Systematic Review and Meta-Analysis

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Efficacy and safety of pinaverium bromide combined with flupentixol-melitracen for diarrhea-type irritable bowel syndrome

A systematic review and meta-analysis

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Abstract

Background: There are many trials on the combination of Pinaverium bromide (PB) and Flupentixol-melitracen (FM) in the treatment of diarrhea-type irritable bowel syndrome (IBS-D), but the sample sizes are small, and the research conclusions are inconsistent. Thus, a meta-analysis was performed, aiming to evaluate the efficacy and safety of this combination therapy in patients with IBS-D.

Methods: A systematic literature search was conducted in 7 databases covering the period up to July 2018 to identify randomized controlled trials (RCTs) of PB combined with FM versus PB alone for IBS-D. The primary outcome was the total symptom relief rate. The other outcomes were the adverse events rate, HAMA/SAS score, and HAMD/SDS score. The methodological quality of the RCTs was assessed independently using 6 criteria according to the Cochrane Collaboration. All data were analyzed using Review Manager 5.3.

Results: Fifteen RCTs with 1487 participants were identified from 2005 to 2018. Compared with PB alone, 15 RCTs showed significant effects of PB plus FM in terms of improved symptom relief in patients with IBS-D (n = 1487, OR = 5.17, 95%CI, 3.79–7.07, $P < .00001$). Eleven RCTs reported adverse effects in both the PB plus FM and PB groups, there was no statistically significant difference in the adverse events rate between the 2 groups (n = 1207, OR = 2.91, 95%CI, 0.91–9.28, $P = 0.07$). Two RCTs and 3 RCTs reported HAMA and HAMD scores respectively, and 3 RCTs reported both SAS and SDS scores. After treatment, the above scores in the PB plus FM group were significantly lower than the PB group (all $P < .01$). However, the trials were deemed to have a medium risk of bias.

Conclusions: The efficacy of PB combined with FM is superior to PB alone in the treatment of IBS-D, and it is safe for clinical use. However, the conclusions still need to be verified by conducting more large-scale and high-quality RCTs.

Abbreviations: FM = flupentixol-melitracen, HAMA = hamilton anxiety scale, HAMD = hamilton depression scale, IBS = irritable bowel syndrome, IBS-D = diarrhea-type irritable bowel syndrome, PB = pinaverium bromide, RCT = randomized controlled trial, SAS = self-rating anxiety scale, SDS = self-rating depression scale.

Keywords: flupenthixol-melitracen, irritable bowel syndrome, pinaverium bromide

1. Introduction

Irritable bowel syndrome (IBS), one of the most common type of functional gastrointestinal disorder on clinic, is a group of clinical symptoms mainly characterized by abdominal pain or discomfort, accompanied by changes in defecation habits. With persistent or intermittent episodes and without morphological and biochemical abnormalities, IBS cannot be explained by organic diseases.[1] It has the features of high prevalence, long course, poor quality of life for patients and high consumption of medical resources. In recent years, the incidence of IBS has gradually increased. Nowadays, the prevalence of IBS is 9% to 22% in western countries and 7% to 12% in China.[2,3] Psychological factors play an important role in the pathogenesis of IBS, and depression and anxiety have been identified as important causes of morbidity and exacerbations of IBS.[4,5] Therefore, many trials treating for IBS with antidepressant and antianxiety drugs have been performed recently.

According to defecation characteristics and fecal traits, IBS can be divided into diarrhea type (IBS-D), constipation type (IBS-C), mixed type and undefined type. And it is mainly IBS-C in western countries, while it is mainly IBS-D in China. Pinaverium bromide

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(PB) is a calcium channel antagonist with high selectivity for gastrointestinal smooth muscle. It is one of the commonly used drugs for the treatment of IBS-D by inhibiting the entry of calcium ions into the smooth muscle cells of the gastrointestinal tract. However, for patients with mental and psychological disorders, PB is often not effective, and PB combined with anti-anxiety and antidepressant drugs for the treatment of IBS-D can achieve better results. Flupentixol-melitracen (FM), a compound preparation, are typical antianxiety and antidepressant drugs. At present, there are many trials on the combination of PB and FM in the treatment of IBS-D, but the sample sizes are small, and the research conclusions are inconsistent. To understand the efficacy and reliability of combination PB with FM, in this study, we chose PB and FM as the subjects and performed a systematic review and meta-analysis based on randomized controlled trials (RCTs) treating for IBS-D.

2. Methods

2.1. Literature search

This meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Review and Meta-analyses statement (PRISMA). Seven databases were searched from their inception until July 2018. These included PubMed, Embase, and the Cochrane Library, as well as 4 Chinese Medical Databases, that is the China National Knowledge Infrastructure Database, VIP Database for Chinese Technical periodicals, Chinese Biomedical Literature Database, and Wan-Fang Database. The following terms were used to find eligible trials: "irritable bowel syndrome", or "functional gastrointestinal disorder", "deanxit" or "flupentixol and melitracen". The search was limited to trials on human subjects published in English or Chinese. Two reviewers (Qin JM and Yang Q) independently screened the database search for titles and abstracts. If either reviewer felt a title and abstract met eligibility criteria of our study, the full text of the study was retrieved.

2.2. Inclusion and exclusion criteria

Inclusion criteria:

1. all data were published publicly;
2. the original study must be an RCT;
3. all patients with IBS-D included in the study were diagnosed according to the Rome II [6] or Rome III [7] diagnostic criteria;
4. the observation group used PB combined with FM, while the control group was treated with PB alone;
5. during treatment, patients were followed up on time and complications were treated in a timely fashion;
6. general information of patients was available;
7. there were unified statistical indicators.

Exclusion criteria:

1. non-Chinese and non-English literature;
2. duplicated published trials;
3. no primary outcome or primary outcome insufficiency with no further data available from the author.

2.3. Quality assessment

The quality of each eligible study was rated independently by two reviewers (Lv XP and Huang LY) by assessing the methodology of each study using a standardized form. The corresponding authors of eligible trials were contacted to clarify any questions about the methodology and to assess each study as accurately as possible. The risk of bias was assessed as recommended in the Cochrane Handbook version 5.1.0.[8] The quality assessment of the included RCTs included random sequence generation, allocation concealment, blinding of participant and personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Agreement between the reviewers on the assessment of each methodology component was measured using a weighted kappa. The risk of bias for each study was assessed on the basis of the primary outcome, that is the total symptom relief rate. Based on the methodology assessment, the two reviewers gave each eligible study an overall rating of high, low, or unclear risk of bias. Agreement between the 2 reviewers on the overall risk of bias assessment was determined using weighed kappa as well. Disagreements were resolved by discussion.

2.4. Data extraction

Two reviewers (Qin JM and Yang Q) independently extracted relevant information from each eligible study using a standard form. In instances where the entries did not match, a third person (Qin LF) was involved for verification. The following data were independently extracted by 2 reviewers from eligible trials using pilot-tested data extraction forms: age and number of participants, male-female ratio, diagnosis criteria, treatment dosage and duration, adverse effects, and quality assessment item. Important missing data were obtained by contacting the authors whenever possible.

2.5. Data pooling and statistics

Data analyses were performed using the statistical package REVIEW MANAGER (RevMan) version 5.3. Dichotomous data were presented as the risk ratio (RR) or odds ratio (OR). Subgroup analyses were conducted in terms of dose of the drug. Mean difference was used to evaluate the continuous outcomes Hamilton anxiety scale (HAMA) scores, Hamilton depression scale (HAMD) scores, self-rating anxiety scale (SAS) scores, and self-rating depression scale (SDS) scores. Ninety-five percent confidence intervals (CI) were used to represent all the total results. Heterogeneity between trials was tested using the I^2 test and considered significant when I^2 was over 50% or $P < .1$. The random effects model was used for the meta-analysis if there was significant heterogeneity, while the fixed effects model was used if heterogeneity was not significant. Publication bias was explored by funnel plot to assess the trials evaluating the primary outcome of total symptom relief rate.

2.6. Data availability

All data generated during and/or analyzed in this study are included in this published article (and its supplementary information files).

2.7. Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

2.8. Informed consent

For this type of study, formal consent is not required.

3. Results

3.1. Search results

We identified 272 potentially relevant articles after duplicates were removed. By screening titles and abstracts, 213 were excluded because they were not clinical RCTs, that is case reports, reviews, basic/mechanistic studies, or studies lacking a control group. We conducted a full-text evaluation of the remaining 59 articles, and 35 articles were excluded for not meeting the inclusion criteria. Two articles were duplicate publications and 7 articles were not about treating IBS-D with PB and FM. Eventually, 15 trials [9–23] involving a total of 1487 participants met the inclusion criteria.

3.2. Study characteristics

A total of 1487 participants were included in the 15 trials. Among them, 761 were in the experimental group, and 726 were in the control group, and the ages ranged from 16 to 69 years old. All trials were conducted in China, published between 2005 and 2018, and were performed at a single center. Every trial was FM plus PB compared with PB alone. In 11 trials,[9,11–17,19,20,23] FM was taken orally as a tablet twice daily, and taken orally a tablet once daily in 4 trials.[10,18,21,22] The duration of trials lasted from 4 to 12 weeks. All trials used the total symptom relief rate as the primary outcome. Two trials [13,19] reported HAMA scores, and 3 trials [13,19,20] reported HAMD scores. In addition, 3 trials [18,21,23] reported both SAS and SDS scores. Adverse effects were reported in 11 trials.[9–14,16–19,23] The detailed characteristics of the included trials are listed in Table 1.

3.3. Risk of bias within trials

All the included trials mentioned randomization, but only 8 trials reported the method of random sequence generation.[11,13,18–23] Eight trials [11,13,18–23] mentioned allocation concealment. Six trials [13,18–21,23] recorded the blinding procedures. There are no incomplete outcome data, selective reporting and other bias in all trials. (Fig. 1).

3.4. Efficacy assessment

3.4.1. Total symptom relief rate. All trials[9–23] adopted the total symptom relief rate to assess clinical improvement. The fixed effects model was used for statistical analysis because heterogeneity was not significant (P = .77, $I^2 = 0\%$). The combined results of these fifteen independent trials indicated that PB plus FM could relieve symptoms significantly in patients with IBS-D when compared with PB alone (n = 1487, OR = 5.17,

Table 1

Characteristics of studies.

Study	Subject	Interventions		Follow-up	Outcomes
	Experimental/Control group	Experimental group	Control group		
Huang[9]	38/35	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	4 weeks	Total symptom relief rate Adverse effects
Huang et al[10]	60/42	PB 50 mg thrice daily FM: one tablet once daily	PB: 50 mg thrice daily	4 weeks	Total symptom relief rate Adverse effects
Yan[11]	120/118	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	12 weeks	Total symptom relief rate Adverse effects
Li and Wang [12]	42/36	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	8 weeks	Total symptom relief rate Adverse effects
Li[13]	77/77	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	4 weeks	Total symptom relief rate HAMA and HAMD scores Adverse effects
Meng[14]	38/38	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	1 month	Total symptom relief rate Adverse effects
Zhang and Cao[15]	40/40	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	8 weeks	Total symptom relief rate
Qin[16]	39/39	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	2 months	Total symptom relief rate Adverse effects
Zhu[17]	43/39	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	8 weeks	Total symptom relief rate Adverse effects
Chen and Zhou[18]	32/32	PB: 50 mg thrice daily FM: one tablet once daily	PB: 50 mg thrice daily	8 weeks	Total symptom relief rate SAS and SDS scores Adverse effects
Ni and Zheng[19]	72/70	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	8 weeks	Total symptom relief rate HAMA and HAMD scores Adverse effects
Shi[20]	32/32	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	4 weeks	Total symptom relief rate HAMD scores
Deng[21]	25/25	PB: 50 mg thrice daily FM: one tablet once daily	PB: 50 mg thrice daily	8 weeks	Total symptom relief rate SAS and SDS scores
Lin[22]	43/43	PB: 50 mg thrice daily FM: one tablet once daily	PB: 50 mg thrice daily	8 weeks	Total symptom relief rate
Peng and Xie[23]	60/60	PB: 50 mg thrice daily FM: one tablet twice daily	PB: 50 mg thrice daily	8 weeks	Total symptom relief rate SAS and SDS scores Adverse effects

FM = Flupentixol-melitracen; HAMA = hamilton anxiety scale; HAMD = hamilton depression scale; PB = Pinaverium bromide; SAS = self-rating anxiety scale; SDS = self-rating depression scale.

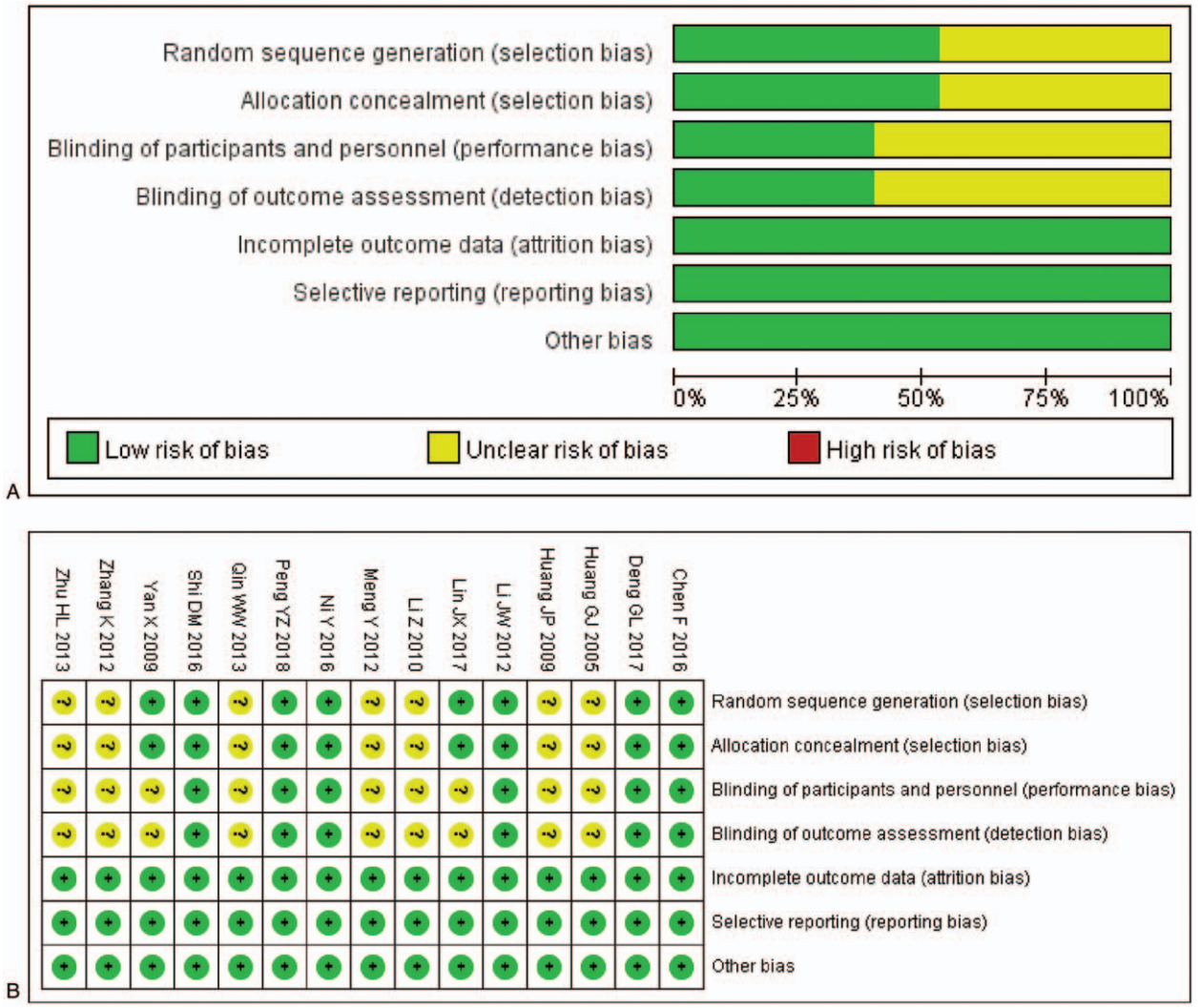

Figure 1. (A) Risk of bias graph; (B) Risk of bias summary.

95%CI, 3.79 to 7.07, $P<.00001$) (Fig. 2). A subgroup analysis was performed to explore whether different dose FM used daily affect the treatment effect. The subgroup analysis showed that no obvious differences of treatment effect were observed after FM treatment with different dose in the included trials ($P=.51$, $I^2=0\%$) (Fig. 2).

3.4.2. HAMA and HAMD scores. HAMA scores data extracted from 2 trials [13,19] showed that there is heterogeneity among trials ($P<.00001$, $I^2=96\%$). The random effects model was used for statistical analysis. The combined effect of 2 independent trial results showed that the HAMA score of PB plus FM group was lower than that of the PB group, and the difference between the 2 groups was statistically significant (n=296, OR=−5.99, 95% CI, −9.68 to −2.30, $P=.001$) (Fig. 3A).

Three[13,19,20] out of 15 trials reported HAMD score in the PB plus FM group and PB group. The random effects model was used for statistical analysis because heterogeneity was significant ($P=.05$, $I^2=67\%$). The overall effect of three independent trial results showed that PB plus FM could significantly reduce HAMD score than PB alone (n=360, OR=−6.80, 95%CI, −8.16 to −5.45, $P<.00001$) (Fig. 3B).

3.4.3. SAS and SDS scores. Three [18,21,23] out of 15 trials assessed SAS and SDS scores. The fixed effects model was used for statistical analysis because heterogeneity was not significant ($P=.98$, $I^2=0\%$; $P=.67$, $I^2=0\%$). The overall effect of 3 independent trial results showed that PB plus FM could significantly decrease SAS and SDS scores than PB alone (n=234, OR=−4.82, 95%CI, −6.28 to −3.35, $P<.00001$; n=234, OR=−5.70, 95%CI, −7.37 to −4.03, $P<.00001$) (Fig. 4).

3.4.4. Adverse events rate. Of the 15 trials, 11 trials[9–14,16–19,23] observed adverse effects, and obvious adverse effects occurred in 4 trials.[9,10,16,19] Specific adverse reactions included lethargy, dizziness, dry mouth, insomnia, and nausea, are relatively minor extent. No severe adverse reactions were found and no treatment was stopped owing to adverse reactions. The fixed effects model was used for statistical analysis because heterogeneity was not significant ($P=.90$, $I^2=0\%$). The overall effect of 11 independent trial results showed that there was no significant statistical difference in the incidence of adverse reactions between PB plus FM and PB alone (n=1207, OR=2.91, 95%CI, 0.91–9.28, $P=.07$) (Fig. 5).

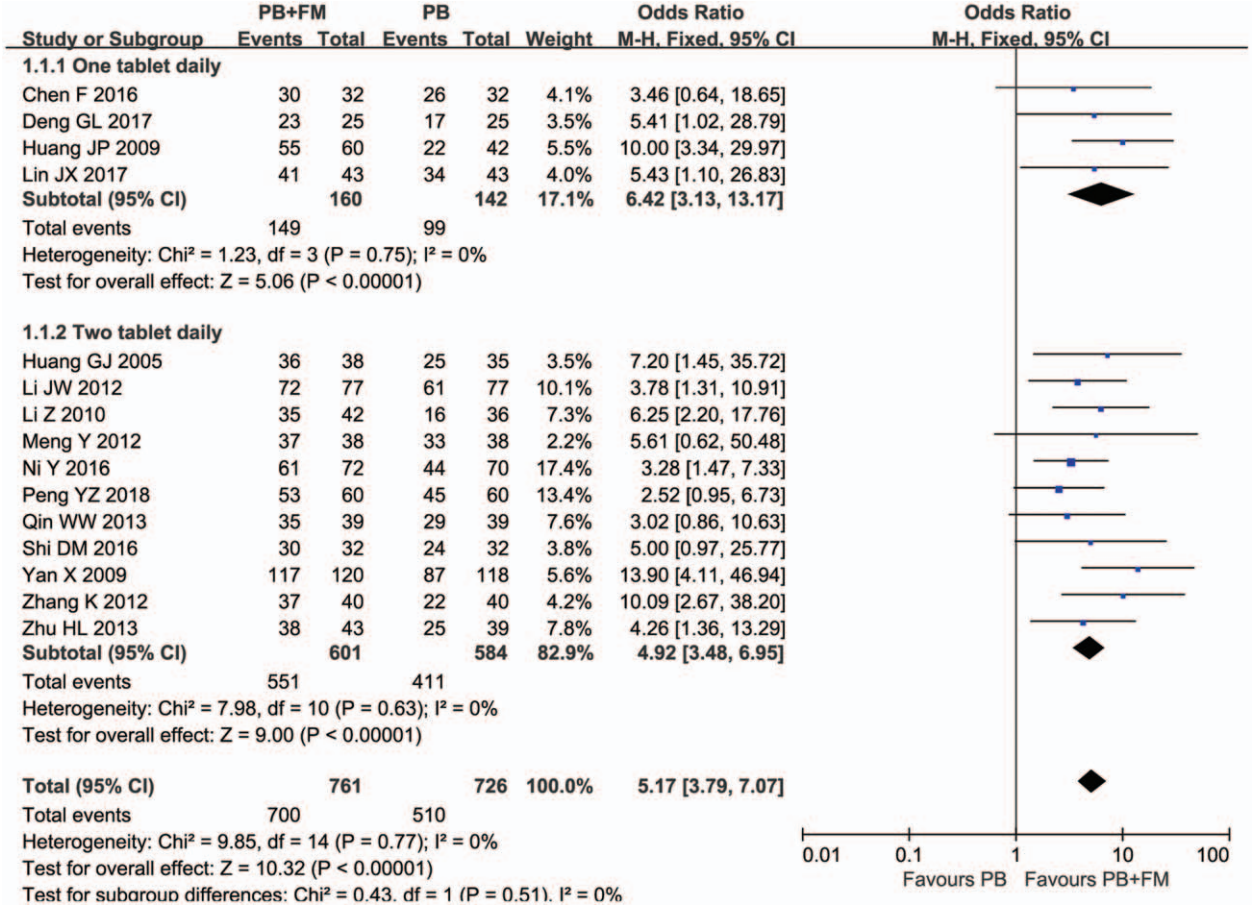

Figure 2. Forest plot of the comparison of PB plus FM versus PB alone: total symptom relief rate. FM = flupentixol-melitracen, PB = pinaverium bromide.

3.5. Assessment of publication bias

A funnel plot of the trials that included a primary outcome of total symptom relief rate was created to explore publication bias. The effects estimate and confidence intervals are shown on the funnel plot and show a nonsymmetrical distribution around the effect estimate, indicating that there may be a certain publication bias in the literature (Fig. 6).

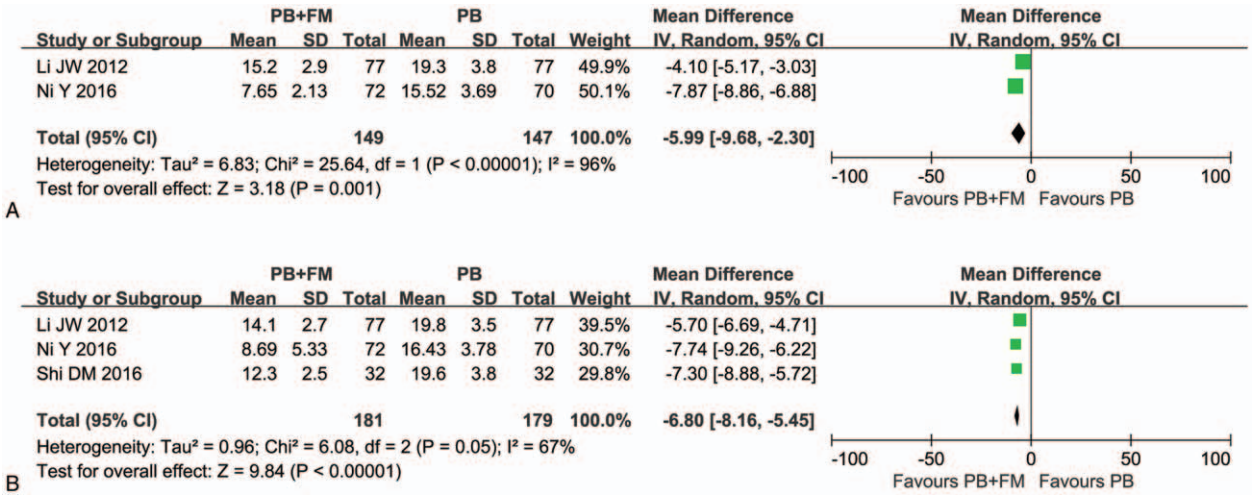

Figure 3. Forest plot of the comparison of plus FM versus PB alone: (A) HAMA score; (B) HAMD score. FM = flupentixol-melitracen, HAMA = hamilton anxiety scale, HAMD = hamilton depression scale, PB = pinaverium bromide.

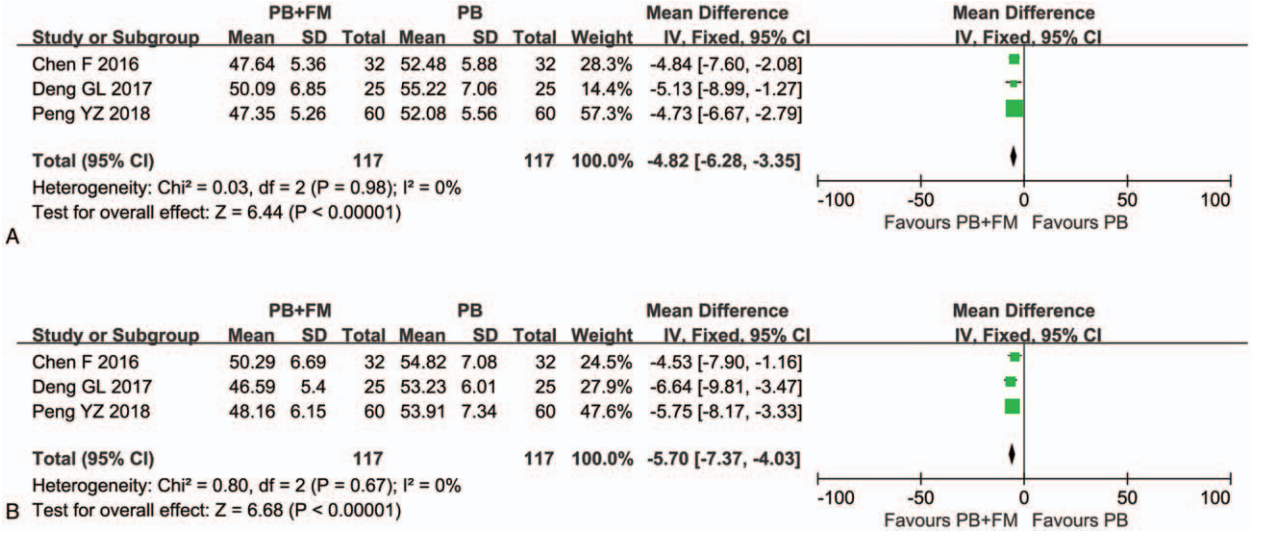

Figure 4. Forest plot of the comparison of PB plus FM versus PB alone: (A) SAS score; (B) SDS score. FM = flupentixol-melitracen, PB = pinaverium bromide, SAS = self-rating anxiety scale, SDS = self-rating depression scale.

4. Discussion

So far, the etiology and pathogenesis of IBS is not clear; it may be associated with intestinal motility disorders, visceral sensory abnormalities, intestinal flora disorders after infection, or psychological factors.[1] Commonly, management of IBS-D includes antispasmodic, antidiarrheal, probiotics and so on. For instance, PB can regulate intestinal motility and relieve the spasticity of intestinal smooth muscle so that improve abdominal pain, bloating, and diarrhea to some extent.[24] However, numerous trials[25–27] have confirmed that the occurrence and development of IBS is closely related to mental and psychological disorders, such as anxiety, depression, fear, obsession, insomnia, and dreaminess. Among them, anxiety and depression are the most common in IBS patients. It has been reported that 40% to 60% of patients with IBS suffer from varying degrees of anxiety and depression.[4,25] Accordingly, drugs such as PB only treating

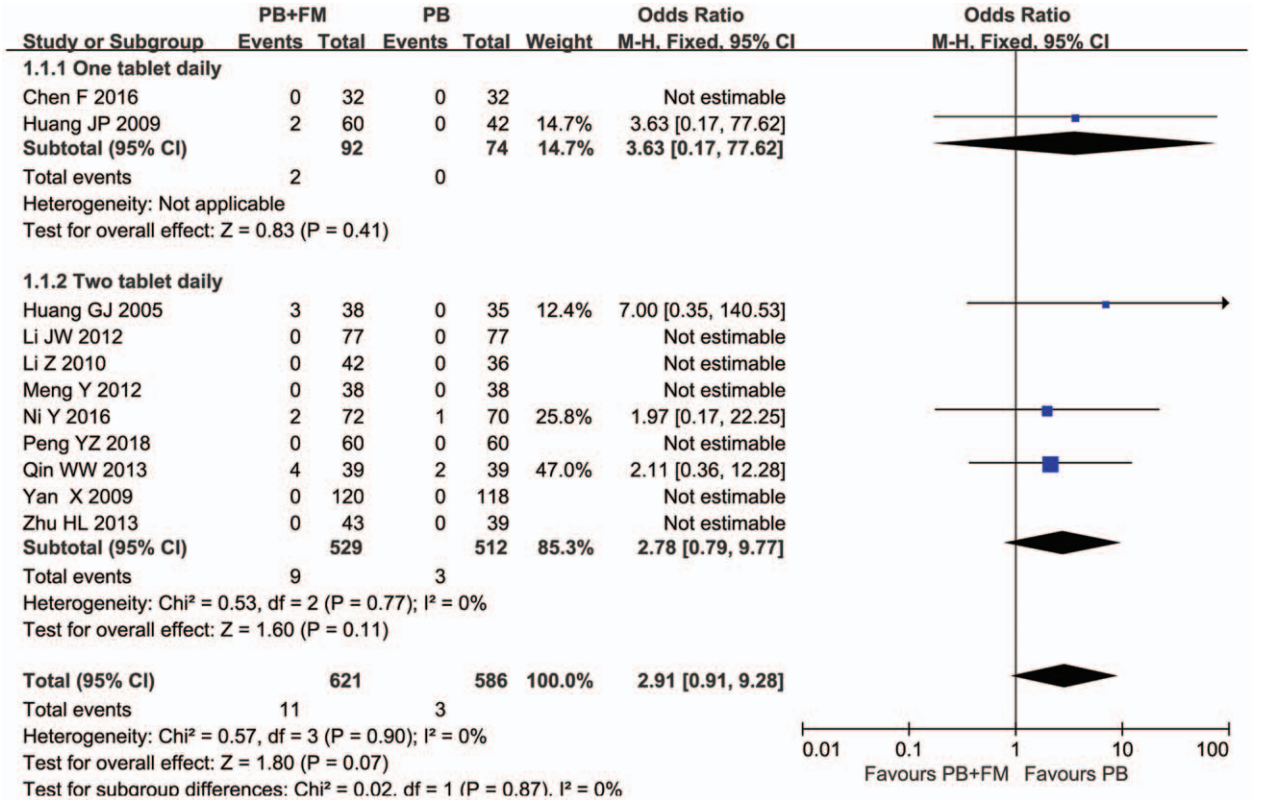

Figure 5. Forest plot of the comparison of PB plus FM versus PB alone: adverse events rate. FM = flupentixol-melitracen, PB = pinaverium bromide.

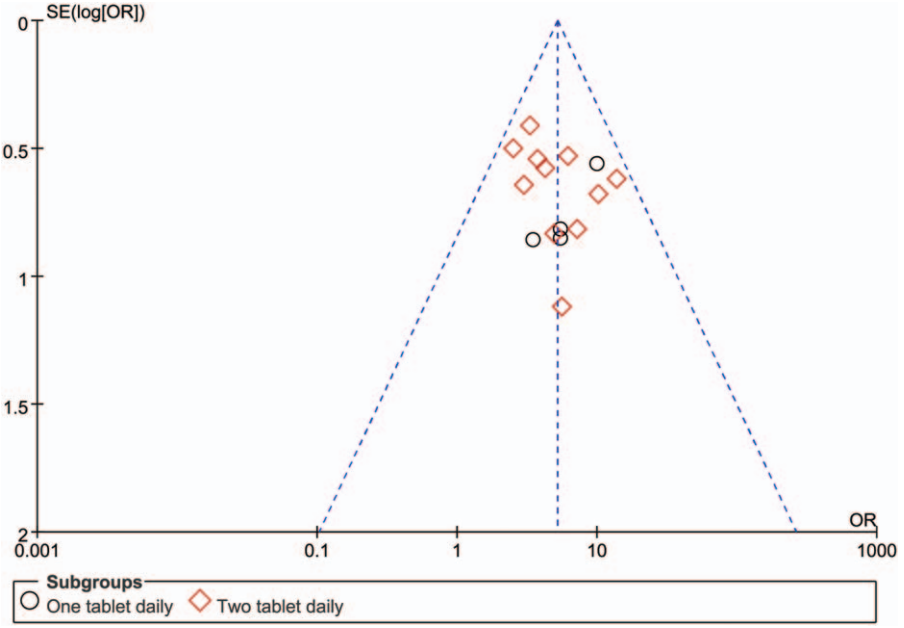

Figure 6. Funnel plot of the comparison of PB plus FM versus PB alone. FM = flupentixol-melitracen, PB = pinaverium bromide.

for intestinal tract are often unable to achieve satisfactory results. In the modern bio-psycho-social medical model, intervention focusing on psychological factors has become a hotspot for IBS treatment.

The brain-gut axis is a bidirectional and integrated system in which thoughts, feelings, memories, and environmental influences can result in neurotransmitter release, which influences sensory, movement, endocrine, and immune of gastrointestinal tract.[28] In patients with IBS, the brain-gut axis may interfere with autonomic nervous and humoral regulation and cause immune dysfunction, leading to gastrointestinal motility disorders, abnormalities in sensory and function, and a reduction of pain threshold.[27] Mayer et al's trial [29] using functional MRI and voxel-based morphometry indicated that the brains of IBS patients differ from those of healthy controls in terms of both function and morphology. Therefore, it is necessary to treat IBS with combination therapy focusing on mentality and intestine simultaneously, especially for IBS patients with anxiety and depression.

The results of our study showed that total symptom relief rate of IBS-D patients using PB plus FM is significantly superior to using PB alone. Moreover, PB plus FM can significantly reduce anxiety and depression scores of patients with IBS-D. The specific mechanism of this treatment strategy is not entirely clear at present. It may be associated with altering functional status of the cerebral cortex and reduced interference from the central nervous system on the enteric intrinsic nervous system. In addition, the mechanism may also involve improving visceral hypersensitivity by modulating the concentrations of neurotransmitters that participate in the regulation of gastrointestinal motility, secretion, and sensory function.[30]

FM is a combination preparation of low-dose tricyclic anxiolytic compounds and low-dose antidepressants, and each tablet contains 0.5 mg of flupentixol and 10 mg of melitracen.[31] Small doses of flupentixol act on presynaptic dopamine receptors, thereby promoting synthesis and release of dopamine, and increasing the content of dopamine in the synaptic gap to exert antianxiety and antidepressant effects. Melitracen inhibits presynaptic membrane reuptake of norepinephrine and serotonin, which increases the content of norepinephrine and serotonin in the synaptic cleft, and thus mitigates depression. The 2 main components work synergistically and their side effects counteract each other so that can play a timely and efficient role in improving neuropsychiatric symptoms, regulating the function of gastrointestinal autonomic nerves, reducing visceral hypersensitivity, and increasing the pain threshold, eventually relieve physical and mental discomfort. Our meta-analysis found that incidence of adverse reactions of PB plus FM was not significantly increased compared with PB, showing that PB plus FM is safe for clinical use. Other trials[32,33] reported that FM can significantly relieve symptoms and improve the quality of life in IBS patients without obvious anxiety, depression, or other psychiatric symptoms. In addition, the combination of FM and PB can complement each other and act more effectively.

5. Conclusions

In conclusion, PB combined with FM could improve intestinal symptoms, anxiety, and depression of patients with IBS-D. Moreover, it is safe for clinical use. However, the included trials in our study were insufficient quality and small sample sizes, and the evidence level was limited. In the future, large sample size and well-conducted RCTs are needed to further validate our conclusions.

Author contributions

Conceptualization: Jinmei Qin, Xiaoping Lv, and Liyi Huang.
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Software: Xiaoping Lv, Liyi Huang.
Supervision: Lifeng Qin, Xiaoping Lv, and Liyi Huang.
Validation: Qian Yang, Xiaoping Lv, and Liyi Huang.
Visualization: Qian Yang, Xiaoping Lv, and Liyi Huang.
Writing – original draft: Lifeng Qin.
Writing – review & editing: Lifeng Qin and Liyi Huang.

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