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Acupoint stimulation for anxiety and depression in patients with inflammatory bowel disease: a systematic review and network meta-analysis protocol

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ADMINISTRATIVE INFORMATION

Support - None.

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

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202640029

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 8 April 2026 and was last updated on 8 April 2026.

INTRODUCTION

Review question / Objective This network meta-analysis will be conducted based on the following PICO framework:

P (Population): Patients with a confirmed diagnosis of inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), accompanied by clinically significant anxiety and/or depression as measured by validated instruments (e.g., HADS, HAMA, HAMD, SAS, SDS, BDI, BAI).

I (Intervention): Single acupoint stimulation modalities, including manual acupuncture (MA), electroacupuncture (EA), acupoint catgut embedding (ACE), acupoint application (AA), transcutaneous electrical acupoint stimulation (TEAS), auricular acupressure/acupuncture (AAu), and moxibustion (Mox). Combined therapies (e.g., EA plus moxibustion) are excluded.

C (Comparison): Conventional therapy alone (e.g., 5-ASA, corticosteroids, immunomodulators, biologics), placebo/sham acupuncture, blank control, or waitlist.

O (Outcomes): Primary: change in anxiety scores and depression scores from baseline. Secondary: clinical response rate for anxiety/depression, IBD disease activity indices (Mayo score for UC, CDAI for CD), quality of life (IBDQ, SF-36), inflammatory biomarkers (CRP, fecal calprotectin), adverse events.

S (Study design): Randomized controlled trials (RCTs) only.

Rationale Inflammatory bowel disease is a chronic relapsing intestinal disorder with increasing global prevalence. Up to 30% of IBD patients experience clinically significant anxiety and/or depression, which are associated with poorer quality of life, increased disease activity, and higher healthcare utilization. Current pharmacological treatments for anxiety and depression have limitations, including

adverse effects, drug interactions, and patient reluctance. Acupoint stimulation therapies have shown potential benefits for both IBD symptoms and psychological comorbidities through mechanisms involving the brain-gut axis, vagal nerve modulation, and anti-inflammatory effects. However, the comparative effectiveness among different acupoint stimulation modalities for anxiety and depression in IBD remains unclear. Existing systematic reviews have focused on individual modalities without direct comparisons. This network meta-analysis will address this gap by providing comparative rankings to inform clinical decision-making.

Condition being studied Inflammatory bowel disease (IBD) is a chronic, non-specific inflammatory condition of the gastrointestinal tract, primarily encompassing Crohn's disease (CD) and ulcerative colitis (UC). It is characterized by relapsing and remitting courses. Beyond gastrointestinal symptoms, IBD is frequently complicated by psychological comorbidities, particularly anxiety and depression. These psychological disturbances not only impair quality of life but also negatively impact disease course, medication adherence, and treatment outcomes. The bidirectional brain-gut interaction plays a key role in this association.

METHODS

Search strategy We will systematically search the following electronic databases from inception to the search date: PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science. Grey literature (including Google Scholar, ClinicalTrials.gov, WHO ICTRP, dissertations, conference abstracts) will not be searched. Reference lists of included studies and relevant systematic reviews will be manually screened to identify additional eligible publications. Only studies published in English will be included.

Participant or population Patients of any age, sex, or ethnicity with a confirmed diagnosis of IBD (UC or CD), accompanied by clinically significant anxiety and/or depression as measured by validated instruments. No restriction on disease duration or activity.

Intervention Single acupoint stimulation modalities:

Manual acupuncture (MA)

Electroacupuncture (EA)

Acupoint catgut embedding (ACE)

Acupoint application (AA)

Transcutaneous electrical acupoint stimulation (TEAS)

Auricular acupressure/acupuncture (AAu)

Moxibustion (Mox)

Excluded: Combined therapies (e.g., EA + moxibustion, MA + AA), acupoint stimulation plus oral herbal medicine, or any intervention that cannot be attributed to a single acupoint modality.

Comparator Conventional therapy alone (5-ASA, corticosteroids, immunomodulators, biologics)

Placebo / sham acupuncture

Blank control / waitlist

Head-to-head comparisons between different acupoint stimulation modalities.

Study designs to be included Randomized controlled trials (RCTs) of parallel or crossover design (first phase only for crossover trials), single-blind, double-blind, or open-label. Cluster-randomized trials will be included if data can be extracted appropriately.

Eligibility criteria Inclusion:
(1) RCTs involving IBD patients with anxiety and/or depression;
(2) Intervention is one of the predefined single acupoint stimulation modalities;
(3) Comparator meets the definition above;
(4) Reports at least one primary outcome (anxiety or depression scale);
(5) Full-text available or sufficient data from conference abstract.
Exclusion:
(1) Non-randomized studies, case series, case reports, animal studies;
(2) Combined acupoint therapies or acupoint stimulation plus oral Chinese medicine;
(3) No validated anxiety/depression scale;
(4) Duplicate publications (only the most complete version included);
(5) Reviews, comments, editorials, protocols without results.

Information sources We will search PubMed, EMBASE, Cochrane CENTRAL, and Web of Science from inception to the search date. No grey literature sources will be searched. Reference lists

of included studies and relevant systematic reviews will be manually screened. Only English-language publications will be considered.

Main outcome(s) Primary outcomes:

Change in anxiety scores from baseline (e.g., HAMA, HADS-A, SAS, BAI) – expressed as standardized mean difference (SMD) with 95% CI.

Change in depression scores from baseline (e.g., HAMD, HADS-D, SDS, BDI) – expressed as SMD with 95% CI.
Secondary outcomes:

Clinical response rate for anxiety/depression (≥50% reduction in scale score or reaching remission threshold).

IBD disease activity indices (Mayo score for UC, CDAI for CD).

Quality of life (IBDQ, SF-36).

Inflammatory biomarkers (CRP, fecal calprotectin).

Adverse events (total and treatment-related).

Additional outcome(s) Relapse rate of anxiety/depression during follow-up (if reported)

Withdrawal rate due to adverse events.

Data management Two reviewers will independently screen titles, abstracts, and full texts against eligibility criteria using Covidence or Excel. Disagreements will be resolved by consensus or a third reviewer. A standardized data extraction form will be developed and piloted on three randomly selected included studies. Extracted data will include: first author, year, country, sample size, participant characteristics (age, sex, IBD subtype, disease duration, baseline anxiety/depression scores), intervention details (modality, acupoints, frequency, duration, session number), comparator details, outcome data (mean changes or endpoint scores with SD, responder counts), adverse events, and funding source. If data are missing or unclear, corresponding authors will be contacted via email up to two times.

Quality assessment / Risk of bias analysis Risk of bias will be assessed independently by two reviewers using the Cochrane RoB 2.0 tool for RCTs. The following domains will be evaluated: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain will be rated as "low risk," "some concerns," or "high risk." An overall risk of bias judgment will be assigned for each included study. For subjective outcomes (anxiety/depression scales), blinding of outcome assessors will be given particular attention. Disagreements will be resolved through discussion or adjudication by a third reviewer. Risk of bias summary figures will be generated using Robvis.

Strategy of data synthesis Pairwise meta-analysis:
Standard pairwise meta-analyses will be conducted using RevMan or Stata where direct comparisons exist between acupoint stimulation and control conditions. For continuous outcomes, SMD with 95% CI will be calculated using the inverse variance method. For dichotomous outcomes (response rate, adverse events), risk ratio (RR) with 95% CI will be calculated using the Mantel-Haenszel method. Heterogeneity will be assessed using the I^2 statistic (low: 60%). A random-effects model will be used if $I^2 \geq 50\%$ or $P \leq 0.10$; otherwise, a fixed-effects model will be applied.

Network meta-analysis:
A frequentist network meta-analysis will be performed using the netmeta package in R or Stata's network commands. The network will combine direct and indirect evidence to compare all seven acupoint stimulation modalities simultaneously. The consistency assumption will be assessed globally using the design-by-treatment interaction test ($P > 0.05$ indicates consistency) and locally using the node-splitting method ($P > 0.05$ for each comparison). If inconsistency is detected, possible explanations will be explored, and the inconsistency model may be used. A random-effects model will be employed accounting for anticipated heterogeneity across studies.

Treatment rankings will be presented using:

Surface Under the Cumulative Ranking Curve (SUCRA) values (0-100%)

Probability of being the best treatment (PreBest)

Mean rank

Rankograms will be generated to visualize ranking distributions.

Heterogeneity assessment:
Between-study heterogeneity will be quantified using τ^2 (standard deviation of underlying effect

sizes) and I^2 for each direct comparison. For the network meta-analysis, heterogeneity will be assessed via τ^2. If substantial heterogeneity is identified ($I^2 > 60\%$ or significant Q test), subgroup and meta-regression analyses will be conducted to explore potential sources.

Publication bias:
Comparison-adjusted funnel plots will be examined for asymmetry if at least 10 studies are included in a comparison. Egger's regression test may be performed to detect small-study effects ($P < 0.10$ considered suggestive). Because grey literature is excluded, the risk of publication bias will be discussed as a limitation.

Certainty of evidence:
The overall certainty of evidence for each outcome will be assessed using the Confidence in Network Meta-Analysis (CINeMA) framework, which evaluates within-study bias, across-study bias, indirectness, imprecision, heterogeneity, and incoherence. The Minimal Clinically Important Difference (MCID) will be defined for each outcome based on prior literature (e.g., for HADS, MCID = 1.5 points; for HAMA/HAMD, MCID = 3 points). Evidence will be rated as high, moderate, low, or very low certainty. Summary of Findings tables will be generated using GRADEpro GDT.

Subgroup analysis Pre-specified subgroup analyses will be conducted based on:

IBD subtype: ulcerative colitis vs. Crohn's disease vs. mixed/unreported.

Single acupoint stimulation modality: as defined above (7 types). Modalities with 4–8 weeks, >8 weeks.

Treatment frequency: ≤3 sessions/week vs. >3 sessions/week.

Disease activity: active IBD vs. remission vs. mixed/unreported, using validated indices (Mayo score for UC, CDAI for CD).

Comparator type: conventional therapy alone vs. placebo/sham acupuncture vs. blank control/ waitlist.

Subgroup analyses will be performed using network meta-regression or separate network meta-analyses within each subgroup, provided sufficient studies are available (≥10 RCTs per subgroup for separate NMA). Heterogeneity between subgroups will be tested using interaction Q-statistics. Findings will be interpreted as exploratory.

Sensitivity analysis Sensitivity analyses will be conducted to assess the robustness of the primary findings:

Excluding high risk of bias studies: Remove studies with an overall RoB 2 rating of "high risk".

Excluding small sample size studies: Remove studies with <30 participants per arm.

Restricting to specific outcome measures: e.g., only studies using HAMA/HAMD for anxiety/ depression.

Using different effect measures: e.g., OR instead of RR for dichotomous outcomes.

Leave-one-out analysis: Sequentially exclude each study to evaluate its impact on pooled estimates and SUCRA rankings.

If the conclusions remain unchanged after these exclusions, the results will be considered robust.

Language restriction English only.

Country(ies) involved China.

Keywords Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Anxiety; Depression; Acupoint stimulation; Acupuncture; Network meta-analysis; Systematic review.

Contributions of each author
Author 1 - JUAN KOU - Literature search, data extraction, risk of bias assessment, drafting the manuscript.Author 1 drafted the manuscript.
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