

## Efficacy of different acupuncture and moxibustion therapies in animal models of diarrhea-predominant irritable bowel syndrome: a systematic review and 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.

**INPLASY registration number:** INPLASY202470113

**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** Efficacy of different acupuncture and moxibustion treatments compared to other measures in animal models of diarrhea-predominant irritable bowel syndrome. Population (P): animal models of diarrhea-predominant irritable bowel syndrome. Intervention (I): manual acupuncture, electroacupuncture, eye needle, auricular acupuncture, moxibustion. Comparison (C): sham acupuncture, medicine, normal group or model group. Outcomes (O): the minimum threshold volume of Abdominal Withdrawal Reflex (AWR) induced by colorectal distension were observed, the rate of loose stools, IL-1 $\beta$ , TNF- $\alpha$ , SP, 5-HT content.

**Rationale** Diarrhea-predominant irritable bowel syndrome (IBS-D) is a common functional gastrointestinal disorder characterized by recurrent episodes of abdominal pain or bloating, discomfort, and diarrhea, and changes in bowel habits, including changes in stool consistency or frequency. Current recommended therapies have significant post-treatment side effects. However, there is a lack of systematic comparative studies. With this study, we investigate to uncover the advantages and mechanisms of different acupuncture and moxibustion therapies of IBS-D, to provide a scientific basis for future clinical applications and theoretical support for further basic research.

**Condition being studied** Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain or bloating and changes in bowel habits, including changes in stool consistency or frequency. It can be clinically subdivided into various subtypes, among which IBS-D is the most common subtype in China. The etiology and pathogenesis of IBS-D are not fully understood, but it is generally believed to be caused by a combination of factors. IBS-D has a significant impact on individuals and society, severely affecting patients' work, study, and quality of life, as well as increasing their financial burden. Currently known therapies cover a wide range of measures from lifestyle modification, cognitive-behavioral therapy to medication, and most of these therapies are able to alleviate the symptoms to varying degrees, but clinically they still face a number of side effects such as recurrence of symptoms after stopping the medication. Acupuncture and moxibustion therapy, as a type of alternative therapy in Chinese medicine, has been shown to have significant efficacy in animal models of IBS-D in a number of studies. The evidence in favor of acupuncture and moxibustion therapy for IBS-D remains insufficient and includes mechanisms.

## METHODS

**Search strategy** The search period was from the establishment of the database to June 2024. The search databases included Chinese databases: the China National Knowledge Infrastructure Database (CNKI), the Wanfang database, the Chinese Scientific Journal Database (VIP database), Chinese Biomedical Literature Database (CBM), and English databases: PubMed, Excerpta Medica (EMBASE), Web of Science, the Cochrane Library for searching. Animal experiments related to the study of The evidence in favor of acupuncture and moxibustion therapies for IBS-D remains insufficient and includes mechanisms. The search is conducted using a combination of subject terms and free words. The search terms are: manual acupuncture, electroacupuncture, eye needle, auricular acupuncture, moxibustion, sham acupuncture, diarrhea, irritable bowel syndrome, animal.

**Participant or population** Animal models of diarrhea-predominant irritable bowel syndrome.

**Intervention** Acupuncture-related therapies such as manual acupuncture, electroacupuncture, eye needle, auricular acupuncture, moxibustion.

**Comparator** Non-acupuncture related therapies such as sham acupuncture, medicine, normal group or IBS-D model group.

**Study designs to be included** Inclusion criteria were: type of study published in Chinese or English randomized controlled animal trials. The exclusion criteria were: type of study published in Chinese or English non-randomized controlled trial design of animal experiments.

**Eligibility criteria** Animals successfully modeled with IBS-D, regardless of modeling method, age, weight, or sex.

**Information sources** Search databases include Chinese databases: the China National Knowledge Infrastructure Database (CNKI), the Wanfang database, the Chinese Scientific Journal Database (VIP database), Chinese Biomedical Literature Database (CBM), English databases: PubMed, Excerpta Medica (EMBASE), Web of Science, the Cochrane Library from inception to June 2024.

**Main outcome(s)** The minimum threshold volume of Abdominal Withdrawal Reflex (AWR) induced by colorectal distension were observed (ml), the rate of loose stools (%).

**Additional outcome(s)** IL-1 $\beta$  (pg/L), TNF- $\alpha$  (ng/ml), SP (pg/ml), 5-HT (pg/L) content. For continuous data we used SMD and 95% CI to summarize when summarizing different units to assess the same outcome.

**Data management** In this study, data extraction was performed by two independent researchers. For each study outcome, the researchers recorded statistics such as effect size, mean difference or standardized mean difference (SMD), and 95% confidence interval. During the data extraction process, researchers worked independently to ensure the accuracy and objectivity of the data. For data entries where there was disagreement, a third researcher intervened in the discussion to reach agreement. Where raw data were not available in this study or were provided in graphical form, the relevant authors were contacted to request the raw data, and the graphical data were extracted using GetData Graph Digitizer 2.26.

**Quality assessment / Risk of bias analysis** The following 10 aspects of the included articles will be assessed by two researchers using SYRCLE's bias risk assessment tool: Sequence generation (Selection bias), Baseline characteristics (Selection bias), Allocation concealment

(Selection bias), Random housing (Performance bias), Blinding (Performance bias), Random outcome assessment (Detection bias), Blinding (Detection bias), Incomplete outcome data (Attrition bias), Selective outcome reporting (Reporting bias), Other sources of bias (Other). The researchers judged each included study as having low bias, high bias, or unclear bias (due to lack of relevant information or uncertainty). For each included article, the above ten indicators were assessed as having a low risk of bias, high risk of bias, or unclear risk of bias. In case of disagreement between two researchers during the assessment process, a third researcher would intervene and make the final decision.

**Strategy of data synthesis** The minimum threshold volume of AWR induced by colorectal distension were observed, the rate of loose stools, IL-1 $\beta$ , TNF- $\alpha$ , SP, 5-HT content indexes are all continuous data, therefore all outcome measures will be quantitatively analyzed. Stata 17.0 software will be used to perform Meta-analysis as well as Network Meta-analysis. Heterogeneity between studies will be tested using  $I^2$ . If  $I^2 > 50\%$ , which indicates a possible high heterogeneity between studies, the outcome measure will be measured using a random effects model; otherwise, the heterogeneity may tend to be insignificant and the outcome will be measured using a fixed effects model.

We use Stata 17.0 software for statistical analysis and graphical representation. Node splitting models are used to assess the consistency between direct and indirect comparisons. We calculated the cumulative ranking probability for each treatment using the surface under the cumulative probability curve area (SUCRA). For the primary outcome, Meta-analysis of more than 10 studies, we will use a funnel plot (effect size relative to standard error) to assess the potential for small sample bias.

**Subgroup analysis** In our primary analyses, where data were sufficient we performed subgroup analyses based on factors that may have led to different intervention effects. Acupuncture treatment duration, point combinations, treatment cycles, and treatment modalities as appropriate were grouped for IBS-D animals using stata 17.0.

**Sensitivity analysis** If there was high heterogeneity  $I^2 > 50\%$ , it could be due to the presence of one or more outlier studies in the included studies whose results conflicted with the remaining studies. If there were sufficient data, we

would have performed sensitivity analyses for all highly heterogeneous trials.

**Language restriction** We plan to search for articles in English or Chinese.

**Country(ies) involved** China.

**Other relevant information** These authors contributed equally to this work.

**Keywords** acupuncture; moxibustion; diarrhea-predominant irritable bowel syndrome; animal; systematic review; network meta-analysis.

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