Systematic Review and Meta-Analysis

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Efficacy of opioid receptor modulators in patients with irritable bowel syndrome

A systematic review and meta-analysis

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Abstract

Background: While irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal diseases in clinical practice, it has diverse pathogenesis. Because of its sudden and lingering intractable symptoms, it seriously affects patients work and life. Opioid receptors are G protein-coupled receptors distributed across the brain, spinal cord, skin, and gastrointestinal tract, and each of the subtypes has a unique role and specific distribution. They play a role in regulating gastrointestinal motility, secretion, and visceral sensations in the gastrointestinal tract. Therefore, this meta-analysis aims to evaluate the effects of opioid receptor modulators on improving the symptoms of IBS.

Methods: Searching the key words (Irritable Bowel Syndromes or Syndrome, Irritable Bowel OR Syndromes, Irritable Bowel OR Colon, Irritable OR Irritable Colon OR Colitis, Mucous OR Colitides, Mucous OR Mucous Colitides OR Mucous Colitis) AND (opioid receptor modulators OR eluxadoline OR Viberzi OR asimadoline OR loperamide), a preliminary search on PubMed (English), EMBASE (English), Cochrane Library (English), China National Knowledge Infrastructure Database (CNKI, Chinese), WanFang (Chinese), VIP citation databases (Chinese) and SinoMed (Chinese) databases yielded 1023 papers published in English and Chinese from inception to July 1, 2019. Nine studies were included in the final meta-analysis. Because this is a systematic review and meta-analysis, ethical approval is not necessary.

Results: The random-effects meta-analysis based on these 9 studies and their 4156 patients found that opioid receptor modulators have a statistically significant beneficial effect on IBS global symptoms (RR = 0.85, 95%CI = 0.79–0.92, $P < .01$) and bowel movement frequency (SMD = −1.26, 95%CI = −2.49–−0.04, $P < .05$), and while there was an improvement trend in stool consistency and quality of life, these findings were not statistically significant.

Conclusions: This is the first meta-analysis to examine the use of opioid receptor modulators in IBS, and few adverse events were reported in the available trials. Compared with the control group, eluxadolin has a better effect in improving IBS global symptoms and abdominal pain and has statistical significance and showed a low rate of constipation development in IBS patients in comparison with known effects of other opioid receptor modulators. However, current findings are based on a considerably limited evidence base with marked heterogeneity. Future studies should aim to identify subpopulations of patients with IBS and need to evaluate the long-term safety of these therapies.

PROSPERO registration number: CRD42020141597.

Abbreviations: 5-HT = 5-hydroxy tryptamine, AEs = adverse effects (AEs), BMs = bowel movements, Cis = confidence intervals (CIs), CNS = central nervous system, DOR = δ-opioid receptor, ENS = enteric nervous system, GI = gastrointestinal, IBS = irritable bowel syndrome, IBS-C = constipation-predominant irritable bowel syndrome, IBS-D = diarrhea-predominant irritable bowel syndrome, IBS-M = mixed irritable bowel syndrome, IBS-U = unspecified irritable bowel syndrome, KOR = κ-opioid receptor, MOR

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= μ-opioid receptor, RCTs = randomized controlled trials, RR = relative risk, SMD = standardized mean difference, TCM = Traditional Chinese Medicine.

Keywords: asimadoline, eluxadoline, irritable bowel syndrome, loperamide, opioid receptor modulators, treatment

1. Introduction

Irritable bowel syndrome (IBS) is a common functional bowel disorder characterized by recurrent abdominal pain that is associated with defecation or a change in bowel habits. Typical abnormal bowel habits can be constipation, diarrhea, or a mix of constipation and diarrhea, and symptoms of abdominal bloating/distention. Symptoms occur over at least 6 months and symptoms should be present within the 3 months prior to diagnosis.[1] According to the Rome IV criteria, based on the proportion of abnormal bowel movements (BMs) that were loose/watery or hard/lumpy, IBS can be subdivided into constipation-predominant (IBS-C), diarrhea-predominant (IBS-D), mixed (IBS-M), and unspecified (IBS-U) subtypes.[2] The global prevalence of this disease is approximately 1.1% to 35.5% in the population,[3] and it places an enormous financial burden on society in addition to an increased consumption of health-related resources.[4] The pathogenesis and etiology of IBS have not been fully identified. Most scholars believe that it is related to abnormal gastrointestinal motility, visceral hypersensitivity, intestinal infection and inflammation, disorders of the gut microbiota, psychosocial factors and destruction of the intestinal mucosal barrier.[5,6]

Current management of IBS includes lifestyle modification, antispasmodics and peppermint oil, interventions that modify the microbiota (antibiotics, probiotics, prebiotics and synbiotics), selective 5-hydroxy tryptamine (5-HT) receptor modulators, colonic secretagogues, antidepressants and opioid-receptor modulator, Traditional Chinese Medicine (TCM) also plays a therapeutic role as a complementary therapy. Lifestyle modification is a popular starting point in the management of IBS, and antispasmodics remain first-line therapy for abdominal pain in patients with IBS.[4,7,8] However, the therapeutic margin over placebo in IBS for both rifaximin and probiotics remains limited, and severe constipation and ischemic colitis have been reported with antagonism at 5-HT3 receptors. There remains a major unmet need for treatments that control both visceral hypersensitivity and disordered gastrointestinal (GI) motility in IBS patients. Opioid receptor modulators can modulate GI motility, which directly affects visceral hypersensitivity and stool patterns. High density of opioid receptors in the gastrointestinal tract and their participation in the maintenance of gastrointestinal homeostasis make opioid receptors ligands an attractive option for developing new anti-IBS treatments.[9]

Opioid receptors are G protein-coupled receptors distributed across the brain, spinal cord, skin, and GI tract. Mu, kappa, and delta (μ, κ and δ) are all subtypes of opioid receptors, although each of them has a unique role and specific distribution.[10,11] Opioid receptors in the GI tract are localized to enteric neurons, interstitial cells of Cajal, and immune cells. They play a role in regulating GI motility, secretion, and visceral sensation. In humans, μ-opioid receptor (MOR), δ-opioid receptor (DOR), and κ-opioid receptor (KOR) link to inhibiting acetylcholine released from enteric neurons and motor neurons and purine/nitric oxide released from inhibitory motor neurons, thereby inhibiting advancing motor patterns.[12,13] Once released from enteric neurons, opioid peptides modify GI function acting via opioid receptors on the enteric circuitries controlling motility and secretion. So it is important to study this opioid receptors and opioid receptor modulators.[14]

Loperamide is a peripheral MOR agonist with well-defined antisecretory properties. It has been used in acute and chronic diarrhea for more than thirty years, because it has the ability to inhibit gastrointestinal motility and secretion.[15] Loperamide actives MOR to decrease gastrointestinal motility and increase the duration of enteral transit, which promotes fluid absorption and reduces stool frequency.[16] Asimadoline is a diarylacetamide KOR agonist with high affinity and selectivity.[17] In animal models, KOR reduces visceral pain responses to colonic distension through peripheral action.[18,19] In preliminary clinical studies, asimadoline has been shown to have good bioavailability and safety profiles in humans. Compared to placebo, asimadoline significantly reduced patients pain symptoms. Eluxadoline is a peripherally acting MOR and KOR agonist and DOR antagonist with low oral bioavailability and systemic absorption.[20] It acts locally at the enteric nervous system and the gut mucosa. Local MOR agonism reduces colonic secretions and slows GI transit, while DOR antagonism can prevents excessive constipation by counteractings excessive MOR inhibition. This finding suggests that eluxadoline can normalize GI motility with a decreased risk of constipation. In addition, concomitant use of these 3 opioid modulators have been shown to have synergistic analgesic effects, which may help reduce abdominal discomfort in patients with IBS.[21]

Recently, several clinical trials from when eluxadoline was a newly FDA-approved drug have been published. Through literatures review, we have found that there is no meta-analysis has yet been done to investigate the efficacy and side effects of eluxadoline and other 2 commonly used opioid receptor modulators, loperamide and asimadoline in the treatment of IBS. We have therefore examined this issue and conducted this systematic review and meta-analysis.

This systematic review and meta-analysis shows that these 3 modulators could improve IBS global symptoms and quality of life, reduce bowel movement frequency of IBS patients. Based only on the results of this review, eluxadoline was better in improving abdominal pain and bowel movement frequency, and it also can normalize GI motility with a decreased risk of constipation.

2. Methods

2.1. Search strategy

A comprehensive search of the medical literature was conducted using the following electronic databases: PubMed (English), EMBASE (English), Cochrane Library (English), China National Knowledge Infrastructure Database (CNKI, Chinese), WanFang (Chinese), VIP citation databases (Chinese) and SinoMed (Chinese) databases were searched for randomized controlled trials (RCTs) from inception to July 1, 2019. In addition,

abstracts presented at annual meetings of gastroenterological societies were searched for eligibility. The searches were limited to the English and Chinese languages. Medical subject headings for our literature review were as follows: (Irritable Bowel Syndromes or Syndrome, Irritable Bowel OR Syndromes, Irritable Bowel OR Colon, Irritable OR Irritable Colon OR Colitis, Mucous OR Colitides, Mucous OR Mucous Colitides OR Mucous Colitis) AND (opioid receptor modulators OR eluxadoline OR Viberzi OR asimadoline OR loperamide).

2.2. Study selection and data extraction

The included studies were selected based on PICOS eligibility criteria. The following inclusion criteria were required to be eligible for the meta-analysis:

1. a clinical RCT study in which the experimental group used the target drugs;
2. a study conducted in participants aged 16 years or older;
3. diagnosis of IBS based on either a clinicians opinion, or meeting symptom-based criteria (Manning, Kruis, Rome I, II, III, or IV);
4. the control group could not use any of the target drugs; and
5. duration of therapy >2 weeks.

The exclusion criteria were:

1. studies were not RCT;
2. do not meet the diagnostic criteria for IBS;
3. treatment group combined with other drugs;
4. data in studies could not be extracted.

All included studies were extracted independently by 2 reviewers (XL and BL) on to a Microsoft Excel spreadsheet. Disagreements were discussed and decided with the help of a third reviewer (JM). For each trial, the following clinical data were extracted: the year of publication, researchers names, sample size and number of each group, study population characteristics (recruitment area, age, gender), criteria used to define IBS, duration and dose of therapy, primary and secondary outcome measures used to define response to therapy, and adverse effects.

2.3. Outcome assessment

The primary outcomes of the assessment were the effects of opioid receptor modulators (loperamide, asimadoline, eluxadoline) on global IBS symptoms or abdominal pain after cessation of therapy or the effect on overall response to therapy for IBS compared to placebo. Secondary outcomes included the effect of opioid receptor modulators on bowel movement frequency and stool consistency scores. We also reviewed the adverse effects.

2.4. Assessment of risk of bias

Risk of bias was assessed according to the Cochrane Collaborations Tool for Assessing Risk of Bias (ROB Table).[22] This scale assesses each study as follows: random sequence generation, distribution methods, participant blindness, blindness of outcome evaluation, incomplete outcome data, selective reporting, and other biases. The risk of bias is judged to be "high risk," "low risk," or "unclear risk", and the assessment results are represented by a bias risk map. Using the grading of recommendations assessment, development and evaluation (GRADE) system to evaluate the quality of evidence, we divided the study quality into high, medium and low to represent the reliability and credibility of the evidence.[23]

2.5. Data synthesis and statistical analysis

The data were pooled using a random effects model to estimate of the effect of opioid receptor modulators and, allowing for any heterogeneity between studies. As mentioned above, response to treatment was assessed through various endpoints. The therapeutic effect in IBS was expressed as a relative risk (RR) of persisting IBS symptoms or abdominal pain in the intervention group compared with the control group, standardized mean difference (SMD) in global IBS symptoms and abdominal pain / bloating scores, and IBS-QOL scores at the end of study, all with 95% confidence intervals (CIs).

Heterogeneity between studies was assessed by using the I^2 statistic and Q test to evaluate the size of heterogeneity. $I^2 > 50\%$ indicates substantial heterogeneity. The data extracted from the study were analyzed by RevMan 5.2 (Review Manager (RevMan) [Computer program]. Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.) to generate forest plots for primary and secondary outcomes and sensitivity analysis by removing individual research reports and assessing their impact on overall results.

3. Results

A total of 1023 related citations were searched in this system analysis including PubMed (n=71), EMBASE (n=456), Cochrane Library (n=92), CNKI (n=42), WanFang (n=85), VIP citation databases (n=32) and SinoMed (n=245). After excluding duplicates and reading titles, abstracts, and full text, 8 full articles and 1 conference abstract were included in the meta-analysis (Fig. 1). There were 4 trials of loperamide,[24–27] 2 of asimadoline,[28,29] and 3 trials of eluxadoline.[30–32]

3.1. Study characteristic

A total of 4184 patients in the 9 studies were included in this article. The proportion of women ranged from 37.8% to 100%, and the age range was 18 to 80. One of the included studies was a randomized crossover trial,[27] 2 studies selected only available patients for inclusion,[25,26] and in 3 studies, patients in the experiment groups were randomly assigned to receive different doses;[29–31] details are shown in Table 1.

3.2. Outcomes

3.2.1. Primary outcome: effect on persistence of global IBS symptoms or abdominal pain. Eight studies compared the effects of opioid receptor modulators and placebo on IBS symptoms; these studies included 14 comparisons and 4156 patients.[24–26,28–32] Because these 3 studies used different doses, therefore, the outcome data of different doses were combined in each study.[29–31] Overall, 1951 (68.8%) of 2834 patients who received the opioid receptor modulators had persistent symptoms, compared with 1034 (78.2%) of 1322 patients who received placebo. The RR of effect on persistence of global IBS symptoms or abdominal pain after treatment with opioid receptor modulators vs. placebo was 0.85 (95%CI=0.79–0.92); therefore, opioid receptor modulators were associated with improvement in global IBS symptoms compared with

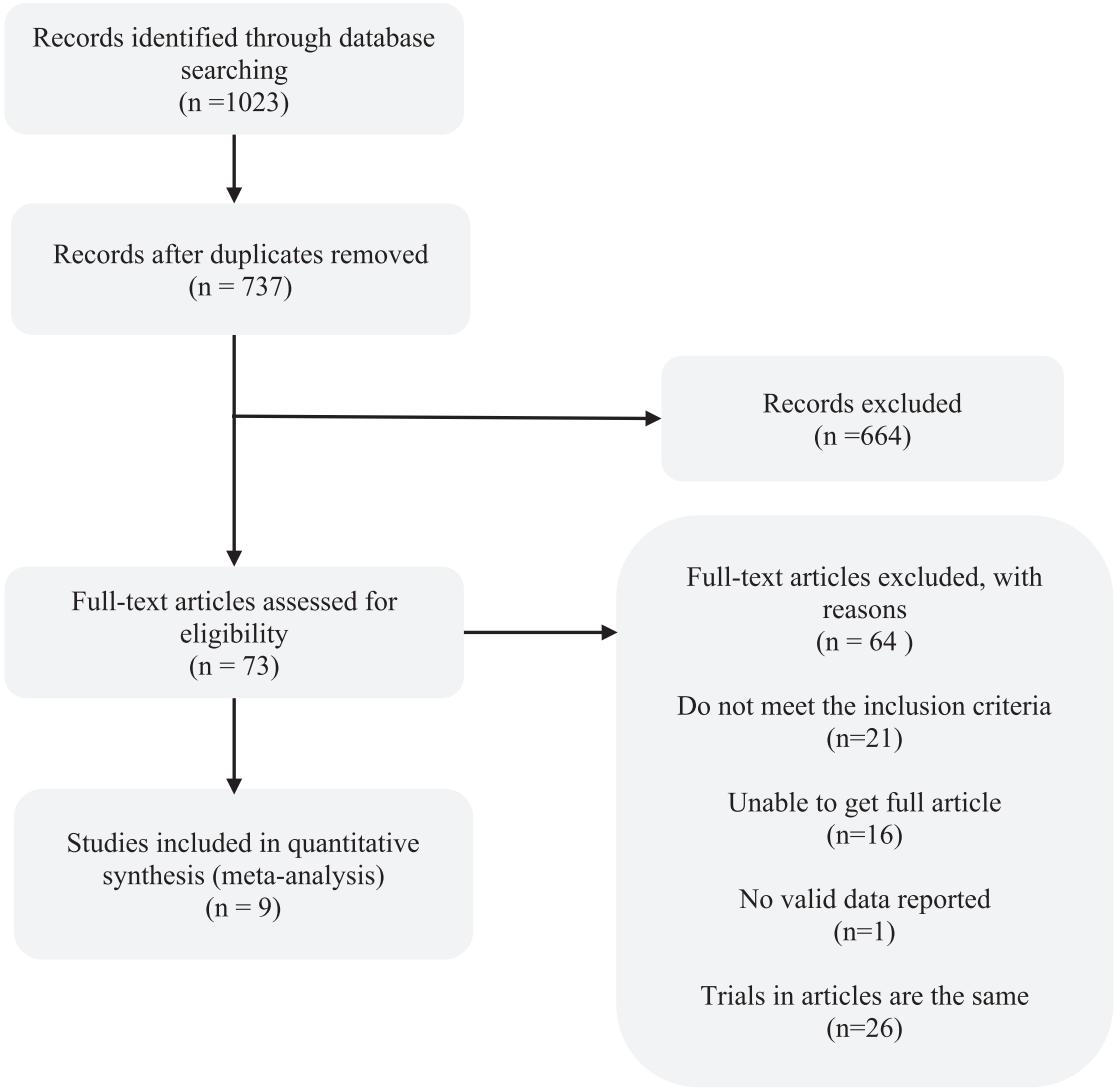

Figure 1. Flow diagram of assessment of studies identified in the updated systematic review and meta-analysis.

placebo ($P < .01$ from random effects). Moderate heterogeneity was identified across the studies ($I^2 = 43\%$, $P = .09$) (Fig. 2). A funnel plot analysis revealed evidence of asymmetry (Fig. 3). Heterogeneity analysis will be conducted in the discussion section.

In the 3 studies that assessed loperamide,[24–26] 6 (12.5%) of 48 patients who received loperamide reported persistent symptoms compared with 15 (44.1%) of 34 in the placebo group (RR = 0.43, 95%CI = 0.18–1.07), with no significant improvement between loperamide and the placebo group ($P > .05$). Mild heterogeneity was identified across the studies ($I^2 = 25\%$, $P = .26$). Two studies assessed asimadoline.[28,29] A. W. Mangel et al[29] randomly assigned patients to receive asimadoline 0.15 mg (n = 113), 0.5 mg (n = 117), 1.0 mg (n = 114) and placebo (n = 107). Two hundred fourteen (53.0%) of the 404 patients in the asimadoline groups vs 100 (68.0%) of 147 patients in the placebo group reported persistence of symptoms (RR = 0.84, 95%CI = 0.63–1.10), with no significant improvement ($P > .05$) between the 2 groups and high heterogeneity ($I^2 = 67\%$, $P = .08$). Three studies assessed eluxadoline,[30–32] and in 2 of these studies used different does in experiment group, eluxadoline 75 mg (n = 806), 100 mg (n = 809), and placebo (n = 808) in Anthony J. Lembo study,[31] eluxadoline 5 mg (n = 105), 25 mg (n = 167) 100 mg (n = 163) 200 mg (n = 160) in Leonard S. dove study.[30] For the eluxadoline group, 1731 (72.7%) of 2382 patients reported persistent symptoms compared with 919 (80.5%) of 1141 in the placebo groups (RR = 0.88, 95%CI = 0.85–0.91). There was, significant improvement between the eluxadoline and placebo groups ($P < .01$), although there was no heterogeneity identified across the studies ($I^2 = 0\%$, $P = .43$).

3.2.2. Secondary outcomes: bowel movement frequency, stool consistency scores and IBS-QOL scores. Three studies examined bowel movement frequency, these studies, used loperamide, asimadoline and eluxadoline separately and included a total of 2579 patients.[27,28,31] There was a statistically significant effect of opioid receptor modulators in reducing bowel movement frequency (SMD = −1.26, 95%CI = −2.49–−0.04, $P = .04$), while high heterogeneity was identified across the studies ($I^2 = 97\%$, $P < .01$) (Fig. 4). Two studies assessed stool

Table 1

GRADE summary of findings table.

Author, Year	Sample number(female)	Study design	Area	Treatment of the experiment and control group	Diagnosis cartier	Criteria used to define symptom improvement following therapy
A.W. Mangel 2008	451 (unknow)	Randomized, parallel-group, double-blind tial. Random method has described	the U.S.	Asimadoline, 0.15 or 0.5 or 1.0 mg bid, 12 weeks VS Placebo	Rome II	Adequate relief of IBS symptoms ("In the past 7 days have you had adequate relief of your IBS symptoms?") reported for all 3 months, monthly and weekly
AnthonyJ.Lembo 2016	2423 (1606)	Randomized, double-blind, parallel-group, multicenter study. Random method has described	the U.S., Canada, the U.K.	Eluxadoline, 75 mg or 100 mg bid, 12weeks VS Placebo	Rome III	FDA responders: patients who recorded on ≥50% of the days a reduction of ≥30% from their average baseline score for their worst abdominal pain and, on the same days, a stool-consistency score of < 5
Bengt Lavo 1987	16 (13)	Randomized, parallel-group, double-blind study. Random method not described	Sweden	Loperamide, 2–8 mg nocte, 13weeks VS Placebo	Based on symptoms and clinician's opinion	Responders who recorded better for the symptoms stool consistency, urgency, pain and over-all response.
Delvaux M.Brenner 2018	346 (unknow)	Randomized, double-blind, parallel-group, multicenter study. Random method not described	the U.S.	Eluxadoline, 100 mg bid, 12weeks VS Placebo	unknow	FDA responders: Patients who achieving ≥30% improvements in WAP score from baseline for ≥50% of treatment days were calculated for the 12-week treatment period
Lawrence A. Szarka 2007	100 (100)	Randomized, parallel-group, double-blind tial. Random method not described	the U.S.	Asimadoline, 0.5 mg-1.0 mg qid, 4 weeks VS Placebo	Rome II	Adequate relief on more than 50% of days with pain.
Leonard S.Dove 2013	807(565)	Randomized, parallel-group, double-blind tial. Random method has described	the U.S.	Eluxadoline, 5 mg or 25 mg or 100 mg or 200 mg bid, 12 weeks VS Placebo	Rome III	FDA responders: if on at least 50% of days during the 12 weeks of the study their daily WAP score was reduced from baseline by ≥30% and they had either a daily Bristol Stool Scale score <5 or reported no bowel movement
Nils Hovdenak 1987	21 (unknow)	Randomized, parallel-group, double-blind study. Random method not described	Norway	Loperamide, 4 mg nocte, 3 weeks VS Placebo	Based on symptoms and clinicians opinion with alternating bowel habits with colicky pain	Patients were asked to evaluate the effect of the treatment on stool frequency, stool consistency, abdominal distension, colicky pain, and overall symptoms at the end of the treatment
P.A. Cann 1984	28 (21)	Double-blind, cross-over trial. Random method not described	England	Loperamide, 2 mg qd-2 mg tid, 5 weeks VS Placebo	Based on symptoms and clinician's opinion	Patients were asked to rate each of 11 symptoms in terms of severity used scores to assess.
Zhang 1995	45 (17)	Randomized, parallel-group trial. Random method not described	China	Loperamide, 2 mg qd, 2 weeks VS Lomotil	Based on symptoms and clinicians opinion	The number of bowel movements is 1 to 2 times per day, abdominal pain symptoms basically disappeared or daily bowel movements is reduced by half or more, the stool is basically formed, the mucus is basically disappeared, and the abdominal pain is significantly improved.

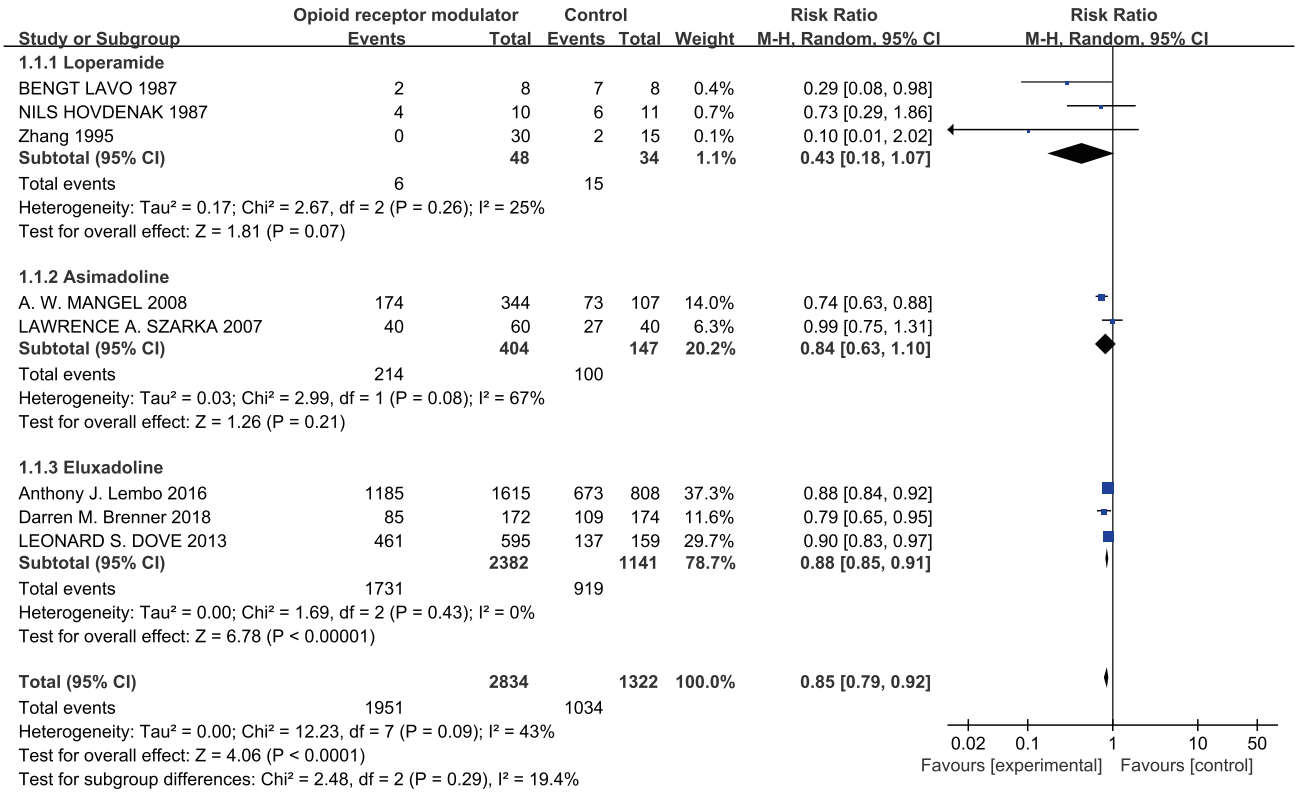

Figure 2. Forest plot of randomized controlled trials of opioid receptor modulators vs. placebo in irritable bowel syndrome (IBS): effect on persistence of IBS global symptoms and abdominal pain.

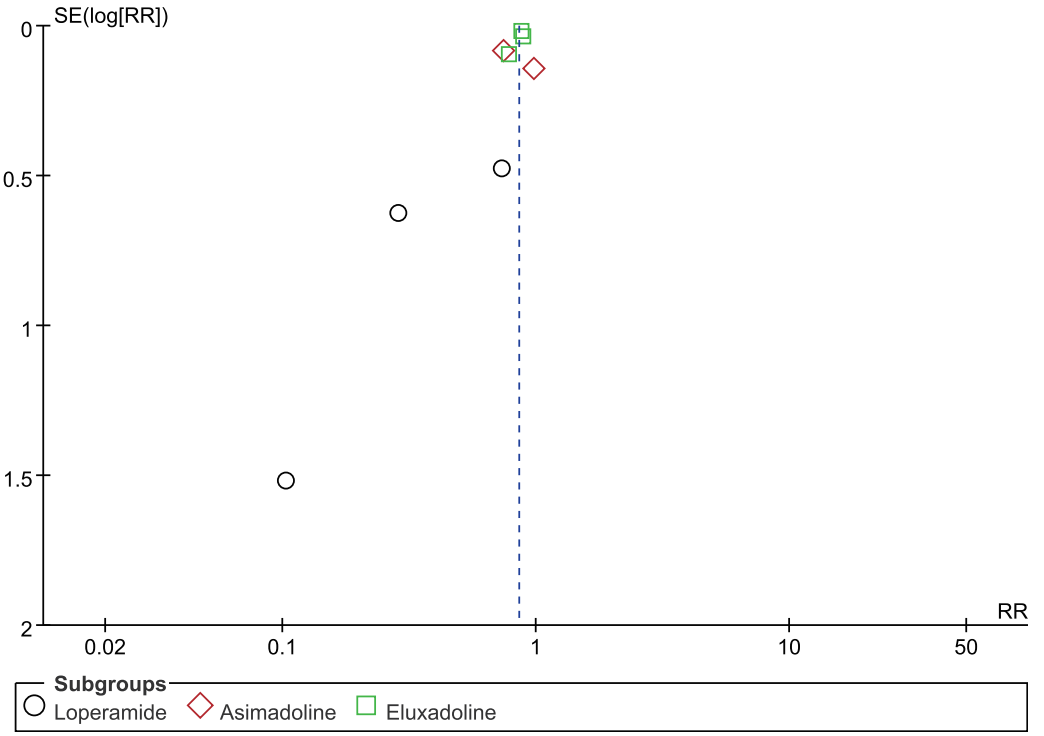

Figure 3. Funnel plot of randomized controlled trials of opioid receptor modulators vs. placebo in irritable bowel syndrome (IBS): effect on persistence of IBS global symptoms and abdominal.

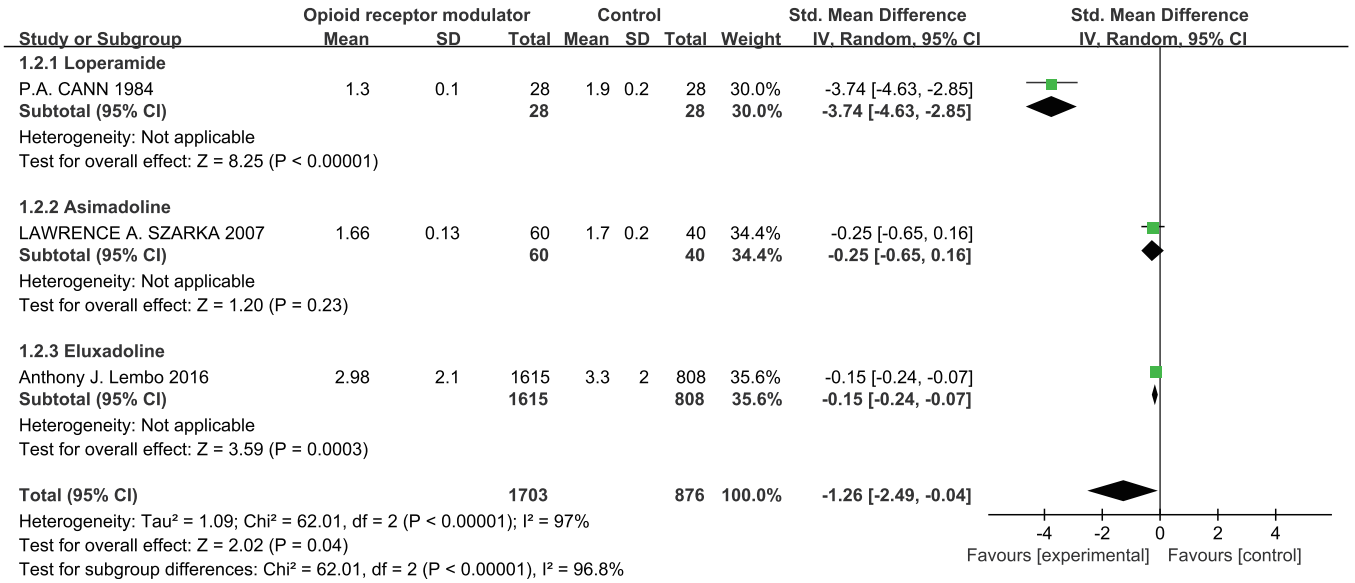

Figure 4. Forest plot of randomized controlled trials of opioid receptor modulators vs. placebo in irritable bowel syndrome (IBS): effect on bowel movement frequency.

consistency scores in 2523 patients. One study used asimadoline[28] and the other used eluxadoline.[31] Pooled estimates showed there was no significant difference between opioid receptor modulators and placebo (SMD = 0.87, 95%CI = −1.37–3.11, $P = .45$); again, these studies were found to have high heterogeneity ($I^2 = 99\%$, $P < .01$) (Fig. 5). A total of 2 studies assessed IBS-QOL or anxiety scores in 3 comparisons including a total of 2523 patients; one study used asimadoline[28] and the other used eluxadoline[31]. Both studies have shown that opioid receptor modulators have an improved effect on patients quality of life and anxiety compared with control group. Heterogeneity analysis will be conducted in the discussion section.

3.3. Adverse effects (AEs)

Accurate AE data were obtained in 6 studies.[24,25,28–31] The most frequent AEs of loperamide was constipation which occurred in both studies including 6 patients.[24,25] A.W. Mangel et al reported the most frequent AEs of asimadoline were diarrhea, abdominal pain, nausea and vomiting.[29] Lawrence A. Szarka reported effects on the central and peripheral nervous systems and the respiratory tract, as well as gastrointestinal symptoms, but these AEs were also reported in the placebo group.[28] The most frequent AEs of eluxadoline were nausea, constipation, abdominal pain and vomiting in 2 studies[30,31] and patients in the 200 mg eluxadoline group reported higher rates of severe adverse events leading to discontinuation. There are 3 studies describing the duration of adverse reactions, Zhang[24] reported that 5 cases of mild constipation occurred in the loperamide group, but disappeared after entering maintenance treatment. P.A. Cann[27] reported that patients in the loperamide and placebo groups only developed symptoms of constipation during treatment, and disappeared after stopping treatment. Leonard S. Dove[30] reported 2 cases treatment with 200 mg eluxadoline occurred within the first 2 doses of study medication and resolved rapidly without sequelae. None of the studies describe longer AEs.

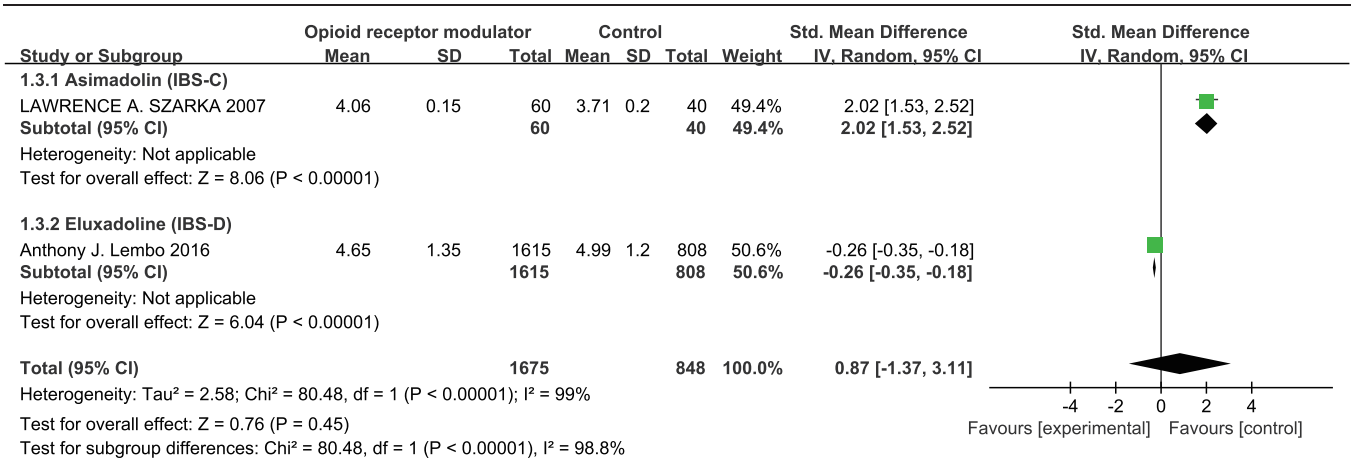

Figure 5. Forest plot of randomized controlled trials of opioid receptor modulators vs. placebo in irritable bowel syndrome (IBS): effect on stool consistency.

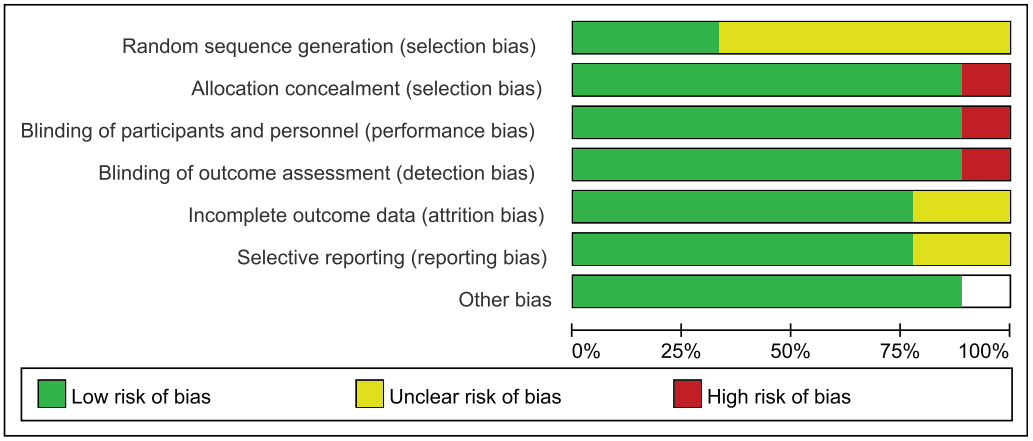

Figure 6. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

3.4. Bias risk assessment

Figures 6 and 7 summarizes the risk of bias across studies. The quality of most of the studies was relatively high. Most studies have mentioned the use of random allocation, although most of them did not detail their randomization methods. Among them, Zhang et al[24] did not use blinded methods, but they rather used a random, open control study design. Accurate values were not obtained in studies by Lavo B et al[25] and Hovdenak N et al.[26] We obtained data from the figures in these 2 studies by used the software Engauge Digitizer ([Computer program]. Version 10.9, Mark Mitchell, 2014).

The quality of the evidence related to the effect on persistence of global IBS symptoms or abdominal pain is moderate because of the publication bias. The quality of evidence for bowel movement frequency, stool consistency was moderate, because of the inconsistency, details related to the evidence quality are shown in Table 2.

4. Discussion

This systematic review and meta-analysis has demonstrated that there is moderate confidence that opioid receptor modulators are effective in improving global IBS symptoms or abdominal pain compared with placebo. There was also a trend towards a beneficial effect of bowel movement frequency, stool consistency and quality of life. Most studies included in this analysis were carefully planned and executed, and provided appropriate protection against biases.

The risk of selection bias of many of the trials that we identified was unclear because the studies did not describe how they implemented randomization and blinding, and there was evidence of heterogeneity between RCTs in some of our analyzes. Heterogeneity was moderate in the primary outcome indicators. Heterogeneity causes from different doses of different drugs. The effect of using 0.5 mg asimadoline was better than other doses of the medication,[29] the persistent percent is 37.6%, lower than all the other experiment groups. The effect of using 5 mg eluxadoline was poor.[30] The persistent percent is 86.7%, higher than all the other experiment groups. After excluding these 2 studies, the overall heterogeneity decreased. In the study by Anthony J. Lembo et al,[31] 2 trials were performed, each using 75 mg and 100 mg doses; the 100 mg dose performed better than the 75 mg dose both in improving IBS global symptoms and abdominal pain, but there was no significant difference. There was high heterogeneity in the assessment of stool consistency scores. After analyzing these 2 studies,[28,31] it was found that the stool

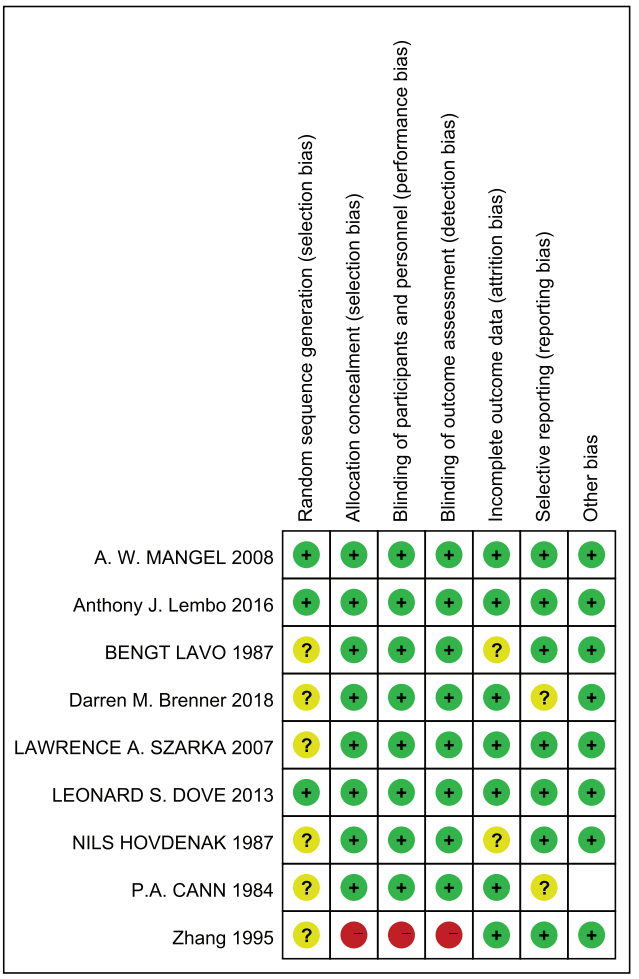

Figure 7. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Table 2

Characteristics of randomized controlled trials of opioid receptor modulators vs placebo in irritable bowel syndrome.

Opioid receptor modulators compared to placebo for Irritable bowel syndrome						
Patient or population: patients with Irritable bowel syndrome Settings: Intervention: Opioid receptor modulators Comparison: placebo						
	Illustrative comparative risks* (95% CI)					
Outcomes	Assumed risk Placebo	Corresponding risk Opioid receptor modulators	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Effect on persistence of global IBS symptoms or abdominal pain		Study population	RR 0.86 (0.81 to 0.92)	5656 (8 studies)	⊕⊕⊕⊖ moderate[1]	⊕⊕⊕⊖
	803 per 1000	690 per 1000 (650 to 738) Moderate				
	758 per 1000	652 per 1000 (614 to 697)				
Bowel movement frequency		The mean bowel movement frequency in the intervention groups was 0.16 standard deviations lower (0.22 to 0.09 lower)		3332 (2 studies)	⊕⊕⊕⊖ moderate[2]	SMD -0.16 (-0.22 to -0.09)
Stool consistency		The mean stool consistency in the intervention groups was 0.36 standard deviations higher (0.15 lower to 0.88 higher)		3332 (2 studies)	⊕⊕⊕⊖ moderate[3]	SMD 0.36 (-0.15 to 0.88)

* The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI = Confidence interval; RR = Risk ratio.

GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

[1]Small sample studies deviate from invalid lines in funnel plots $^{2}I^{2}$ = 95%, suggested the high heterogeneity $^{3}I^{2}$ = 98%, suggested the high heterogeneity.

consistency scores of the experimental group were both close to normal stool characteristics, which was improved compared with before treatment. The control group of one[28] the studies reported dry stools (IBS-C) and the other[31] reported loose stools (IBS-D), therefore creating the resultant heterogeneity. The improvement in bowel movement frequency using loperamide vs placebo was significantly better than the other 2 comparator treatments. When this study was removed, there was no heterogeneity overall. Similarly, we also found that in the studies that included loperamide,[25,26] asimadoline[29] or eluxadoline,[30] there was improvement in bowel movement frequency and stool consistency, compared with placebo. In the IBS-QOL assessment, there was a trend that patients in the experiment group are better than those in the control group. Anthony J. Lembo et al[31] suggested that both doses of eluxadoline were significantly superior to placebo with respect to the scores on the IBS-QOL, and the endpoint scores is higher than baseline (meaning the higher the score, the better the quality of life); Lawrence A. Szarka et al,[28] however suggested that there was a trend towards better effect on IBS-QOL, but no significant effect existed between the asimadoline and placebo groups and the endpoint scores were lower than baseline (meaning that the lower the score, the better the quality of life).

Opioid receptors, present in the central nervous system (CNS) and the enteric nervous system (ENS), are involved in visceral sensitivity and gastrointestinal motility control.[9] Enteric neurons synthesize and release opioid peptides as neurotransmitters next to other neurotransmitters as ace-tylcholine, substance P, and vasoactive intestinal peptide. Amongst these are met-enkephalin, leu-enkephalin, b-endorphin and dynorphin, all endogenous opioids. These play a major regulatory role in gastrointestinal signaling, causing changes in motility, secretion and transport of fluids and electrolytes.[33] Opioid receptor modulators can change the secretion of opioid by binding to opioid receptors, used for the management of patients with abdominal pain, abdominal distension, and changes in bowel habits, and improve patients quality of life.

Loperamide is one of the first-line treatments, known to be effective for chronic diarrhea and urgency, and its response in terms of stool consistency in the included studies was excellent. Studies of loperamide have shown a decrease in diarrhea but a minimal effect on abdominal pain, and patients with constipation generally do not benefit from this therapy.[25,27,34] Loperamide treats IBS through its effect on motor activity with little or no stimulation of fluid absorption.[35,36] Hovdenak N et al[26] showed that colic pain, when associated with alternating bowel habits, is significantly improved by loperamide, as are stool frequency and stool consistency. The only symptoms that showed both a clinically and statistically significant response to loperamide over placebo in the included studies were diarrhea and urgency. However, another main symptom of IBS, abdominal distension, was not influenced. In the treatment of these other symptoms, outcomes were similar between loperamide and placebo, and adjusting doses as needed could reduce unwanted symptoms.

Asimadoline has displayed analgesic properties against somatic and visceral pain in several human and animal studies,[36] and it influence peripheral nociceptive reflexes of the gut to reduce sensation in response to gastric and colorectal distension.[37] Asimadoline has been suggested to be suitable for testing for the treatment of visceral pain. Low doses of asimadoline (0.5 mg) can decrease visceral perception in humans without deleterious effects on gut motor functions[38]; this finding is in accordance with animal studies. A pharmacodynamic study suggested that the highest dose of asimadoline tested (1.5 mg) was associated with less relief, as it did not influence perception of nonpainful colonic distension or colonic compliance.[39] Asimadoline did produce improvements in IBS symptoms, however the

treatment showing effectives at 2 to 3 weeks and maintaining the effect thereafter. For IBS-D patients, 0.5 mg was more effective, and for IBS-M patients, 1.0 mg was more effective at improving pain and overall symptoms, especially in patients who had at least moderate pain at baseline. Additionally, 0.5 mg of asimadoline caused no constipation, there were no significant effects on bowel function or any adverse effects to suggest motor effects of asimadoline, at least in individuals with normal bowel function.[28,29] Therefore, after the study of 5 mg was removed and the analysis was performed, the heterogeneity between the groups was greatly reduced.

In animal models, eluxadoline has demonstrated the ability to alter gastrointestinal function; it can normalize fecal output without completely blocking gastrointestinal transit, which differs from loperamide, which is a pure MOR agonist.[40] Eluxadoline also simultaneously relieved the IBS-D symptoms of abdominal pain and diarrhea, and these effects appeared to increase with time on treatment. In both the composite response and the individual symptoms of bowel movement frequency, urgency and quality of life, the response rates at week 12 were all better than at week 4, particularly at the 100 mg twice daily dose. The effect of a low dose of 5 mg was poor, resulting in moderate heterogeneity between groups,[30,31] and the effect of eluxadoline did not rebound significantly during follow-up. Susceptibility to severe AEs increased at a dose of 200 mg leading to withdrawals from the study and the need to exclude patients who may have been predisposed to pancreatitis.

This manuscript discusses these 3 drugs together because they are all modulate opioid secret. Although the types of receptors they bind to are different, their regulatory effects are similar. After opioid receptor modulators binding, recruitment of G-protein receptor kinases, phosphorylation, binding of b-arrestin proteins, endocytosis through inactivation of ADP-ribosylation factor, and recycling at varying rates takes place, makes a range of different effects such as changes in stress response, analgesia, motor activity and autonomic functions,[41] they all play a role in regulating gastrointestinal motility, secretion, and visceral sensation.

Opioid receptor modulators were associated with improvement in global IBS symptoms compared with placebo. In these 3 modulators, according to the analysis results, compared with the control group, although loperamide and asimadolin have a trend of improving IBS global symptoms and abdominal pain, there are not statistically significant. Eluxadoline is a peripherally acting MOR and KOR agonist and DOR antagonist, compared with the control group, it has a better effect in improving IBS global symptoms and abdominal pain and has statistical significance. Because DOR antagonism was found able to increase analgesia derived from MOR agonism, while preventing the development of morphine tolerance and constipation and its safety has been evaluated in the same studies. Eluxadoline showed a low rate of constipation development in IBS patients in comparison with known effects of other opioid receptor modulators. Therefore, Eluxadoline is the best to treat the IBS in this meta-analysis.

A meta-analysis of RCTs of IBS treatments showed that the average placebo response rate was approximately 40% based on various global response criteria, such as patients assessment of subjective responses.[42] In our study, the response rates of the loperamide and asimadoline groups were above 40%. The response rate of the eluxadoline group, however, was approximately 30%, and in the control group, it was only 17.4%, which may have been due to different standards for efficiency. These results proved that opioid receptor modulators had a better effect on IBS symptoms compared to the control group.

A strength of this systematic review and meta-analysis is that there has not previously been any meta-analysis of opioid receptor modulators. Another advantage was the use of rigorous methodology: we reported our search strategy in full, we conducted qualification assessments and data extraction independently, we pooled data with a random effects model to minimize the possibility of overestimating the treatment effect. We collected data on more than 2800 patients with IBS treated with opioid receptor modulators. We performed subgroup analyzes in an attempt to assess the treatment effect according to the different modulators used, and we aggregated the reported adverse event data. The limitations of this systematic review are following: One is that the studies and samples used for this study are too small, because asimadoline and loperamide have been used for a long time, some of retrieved studies were not RCT, no clear data was given and could not be extracted, and some studies did not have specified outcome indicators. Eluxadoline is a new drug that has just been approved by the FDA, and only reports of Phase II, III, and IV clinical trials were retrieved. Finally, we searched all databases and after screening, only 9 articles that met the requirements were included. Another is that conference abstract was included in our manuscript, although it can help us make the data more complete, but it has difficulties in adequately assessing the methodological quality and AEs of the study. The last is that there is no description of duration of AEs and longer AEs in the included studies. Future studies should be aimed at identifying subpopulations of patients with IBS and evaluating the long-term safety of these therapies.

Author contributions

X. L. and B. L. co-conceived research, designed schemes and wrote the article. X. L. was responsible for searching the literature. J. Z. and H. W. supervised the study. T. C. and X. S. contributed to data analysis. J. M. and J. Q. contributed to extracting data. All authors contributed to the manuscript and critical revision of the article and agreed to be responsible for all aspects. F.W. and X.T. were responsible for editing the article.
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