INPLASY PROTOCOL

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None declared.

Placebo effect in patients with diarrhea-type irritable bowel syndrome: a literature review of randomized, placebo-controlled trials

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Review question / Objective: **The aim of this systematic review is to explore the magnitude of the placebo effect in randomized controlled trials for diarrhea-type irritable bowel syndrome and to understand possible relevant factors that affect the placebo effect.**
Condition being studied: **Irritable bowel syndrome is a chronic functional gastrointestinal disorder characterized by abdominal pain related to defecation and a change in frequency and form of stool. Epidemiological study indicates that the prevalence of irritable bowel syndrome in different countries is high. It is estimated conservatively that direct costs related to irritable bowel syndrome causes a huge economic burden in the United States. In the latest Rome IV criteria, irritable bowel syndrome is divided into 4 subtypes based on abnormal bowel habits: irritable bowel syndrome with predominant constipation, irritable bowel syndrome with predominant diarrhea, irritable bowel syndrome with mixed bowel habits, and irritable bowel syndrome unclassified. Regarding treatment for irritable bowel syndrome, there is no cure or curative treatment. Any agent should be compared with placebo to identify its efficacy. In fact, the placebo response rate of irritable bowel syndrome is high. However, the placebo response rate of IBS-D and the moderators of the magnitude of the placebo response rate are not clear.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 June 2022 and was last updated on 06 June 2022 (registration number INPLASY202260019).

INTRODUCTION

Review question / Objective: **The aim of this systematic review is to explore the magnitude of the placebo effect in randomized controlled trials for diarrhea-type irritable bowel syndrome and to**

understand possible relevant factors that affect the placebo effect.

Rationale: Irritable bowel syndrome is a chronic functional gastrointestinal disorder characterized by abdominal pain related to defecation and a change in frequency and form of stool. Epidemiological study indicates that the prevalence of irritable bowel syndrome in different countries is high, ranging from 1.1% to 45% depending on various diagnostic criteria, and it is more common in women and young people. It is estimated conservatively that direct costs related to irritable bowel syndrome in the United States are more than $1billion, which causes a huge economic burden. Irritable bowel syndrome with predominant diarrhea (IBS-D) is the most common subtype in the clinic. Regarding treatment for irritable bowel syndrome, any agent should be compared with placebo to identify its efficacy. In fact, the placebo response rate of irritable bowel syndrome ranged from 16% to 71.4%. However, the placebo response rate of IBS-D is unclear. In addition, the moderators of the magnitude of the placebo response rate is not clear.

Condition being studied: Irritable bowel syndrome is a chronic functional gastrointestinal disorder characterized by abdominal pain related to defecation and a change in frequency and form of stool. Epidemiological study indicates that the prevalence of irritable bowel syndrome in different countries is high. It is estimated conservatively that direct costs related to irritable bowel syndrome causes a huge economic burden in the United States. In the latest Rome IV criteria, irritable bowel syndrome is divided into 4 subtypes based on abnormal bowel habits: irritable bowel syndrome with predominant constipation, irritable bowel syndrome with predominant diarrhea, irritable bowel syndrome with mixed bowel habits, and irritable bowel syndrome unclassified. Regarding treatment for irritable bowel syndrome, there is no cure or curative treatment. Any agent should be compared with placebo to identify its efficacy. In fact, the placebo response rate of irritable bowel syndrome is high. However, the placebo response rate of IBS-D and the moderators of the magnitude of the placebo response rate are not clear.

METHODS

Search strategy: The Medline (via Ovid), the Cochrane Library, EMBASE, Pubmed, China National Knowledge Infrastructure, Chinese Scientific Journal Database, SinoMed, and Wanfang Data will be searched until April 2022. We also explored the World Health Organization International Clinical Trials Registry Platform (https://www.who.int/clinical-trials-registry-platform), ClinicalTrials.gov (www.clinicaltrials.gov/), and the Chinese Clinical Trial Registry (http://www.chictr.org.cn/index.aspx) for ongoing or unpublished trials to April 2022. In addition, the reference lists of all identified studies will also be searched to find any further relevant trials for inclusion.

Participant or population: We will include trials involve patients with IBS-D, who were diagnosed according to Rome II criteria, Rome III criteria, or Rome IV criteria, of both genders and any age.

Intervention: Experimental interventions included conventional therapy that recommended by the guidelines, including but not limited to probiotics, prebiotics, selective 5-hydroxytryptamine reuptake inhibitor, pinaverium bromide, will be included, as long as the comparison group is a placebo. Chinese herbal medicines, whether formulation, Chinese patent herbal medicine, or extracts, will be also included, as long as the comparison group is a placebo.

Comparator: The control intervention will include placebo.

Study designs to be included: Parallel group, randomized, placebo controlled, double blind trials will be included, irrespective of publication status and language.

Eligibility criteria: All randomized controlled trials in IBS-D patients that compare conventional therapy recommended by the guidelines or Chinese herbal medicine with placebo will be included.

Information sources: The Medline (via Ovid), the Cochrane Library, EMBASE, Pubmed, China National Knowledge Infrastructure, Chinese Scientific Journal Database, SinoMed, and Wanfang Data will be searched until April 2022. We also explored the World Health Organization International Clinical Trials Registry Platform (https://www.who.int/clinical-trials-registry-platform), ClinicalTrials.gov (www.clinicaltrials.gov/), and the Chinese Clinical Trial Registry (http://www.chictr.org.cn/index.aspx) for ongoing or unpublished trials to April 2022. In addition, the reference lists of all identified studies will also be searched to find any further relevant trials for inclusion.

Main outcome(s): The main outcome measures sought at the end of treatment will be the global improvement of symptoms (global symptoms improvement, as defined by the included trials and verified reliability and validity).

Additional outcome(s): The secondary outcome assessed will be the effect of various trial and patient characteristics (ie, moderators) on the pooled placebo response rate. The moderators assessed will include but are not limited to trial sample size, trial center numbers, geographical setting, treatment duration, treatment intervention, publication language, and funding support.

Data management: We will import all retrieved results into reference management software Endnote (Thomson Research Soft Company, version 20.0.1). Duplicate data from different databases will be identified first and screened by the software. Two reviewers (QYH and QW) will independently screen the titles and abstracts to select potential trials, and then review full texts for eligible trials according to the criteria described above. Any disagreements will be resolved through discussion or by consultation with a third review author (JPL). Data collection form will be designed using Microsoft Excel.

Quality assessment / Risk of bias analysis: The methodological quality of individual trials will be assessed by the Cochrane Risk of Bias tool 2.0. The tool includes the following five domains: randomization process, deviation from established interventions, outcome measures, missing outcome data, selective reporting of results, and overall bias. The included studies will be assessed as low risk of bias, some concern, or high risk of bias in each domain.

Strategy of data synthesis: The placebo response and the control intervention response were respectively performed by Comprehensive Meta-Analysis software (Biostat Inc, version 3.3) and a random-effects model. Dichotomous data were presented as risk ratio (RR) with 95% confidence intervals (CI). I2 test will be used to assess heterogeneity. As recommended by the Cochrane Handbook 5.1.0, we define I2 as follows: (1) less than 50%: represents mild heterogeneity; (2) 50%-75%: represents moderate heterogeneity; (3) more than 75%: represents severe heterogeneity. A random-effect model will be used.

Subgroup analysis: If sufficient data are available, the subgroup analysis will be carried out to reveal any effect that might explain any heterogeneity, including but not limited to diagnostic criteria (Rome II criteria versus Rome III criteria versus Rome IV criteria), treatment intervention (conventional therapy versus Chinese herbal medicine), allocation sequence concealment (adequate blinding versus unclear blinding).

Sensitivity analysis: We will ensure the stability of the comprehensive results by performing sensitivity analysis if necessary.

Language: No language limitations.

Country(ies) involved: This systematic review is being carried out in China.

Other relevant information: No.

Keywords: Placebo; placebo response rate; placebo effect; irritable bowel syndrome; IBS-D; conventional therapy; Chinese herbal medicine; systematic review; meta-analysis.

Dissemination plans: This systematic review results will be submitted for publication in peer review journal.

Contributions of each author:

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