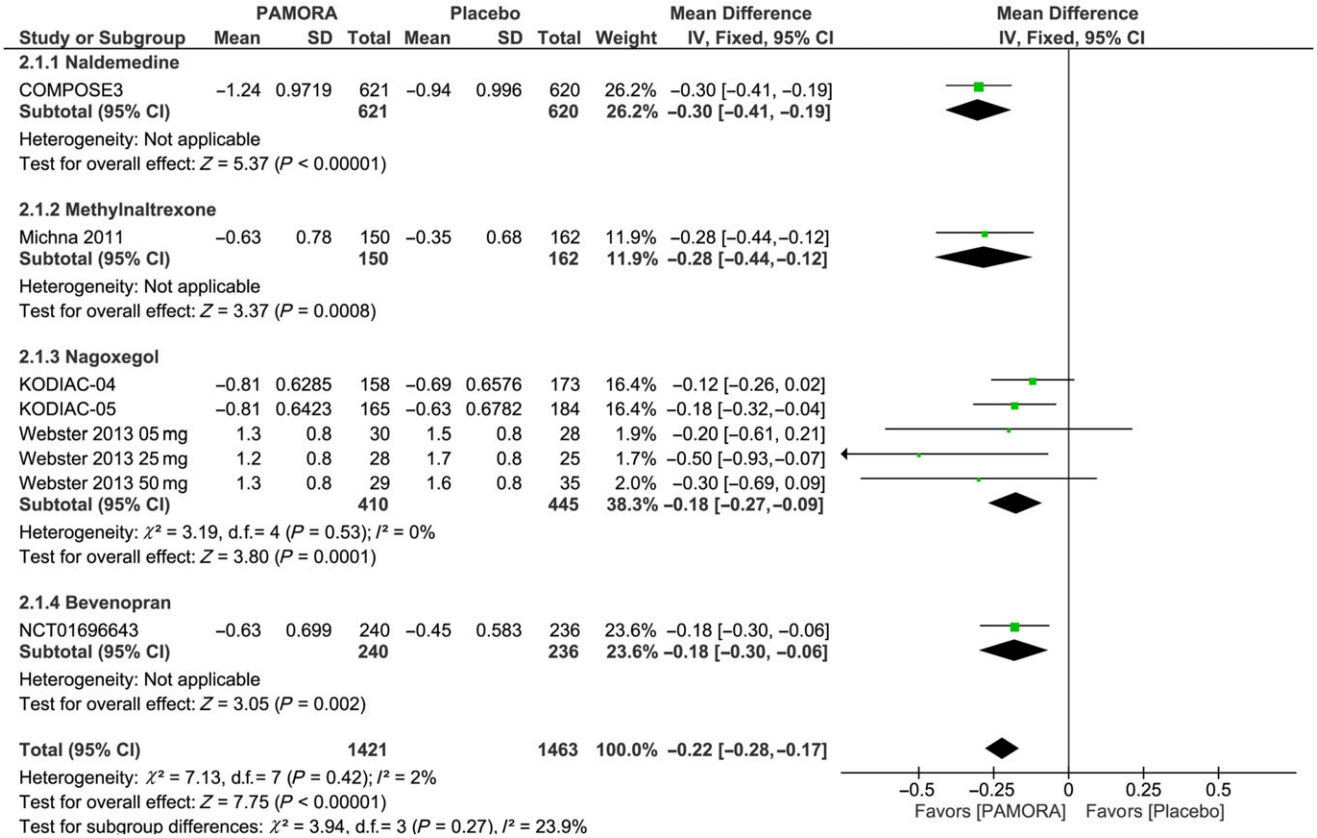


Figure 3 Quality of life. CI, confidence interval; PAMORA, peripherally acting μ-opioid receptor antagonist. [Color figure can be viewed at wileyonlinelibrary.com]

of PAMORA should lead to the development of managements and improved regimens resulting in reduced gastrointestinal AEs.[11]

A recent review by Nee *et al*. reported a meta-analysis of 27 studies on OIC.[44] They also analyzed lubiprostone and naloxon, which were not PAMORAs. Therefore, their study could not estimate the true efficacy of PAMORA for OIC. Moreover, their meta-analysis was conducted based on only published data, which is not a desirable method. The strength of our research is that it focuses on PAMORA and includes unpublished data, such as those on axelopran and bevenopran.

On the other hand, healthcare resource utilization in cancer patients on opioid therapy was quantified.[6,45] Patients with constipation had more hospital admissions and spent more days in the inpatient setting than patients without constipation. This may result in additional costs to the healthcare system as well as to the society.[46,47] These data indicated that effective treatment of OIC is necessary and the importance of the results of this meta-analysis is emphasized. Surveys on the cost-effectiveness of PAMORA are limited. In the analysis for methylnaltrexone, including subcutaneous injection for patients with advanced illness with OIC, the total costs were increased, but there was a gain in quality-adjusted life years (QALY) compared with standard care.[48] The incremental cost per QALY was €40 865, and using methylnaltrexone was cost-effective. On the other hand, naloxegol, which was half the cost of methylnaltrexone in the UK, was estimated to have an incremental cost-effectiveness ratio of £10 849 per QALY gained *versus* placebo and £11 179 when rescue laxatives are used in both arms.[49]

This trial had some limitations. First, publication bias seems to show asymmetry in the funnel plot. As especially the naldemedine study seemed to show publication bias, we contacted the pharmaceutical company (Shionogi & Co., Ltd.). They answered that some studies were preparing for publication. When we confirmed the registry (e.g. clinicaltrials.gov), we found some trials had not been published despite sufficient time passing after the study. The use of alvimopan has been evaluated in clinical trials involving patients who had OIC that also remained unpublished, and a large study was performed to examine the long-term efficacy and safety of alvimopan *versus* placebo in treating patients with OBD.[50] A preliminary analysis of the safety data from this study revealed serious AEs, the most worrisome of which was serious cardiovascular toxicity. According to reports submitted to the FDA, these cardiovascular events are seen in patients at high risk for cardiovascular disease. However, these cardiovascular adverse effects were not observed in subsequent studies of alvimopan.[51,52] William *et al*. reported in comprehensive analysis of four clinical studies that nagoxegol did not increase the cardiovascular risk.[53] In clinical trials of methylnaltrexone and naldemedine, the incidence of cardiovascular events was reportedly equal to or less than that of placebo.[16,23]

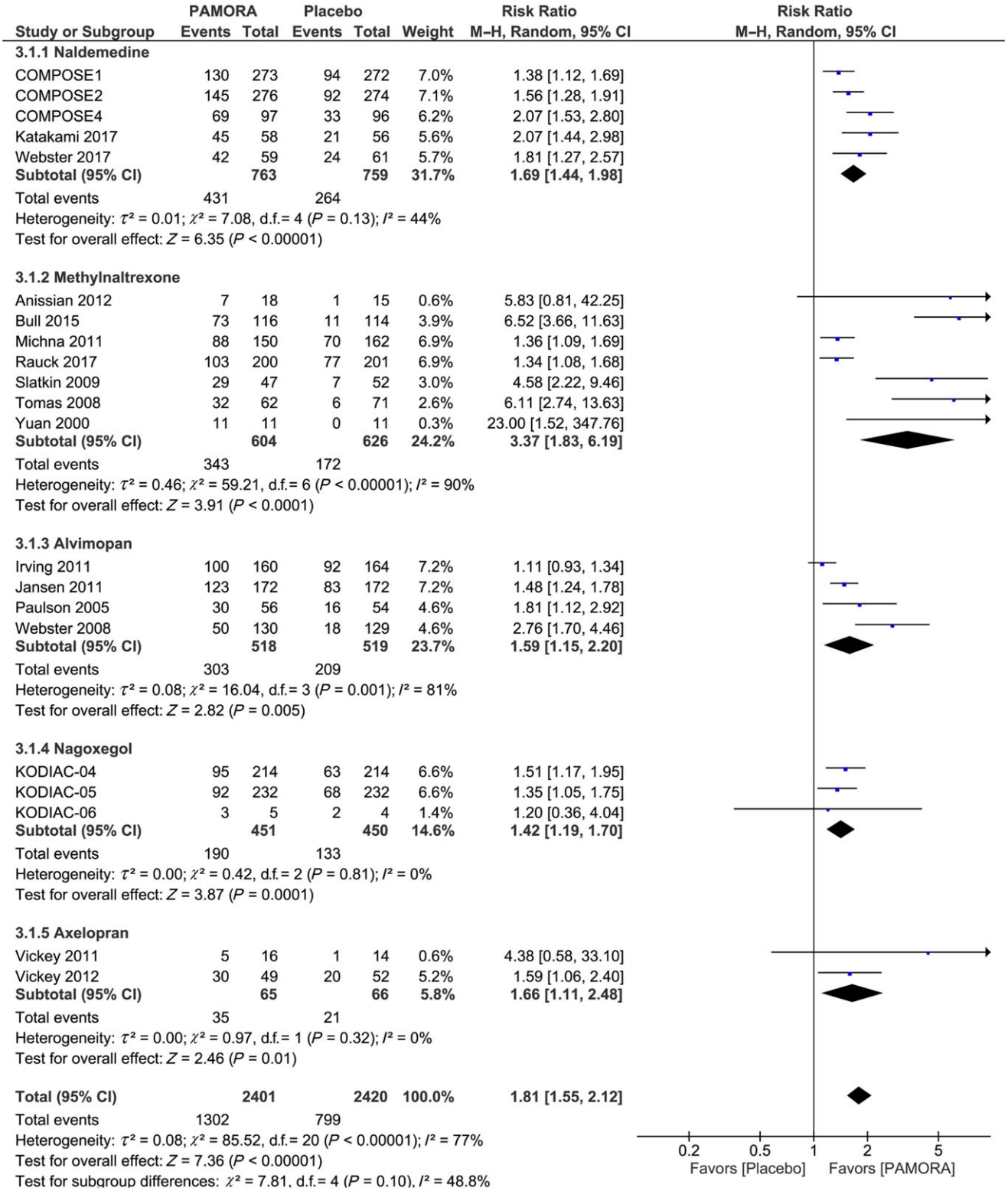
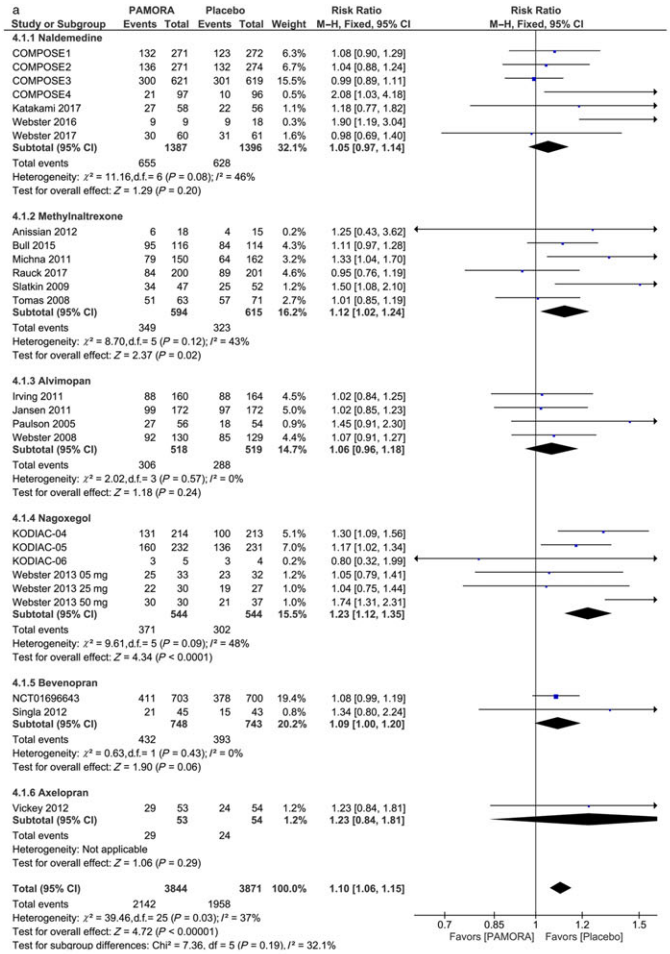


Figure 4 Proportion of responders. CI, confidence interval; PAMORA, peripherally acting μ-opioid receptor antagonist. [Color figure can be viewed at wileyonlinelibrary.com]



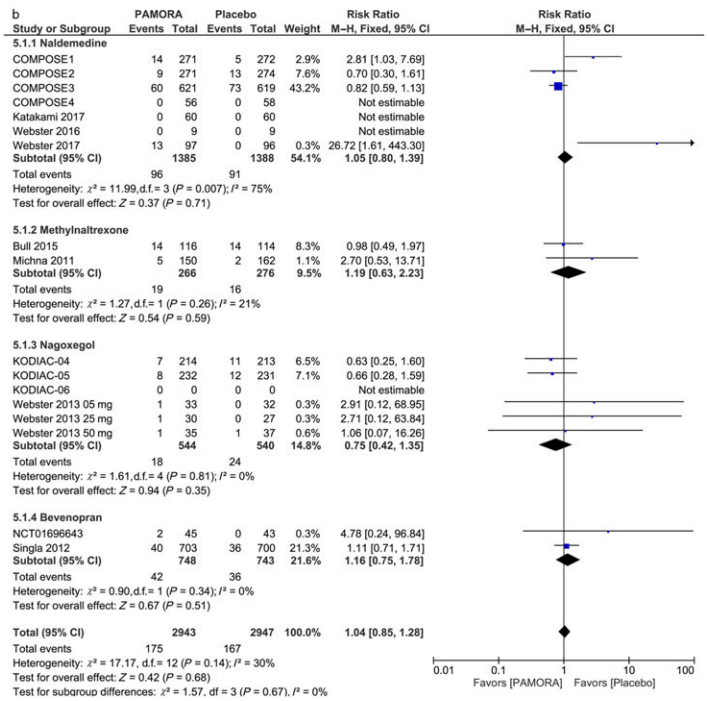


Figure 5 (a) All and (b) serious adverse events. CI, confidence interval; PAMORA, peripherally acting μ-opioid receptor antagonist. [Color figure can be viewed at wileyonlinelibrary.com]

Secondly, using self-recorded diaries to determine subjective outcomes, including straining, constipation, patient satisfaction, and pain, may have caused some bias. However, such a diary is an unavoidable element in estimating the effectiveness of PAMORA for OIC.

In conclusion, this meta-analysis has shown PAMORAs to be effective in the change in baseline SBM, QOL, and responder rate. We hope that this research contributed to the establishment of standard protocols for OIC and improvement of recognition rate.

References

1 Bruera E, Paice JA. Cancer pain management: safe and effective use of opioids. *Am. Soc. Clin. Oncol. Educ. Book.* 2015: e593–9.
2 Dorn S, Lembo A, Cremonini F. Opioid-induced bowel dysfunction: epidemiology, pathophysiology, diagnosis, and initial therapeutic approach. *Am. J. Gastroenterol. Suppl.* 2014; **2**: 31–7.
3 Abramowitz L, Beziaud N, Labreze L *et al*. Prevalence and impact of constipation and bowel dysfunction induced by strong opioids: a cross-sectional survey of 520 patients with cancer pain: DYONISOS study. *J. Med. Econ.* 2013; **16**: 1423–33.
4 Ketwaroo GA, Cheng V, Lembo A. Opioid-induced bowel dysfunction. *Curr. Gastroenterol. Rep.* 2013; **15**: 344.
5 Brock C, Olesen SS, Olesen AE, Frokjaer JB, Andresen T, Drewes AM. Opioid-induced bowel dysfunction: pathophysiology and management. *Drugs* 2012; **72**: 1847–65.
6 Candrilli SD, Davis KL, Iyer S. Impact of constipation on opioid use patterns, health care resource utilization, and costs in cancer patients on opioid therapy. *J. Pain Palliat. Care Pharmacother.* 2009; **23**: 231–41.
7 Bell T, Annunziata K, Leslie JB. Opioid-induced constipation negatively impacts pain management, productivity, and health-related quality of life: findings from the National Health and Wellness Survey. *J. Opioid. Manag.* 2009; **5**: 137–44.
8 Tamayo AC, Diaz-Zuluaga PA. Management of opioid-induced bowel dysfunction in cancer patients. *Support Care Cancer* 2004; **12**: 613–8.
9 LoCasale RJ, Datto CJ, Margolis MK, Tack J, Coyne KS. The impact of opioid-induced constipation among chronic pain patients with sufficient laxative use. *Int. J. Clin. Pract.* 2015; **69**: 1448–56.
10 Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. *Am. J. Surg.* 2001; **182**: 11S–8S.
11 Camilleri M, Drossman DA, Becker G, Webster LR, Davies AN, Mawe GM. Emerging treatments in neurogastroenterology: a multidisciplinary working group consensus statement on opioid-induced constipation. *Neurogastroenterol. Motil.* 2014; **26**: 1386–95.
12 Muller-Lissner S, Bassotti G, Coffin B *et al*. Opioid-induced constipation and bowel dysfunction: a clinical guideline. *Pain Med.* 2017; **18**: 1837–63.
13 Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Open Med.* 2009; **3**: e123–30.
14 Katakami N, Harada T, Murata T *et al*. Randomized phase III and extension studies of naldemedine in patients with opioid-induced constipation and cancer. *J. Clin. Oncol.* 2017; **35**: 3859–66.
15 Katakami N, Oda K, Tauchi K *et al*. Phase IIb, randomized, double-blind, placebo-controlled study of naldemedine for the treatment of opioid-induced constipation in patients with cancer. *J. Clin. Oncol.* 2017; **35**: 1921–8.
16 Hale M, Wild J, Reddy J, Yamada T, Arjona Ferreira JC. Naldemedine versus placebo for opioid-induced constipation (COMPOSE-1 and COMPOSE-2): two multicentre, phase 3, double-blind, randomised, parallel-group trials. *Lancet Gastroenterol. Hepatol.* 2017; **2**: 555–64.
17 Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0: the Cochrane collaboration, 2011.
18 Yuan CS, Foss JF, O'Connor M *et al*. Methylnaltrexone for reversal of constipation due to chronic methadone use: a randomized controlled trial. *JAMA* 2000; **283**: 367–72.
19 Webster L, Nagata T, Yamada T, Arjona FJ. (479) A phase 2a, randomized, double-blind, placebo-controlled, single ascending-dose study to evaluate the safety and efficacy of naldemedine in patients with chronic non-cancer pain and opioid-induced bowel dysfunction. *J. Pain*; **17**: S94.
20 Webster LR, Yamada T, Arjona Ferreira JC. A phase 2b, randomized, double-blind placebo-controlled study to evaluate the efficacy and safety of naldemedine for the treatment of opioid-induced constipation in patients with chronic noncancer pain. *Pain Med.* 2017; **18**: 2350–60.
21 Webster L, Jansen JP, Peppin J *et al*. Alvimopan, a peripherally acting mu-opioid receptor (PAM-OR) antagonist for the treatment of opioid-induced bowel dysfunction: results from a randomized, double-blind, placebo-controlled, dose-finding study in subjects taking opioids for chronic non-cancer pain. *Pain* 2008; **137**: 428–40.
22 Webster L, Dhar S, Eldon M, Masuoka L, Lappalainen J, Sostek M. A phase 2, double-blind, randomized, placebo-controlled, dose-escalation e_k; study to evaluate the efficacy, safety, and tolerability of naloxegol in patients with opioid-induced constipation. *Pain* 2013; **154**: 1542–50.
23 Thomas J, Karver S, Cooney GA *et al*. Methylnaltrexone for opioid-induced constipation in advanced illness. *N. Engl. J. Med.* 2008; **358**: 2332–43.
24 Slatkin N, Thomas J, Lipman AG *et al*. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. *J. Support Oncol.* 2009; **7**: 39–46.
25 Singla NK, Techner LM, Gabriel K, Mangano R. CB-5945 0.25 mg twice daily is associated with significantly increased spontaneous bowel movement and greater proportion of responders compared with placebo in patients on chronic opioid therapy for noncancer pain (45CL242; NCT01207427). *Gastroenterology* 2012; **143**: e26–7.
26 Ross V, Yu-Ping L, Ullrich S, Neil S, Lynn W, Daniel C. Phase 2b evaluation of TD-1211 in opioid-induced constipation. American Academy of Pain Management, 2012 Annual Clinical Meeting. Phoenix, AZ American Academy of Pain Management, 2012.
27 Rauck R, Slatkin NE, Stambler N, Harper JR, Israel RJ. Randomized, double-blind trial of oral methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic noncancer pain. *Pain Pract.* 2017; **17**: 820–8.
28 Paulson DM, Kennedy DT, Donovick RA *et al*. Alvimopan: an oral, peripherally acting, μ-opioid receptor antagonist for the treatment of opioid-induced bowel dysfunction—a 21-day treatment-randomized clinical trial. *J. Pain.* 2005; **6**: 184–92.
29 Michna E, Blonsky ER, Schulman S *et al*. Subcutaneous methylnaltrexone for treatment of opioid-induced constipation in patients with chronic, nonmalignant pain: a randomized controlled study. *J. Pain.* 2011; **12**: 554–62.
30 Lynn WS, Yamada AT, Jyotsna R, Yuko B, Juan C, Arjona F. Long-term safety and efficacy of naldemedine for the treatment of opioid-induced constipation in subjects with chronic non-cancer pain receiving opioid therapy: results from a 52-week phase 3 clinical trial in PAINWeek Abstract Book 2016. *Postgrad. Med.* 2016; **128**.
31 Jansen JP, Lorch D, Langan J *et al*. A randomized, placebo-controlled phase 3 trial (study sb-767905/012) of alvimopan for opioid-induced bowel dysfunction in patients with non-cancer pain. *J. Pain.* 2011; **12**: 185–93.
32 Irving G, Pénzes J, Ramjattan B *et al*. A randomized, placebo-controlled phase 3 trial (study sb-767905/013) of alvimopan for opioid-induced bowel dysfunction in patients with non-cancer pain. *J. Pain.* 2011; **12**: 175–84.

33 Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. *N. Engl. J. Med.* 2014; **370**: 2387–96.
34 Bull J, Wellman CV, Israel RJ, Barrett AC, Paterson C, Forbes WP. Fixed-dose subcutaneous methylnaltrexone in patients with advanced illness and opioid-induced constipation: results of a randomized, placebo-controlled study and open-label extension. *J. Palliat. Med.* 2015; **18**: 593–600.
35 Anissian L, Schwartz HW, Vincent K *et al*. Subcutaneous methylnaltrexone for treatment of acute opioid-induced constipation: phase 2 study in rehabilitation after orthopedic surgery. *J. Hosp. Med.* 2012; **7**: 67–72.
36 Efficacy and Safety Study of CB-5945 for the Treatment of Opioid-Induced Constipation. https://ClinicalTrials.gov/show/NCT01901302.
37 The Efficacy and Safety Study of CB-5945 for the Treatment of Opioid-Induced Constipation. https://ClinicalTrials.gov/show/NCT01901341.
38 Safety Study of CB-5945 for the Treatment of Opioid-Induced Constipation. https://ClinicalTrials.gov/show/NCT01696643.
39 Vickery R, Li YP, Kohler R, Webster L, Singla N, Daniels O. TD-1211 demonstrates constipation-relieving effects, including decrease in rescue laxative use, in patients with opioid-induced constipation 2011 ACG presidential poster. *Am. J. Gastroenterol.* 2011; **106**: S513–4.
40 Roenn J., Tack J., Barker P., Lowe E., Fleischmann CMS. Challenges in patient recruitment during KODIAC-06, a randomized, placebo-controlled, multicentre, phase III trial of naloxegol in patients with neoplasia and opioid-induced constipation (OIC). *MASCC/ISOO International Symposium on Supportive Care in Cancer*. Berlin, Germany: Support Care Cancer 2013.
41 Schmier JK, Palmer CS, Flood EM, Gourlay G. Utility assessments of opioid treatment for chronic pain. *Pain. Med.* 2002; **3**: 218–30.
42 Mathew B, Lennon FE, Siegler J *et al*. The novel role of the mu opioid receptor in lung cancer progression: a laboratory investigation. *Anesth. Analg.* 2011; **112**: 558–67.
43 Janku F, Johnson LK, Karp DD, Atkins JT, Singleton PA, Moss J. Treatment with methylnaltrexone is associated with increased survival in patients with advanced cancer. *Ann. Oncol.* 2016; **27**: 2032–8.
44 Nee J, Zakari M, Sugarman MA *et al*. Efficacy of treatments for opioid-induced constipation: a systematic review and meta-analysis. *Clin. Gastroenterol. Hepatol.* 2018.
45 Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). *Pain. Med.* 2009; **10**: 35–42.
46 Coyne KS, LoCasale RJ, Datto CJ, Sexton CC, Yeomans K, Tack J. Opioid-induced constipation in patients with chronic noncancer pain in the USA, Canada, Germany, and the UK: descriptive analysis of baseline patient-reported outcomes and retrospective chart review. *Clinicoecon. Outcomes Res.* 2014; **6**: 269–81.
47 Hjalte F, Berggren AC, Bergendahl H, Hjortsberg C. The direct and indirect costs of opioid-induced constipation. *J. Pain. Symptom Manage* 2010; **40**: 696–703.
48 Mehta N, O'Connell K, Giambrone GP, Baqai A, Diwan S. Efficacy of methylnaltrexone for the treatment of opiod-induced constipation: a meta-analysis and systematic review. *Postgrad. Med.* 2016; **128**: 282–9.
49 Lawson R, Ryan J, King F, Goh JW, Tichy E, Marsh K. Cost effectiveness of naloxegol for opioid-induced constipation in the UK. *Pharmacoeconomics* 2017; **35**: 225–35.
50 Food and Drug Administration Center for Drug Evaluation and Research (2008)
51 Delaney CP, Craver C, Gibbons MM *et al*. Evaluation of clinical outcomes with alvimopan in clinical practice: a national matched-cohort study in patients undergoing bowel resection. *Ann. Surg.* 2012; **255**: 731–8.
52 Delaney CP, Wolff BG, Viscusi ER *et al*. Alvimopan, for postoperative ileus following bowel resection: a pooled analysis of phase III studies. *Ann. Surg.* 2007; **245**: 355–63.
53 White WB, Kowey P, Diva U, Sostek M, Tummala R. Cardiovascular safety of the selective μ-opioid receptor antagonist naloxegol: a novel therapy for opioid-induced constipation. *J. Cardiovasc. Pharmacol. Ther.* 2018; **23**: 309–17.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Funnel plot.
Figure S2. (a) Adverse events in diarrhea.
Figure S2. (b) Adverse events in abdominal pain.
Figure S2. (c) Adverse events in vomiting.
Figure S2. (d) Adverse events in flatulence.
Figure S2. (e) Adverse events in nausea.