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Efficacy and safety of Non-pharmacological therapies for Diarrhea-predominant irritable bowel syndrome：protocol for a network meta-analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 July 2024 and was last updated on 28 July 2024.

INTRODUCTION

Review question / Objective Systematic comparison of the efficacy and safety of non-pharmacological therapies for the treatment of patients with diarrhea-predominant irritable bowel syndrome by network meta-analysis.
P: patients with diarrhea-predominant irritable bowel syndrome.
I: non-pharmacological therapies.
C: medicine or placebo.
O: IBS-SSS, IBS-QOL, HADS.
S: RCT.

Condition being studied Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder associated with recurrent abdominal pain and altered bowel habits, of which diarrhea-predominant irritable bowel syndrome (IBS-D) is a common subtype. The prevalence of IBS is increasing in Asian countries, with the overall prevalence in China ranging from 1.4% to 11.5%, with a higher prevalence in women than in men, and occurring in young and middle-aged people. According to the Rome IV diagnostic criteria, IBS is classified into four subtypes: constipated (IBS-C), diarrhea (IBS-D), mixed (IBS-M), and undetermined (IBS-U). Among the guideline-recommended therapies, pharmacological therapies need to be selected with great caution in clinical settings due to the serious side effects associated with long-term use. Non-pharmacological therapies, which have fewer side effects and are safer during long-

term treatment, continue to be the choice for patients with IBS. However, the variety of non-pharmacological therapies and their modalities make it a serious challenge for clinicians to choose which therapy is the best option for IBS patients in clinical practice. Therefore, it is of clinical significance to identify and compare the efficacy and safety comparisons of current non-pharmacological therapies for IBS-D. Therefore, this study searched Chinese and English databases for RCTs of non-pharmacological therapies for IBS-D and performed a systematic review as well as a network meta-analysis to provide partial evidence support for clinicians in choosing which therapies to use for IBS.

METHODS

Search strategy We will search all disease-related randomized controlled trials electronically and manually with no language or publication restrictions: including the Chinese Biomedical Literature Database (CBM), Web of Science, PubMed, the Cochrane Library, Excerpta Medica (EMBASE), the China National Knowledge Infrastructure Database (CNKI), the Wanfang database and the Chinese Scientific Journal Database (VIP database) will be searched from database establishment to June 2024. The following search terms will be used: "irritable bowel syndrome", "diarrhea-predominant irritable bowel syndrome", "IBS-D", "irritable bowel", "cognitive behavioral therapy", "dietary therapy", "probiotics", "fecal microbiota transplantation ", "Acupuncture", "Moxibustion", "Randomized Controlled Trial", "Randomized Control", "RCT", "randomized". When searching other databases, the search terms will be adjusted accordingly. In addition, we will manually search the references of all relevant articles to identify additional eligible studies.

Participant or population All participants who have been diagnosed as diarrhea-predominant irritable bowel syndrome and met the clinical diagnostic criteria of the International RomeIII or Rome IV diagnostic criteria. There will be no restrictions on age, sex and race.

Intervention The experimental group use Cognitive Behavioral Therapy (CBT), Dietary Therapy (DT), Probiotics (Pro), Fecal Microbiota Transplantation (FMT), Acupuncture (Acu) and Moxibustion (Mox).

Comparator The control group is medicine (WM) or placebo (Pla).

Study designs to be included Randomized controlled trials will be included and no restrictions on language.

Eligibility criteria
Inclusion criteria:
1. Type of study: randomized controlled trial.
2. Subjects: patients with a clear diagnosis of IBS-D (disease diagnostic criteria refer to RomeIII or Rome IV diagnostic criteria), with no restriction on age, sex and race.
4. Outcome indicators: the primary outcome indicator was IBS-symptom severity scale (IBS-SSS); the secondary outcome indicators were IBS-Quality Of Life (IBS-QOL), Hospital Anxiety and Depression Scale (HADS).
Exclusion criteria:
1. Animal experimental studies, conferences, dissertations, case reports, reviews.
2. Combination of other functional gastrointestinal diseases or other serious diseases of the heart, brain, liver, kidney, blood and mental system.
3. The outcome indicators are not relevant to this study.
4. Lack of original data or incomplete data.
5. Duplication of studies with the same data.

Information sources We will electronically search the randomized controlled trials in the following databases: including the Chinese Biomedical Literature Database (CBM), Web of Science, PubMed, the Cochrane Library, Excerpta Medica Database (EMBASE), the China National Knowledge Infrastructure Database (CNKI), Wanfang database and the Chinese Scientific Journal Database (VIP database) will be searched from their inception to June 2024. We will also try to search manually for other sources.

Main outcome(s) The primary outcome include IBS-symptom severity scale (IBS-SSS).

Additional outcome(s) The secondary outcome include IBS-Quality Of Life (IBS-QOL), Hospital Anxiety and Depression Scale (HADS).

Data management After importing the search results into Endnote20 to exclude repetitive literature, two reviewers independently screened out the required studies by reading the titles and abstracts, and then read the full text to determine the final included studies according to the inclusion criteria. When an analysis arises between two reviewers, further discussion will be conducted, any unresolved issues will be decided by the third reviewer.

Quality assessment / Risk of bias analysis The risk of quality bias assessment using the Cochrane risk of bias assessment tool, will be used by two reviewers for each study. Assessment will consist of seven areas: Random sequence generation, Allocation concealment, Blinding of participants and personnel, Blinding of outcome assessment, Incomplete outcome data, Selective reporting, and Other bias. Risk of bias will be rated as 'high risk', 'low risk' or 'unclear'. Any disagreements will be arbitrated by the third reviewer.

Strategy of data synthesis Statistical analysis will be performed using Stata 18.0 software. IBS-SSS, IBS-QOL, and HADS are continuous data and analyzed using standardized mean deviation (SMD) with 95% confidence intervals (CI). Heterogeneity between study data will be analyzed using chi-square test, with I^2 of 25-50% indicating "low heterogeneity", I^2 >50% indicating "medium heterogeneity" and I^2 >75% indicating "high heterogeneity ". If it is $I^2 \leq 50\%$ or $P>0.05$, meta-analysis will be performed using a fixed-effects model; otherwise, sources of heterogeneity need to be further explored and meta-analysis will be performed using a random-effects model. To show the network relationships between non-pharmacological therapies, we created a network graph, which mainly consists of nodes and lines, where each node represents an intervention, nodes connected by a line indicate that there is a direct or indirect comparative relationship between the two, the size of the node indicates the number of participants who received this treatment, and the thickness of the line indicates the number of studies. We analyzed the results of all direct or indirect comparisons to assess which non-pharmacological therapy was most effective for people with diarrhea-predominant irritable bowel syndrome, producing surface under the cumulative ranking curve (SUCRA) plot, with larger SUCRA scores indicating that this intervention was more effective in treatment.

Subgroup analysis If studies are high heterogeneity, we will conduct subgroup analysis according to sex, and treatment duration, and sources of heterogeneity in clinical differences will be explored.

Sensitivity analysis To assess the robustness of our results, a sensitivity analysis will be conducted to address whether the main decision made during the review process is dominated by one or several studies. We will eliminate studies with poor study quality, small sample sizes, and high risk of bias.

Language restriction We will use Chinese and English.

Country(ies) involved China.

Other relevant information These authors contributed equally to this work.

Keywords Non-pharmacological therapies; irritable bowel syndrome; network meta-analysis.

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