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Acupuncture for emotional disorders in patients with inflammatory bowel disease: a systematic review protocol

Yuan-Fang Zhou ,[1] Gui-Long Zhang ,[2] Ning Sun ,[3,4] Zhong-Quan Wang,[5] Xiang-Yin Ye,[1] Jian Xiong,[1] Xiao-Dong Deng,[1] Xin Lin,[5] Pei Zhang,[5] Hao Zheng,[5] Yong Zhang,[5] Kun Yang,[5] Ze-Da Gao,[5] Rui-Rui Sun ,[1] Fan-Rong Liang [1]

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Y-FZ, G-LZ and NS are joint first authors.

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For numbered affiliations see end of article.

Correspondence to
Dr Rui-Rui Sun; sunruirui@cdutcm.edu.cn and Dr Fan-Rong Liang; acuresearch@126.com

ABSTRACT

Introduction Emotional disorders are often observed in inflammatory bowel disease (IBD). IBD with emotional disorders leads to poor quality of life. This systematic review aims to assess the effectiveness of acupuncture in patients with IBD with emotional disorders.

Methods and analysis Nine electronic databases, including Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Allied and Complementary Medicine Database, Cumulative Index to Nursing & Allied Health Literature, China National Knowledge Infrastructure, Chinese Biomedical Literature Database, VIP Database and Wanfang Database, will be searched from inception to October 2021 without language restriction. The grey literature containing conference proceedings, as well as systematic reviews listed in the reference of definite publications, will also be retrieved. Randomised controlled trials either in English or Chinese reporting acupuncture therapy for IBD with emotional disorders will be included. The primary outcome is changes of emotional functioning outcomes. The Colitis Activity Index, Crohn's Disease Activity Index, C reactive protein and adverse events will be assessed as the secondary outcomes. More than two assessors will conduct the study retrieval and selection, as well as the data extraction and evaluation of the risk of bias. Data synthesis will be performed using a random-effects model based on the results of heterogeneity. Data analysis will be performed using RevMan software (V.5.4). Moreover, the dichotomous data will be presented as risk ratios, and the continuous data will be calculated using weighted mean difference or standard mean difference.

Ethics and dissemination This systematic review contains no individual patient data; thus, ethical approval is not required. Moreover, this review will be disseminated in a peer-reviewed journal or relevant conference.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This will be the first systematic review to assess the effectiveness of acupuncture for relieving emotional problems of patients with inflammatory bowel disorder (IBD).
- ⇒ The qualitative estimates and quantitative synthesis help to provide more robust evidence of the effect of acupuncture for patients with IBD with emotional disorders for clinical managers and guideline developers.
- ⇒ The relevant randomised controlled trials from both the Chinese and English databases will be fully retrieved.
- ⇒ Different types of acupuncture therapies included may cause considerable heterogeneity, which is the limitation of this study.

INTRODUCTION

Inflammatory bowel disease (IBD) is characterised by chronic relapsing inflammation of the gastrointestinal tract, and its presenting symptoms include abdominal pain, diarrhoea and rectal bleeding.[1–3] Both the prevalence and incidence of IBD have increased substantially in recent years. The prevalence of IBD in North America, Oceania and many countries in Europe is reported having exceeded 0.3%.[4] In Asian countries, such as Korea, the average annual percentage increase in the incidence of IBD is 3.3% from 2006 to 2015.[5] Although the mortality rate of IBD is only 0.07% in 195 countries, IBD has a relatively high number of years lived with disability in digestive disease, following upper digestive disease, hernia and cirrhosis in 2017.[6] Moreover, severe disability can lead to dropping out of school and absenteeism, posing a heavy social and economic burden on governments and the health systems.[7]

Patients with chronic diseases are often associated with higher epidemiology of emotional disorders than normally healthy individuals.[8] As a chronic disease, the incidence of emotional problems in IBD is also common.[9 10] Furthermore, the prevalence of IBD sufferers with emotional disorders is higher than other chronic diseases.[11] For instance, the prevalence rate of anxiety in IBD is 20%–32.1%, and the incidence rate of depression in IBD is 15%–25.2% worldwide.[12–14] IBD is accompanied by mood disorders, which include anxiety and

depression. Anxiety manifested as decreased and restless sleep, distraction, racing thoughts, irritability, agitation and other symptoms.[15] Meanwhile, depression is characterised by insomnia, hypersomnia, fatigue, indecisiveness and so on.[16] Moreover, anxiety and depression have aggravated the severity of IBD and affected its prognosis.[17 18] If the emotional disorders in IBD are untreated, it will lead to poor treatment compliance, serious disease duration and reduced quality of life.[10 19 20] In addition, depression and anxiety are the second and sixth causes of disability, respectively.[21–23] Although medical treatments, such as duloxetine, bupropion and phenelzine, are suggested for anxiety and depression, IBD with emotional disorders is often treated without customised guidelines.[24] Furthermore, several adverse effects are observed with antidepressant use, including increased risk of falls, nausea and vomiting, overweight and sleep problems.[25–27]

Acupuncture is increasingly used as a component complementary therapy for IBD improvement, such as the remission of diarrhoea, abdominal pain, bloody purulent stool, fatigue, etc.[28–32] There has been a systematic review showing that acupuncture is more effective than oral medication in the overall efficacy of IBD treatment.[33] For IBD complicated with emotional disorders, acupuncture has also been found to be effective for emotional improvement. For instance, some clinical studies have indicated that acupuncture improves emotional disorders. Sabbagh *et al* confirmed that acupuncture plays an additive anti-anxiety role.[34] Meanwhile, Zhang *et al* have found that acupuncture combined with low-dose fluoxetine is effective and has no side effects for patients with depression.[35] More importantly, Chunhui *et al* have shown that acupuncture can relieve the anxiety and depression of patients with Crohn's disease (CD) to decrease the self-rating anxiety scale and self-rating depression scale scores.[36] At the same time, Bao *et al* have also confirmed that acupuncture can improve the anxiety and depression in patients with CD at mild and moderate active stage to reduce the score of the Hospital Anxiety–Depression Scale (HADS).[37] The mechanism of the effect of acupuncture on the emotional problems of IBD may be associated with activation of the immunoinflammatory response,[38–40] adjustment of the brain–gut axis[41–43] and regulation of the plasma tryptophan–kynurenine metabolic pathway levels.[37]

Although the above clinical and mechanistic studies have indicated that acupuncture is possible to alleviate emotional symptoms of IBD, there still lacks a systematic review and data synthesis to prove the effects and safety of acupuncture for relieving emotional disorders of patients with IBD. Therefore, a systematic review with qualitative and quantitative meta-analysis will be conducted to seek whether acupuncture is effective for treating emotional disorders in patients with IBD.

This meta-analysis or systematic review aims to verify the effectiveness of acupuncture in alleviating emotional problems in patients with IBD.

METHODS

Criteria for considering studies in this review

Types of studies

Randomised controlled trials (RCTs) without language limitations reporting that acupuncture treats IBD with emotional disorders or assessing acupuncture treatment for IBD accompanied by assessment of outcome indicators of emotional disorders will be incorporated. However, non-RCTs and semi-RCTs will be eliminated.

Types of participants

Patients with IBD, ulcerative colitis (UC) or CD will be included without age or sex restriction. For instance, if the score of the HADS is greater than 8, the patient with IBD will be included. However, patients diagnosed with IBD but without emotional transformation will be eliminated. At the same time, patients with symptoms similar to IBD, such as irritable bowel syndrome and acute gastroenteritis, will be excluded.

Types of interventions

Acupuncture, including manual acupuncture, electroacupuncture, auricular acupuncture, scalp acupuncture, abdominal acupuncture, acupoint catgut embedding and warm needling, will be included. Acupuncture with positive interventions will also be included. However, non-invasive interventions, such as yoga, meditation and massage, will be eliminated.

Types of comparator(s)/control

The following comparators or control groups will be included:

1. Acupuncture versus sham/placebo acupuncture.
2. Acupuncture versus conventional therapy.
3. Acupuncture versus waiting list/no treatment.
4. Acupuncture combined with useful treatment versus other useful treatments alone.

Studies in which different acupoints or different forms of acupuncture were used in the control groups will be removed.

Types of outcome measures

Primary outcomes

The emotional functioning outcomes scale, comprising the Beck Depression Index (BDI), Beck Anxiety Inventory (BAI), Hamilton Anxiety Rating Scale (HAM-A), Hamilton Depression Rating Scale (HAM-D) and HADS, and the subscale for detecting emotional changes in the Inflammatory Bowel Disease Questionnaire (IBDQ), will be applied as the primary outcomes.

Secondary outcomes

1. The Colitis Activity Index (CAI) and Crohn's Disease Activity Index (CDAI) will be detected.
2. The C reactive protein will be measured.
3. Adverse events, including haematoma and syncope, and the number of participants dropping out.

Table 1 Search strategy used in MEDLINE database

No	Search items
#1	randomized controlled trial [pt]
#2	controlled clinical trial [pt]
#3	randomized [tiab]
#4	placebo [tiab]
#5	clinical trials as topic [sh]
#6	randomly [tiab]
#7	trial [ti]
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	animals [exp]/not humans [sh]
#10	#8 not #9
#11	Inflammatory bowel disease [exp]
#12	Crohn Disease [exp]
#13	Ulcerative colitis [exp]
#14	Colitis, Ulcerative [exp]
#15	Proctitis [exp]
#16	crohn*[mp]
#17	ulcerative adj colitis [mp]
#18	inflammatory bowel disease* [mp]
#19	IBD [mp]
#20	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
#21	acupuncture [exp]
#22	acupuncture therapy [exp]
#23	(body acupuncture or manual acupuncture or electroacupuncture or acupuncture points or auricular acupuncture or laser acupuncture or warm needling or acupuncture point embedding or moxibustion) [mp]
#24	#21 or #22 or #23
#25	#10 and #20 and #24

The first outcome after treatment will be chosen for the repeated measures of outcome in primary outcomes and secondary outcomes.

Search methods for the identification of studies

Electronic searches

The search terms, such as IBD, CD, UC, acupuncture and RCTs, will be sought in the electronic databases from inception to October 2021. Similarly, Chinese retrieval will use the matching words for English retrieval. The search strategy for MEDLINE is presented in table 1.

The databases are as follows: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Allied and Complementary Medicine Database, Cumulative Index to Nursing & Allied Health Literature, China National Knowledge Infrastructure, Chinese Biomedical Literature Database, VIP Database and Wanfang Database. The search strategy of electronic databases will be presented in online supplemental file.

Searching other resources

The following clinical registration platform will be retrieved to collect the data of ongoing trials: Chinese Clinical Trial Register (http://www.chictr.org/), WHO International Clinical Trial Registration Platform search portal (http://www.who.int/trialsearch/), Australian New Zealand Clinical Trials (http://www.anzctr.org.au/) and Clinical Trials.gov (http://www.clinicaltrials.gov/). Related trials in the reference lists will be inspected and further identified. The search strategy of clinical registration platform will be shown in online supplemental file. The first author and corresponding author will be contacted to complete the insufficient data.

Data collection and analysis

Selection of studies

The titles and abstracts of the literature from national and international databases will be cross-examined independently to meet the inclusion and exclusion criteria by two reviewers (G-LZ and NS). If the research cannot be identified by the titles and abstracts, the full text will be downloaded for further confirmation by a third reviewer (Y-FZ). Moreover, the references of full texts will be browsed and checked to identify possible RCTs of acupuncture treatment for IBD. The preclusive studies will be marked with a clear interpretation. In the process of literature selection, any arguments will be analysed and adjudicated by other reviewers (RS). A flow chart of the selection of studies is displayed in figure 1.

Data extraction and management

The data of qualified studies will be extracted separately by two reviewers (Z-QW and XY) according to the preformulated items in Microsoft Excel. In the extraction process, if a dispute arises but cannot be resolved, it will be decided by arbitration of the third party (JX). The data collection form will consist of the following information: reference ID, author information, publication year, study methods (experimental design, randomised method, method of assigning hidden, blinding method), participants (inclusion and exclusion criteria, sample size, age, sex, IBD type, duration of IBD), acupuncture and control group (type of acupuncture, style of the control group, duration of treatment, needle details, operational details), follow-up, outcomes (BDI, HAM-A, IBDQ, C reactive protein, CAI, CDAI), analysis data (intention-to-treat (ITT) and per-protocol analysis) and adverse events. Incomplete data will be provided by contacting the study authors. All data will be cross-tested and imported to RevMan software (V.5.4) by XL and XD.

Assessment of risk of bias in the included studies

The included studies will be evaluated according to the risk of bias involving sequence generation, allocation concealment, blinding of patients, acupuncture operators and outcome evaluators, incomplete outcome data, selective reporting, and other biases with low risk, high risk, and unclear of three levels of stratification according

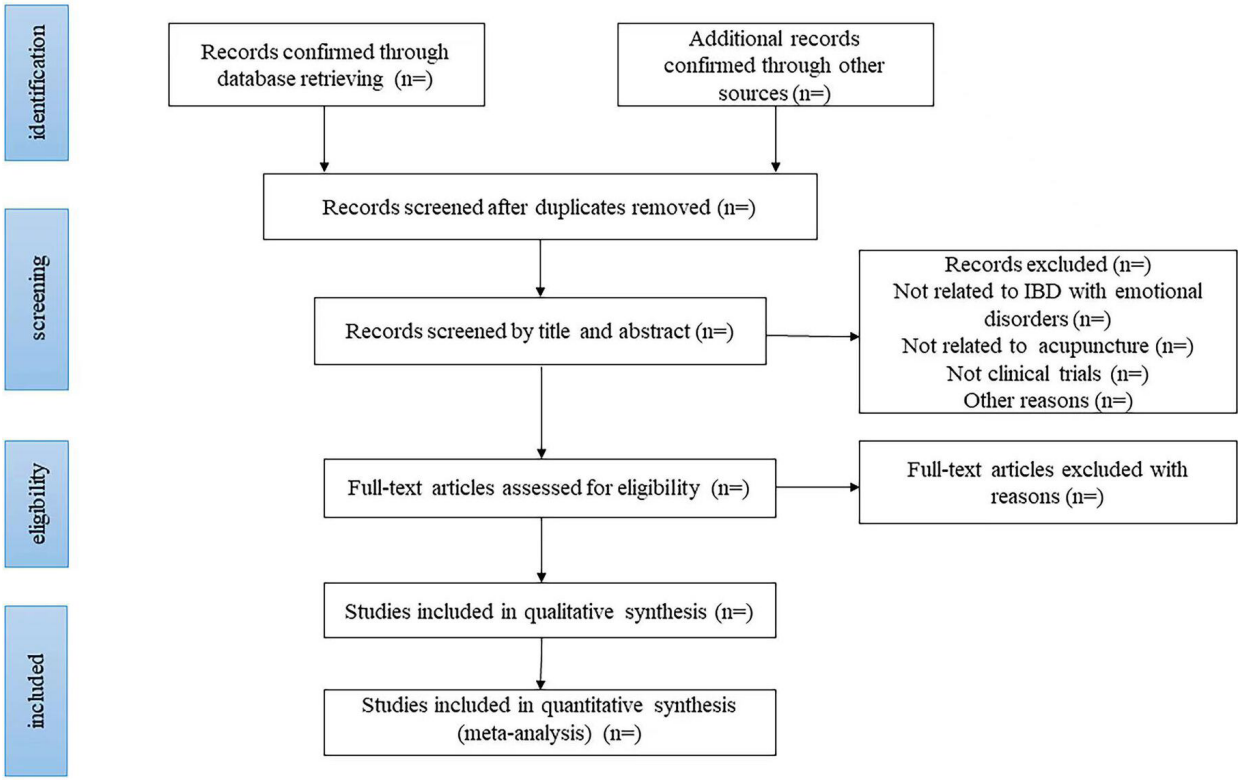

Figure 1 Flow diagram of the study selection process. IBD, inflammatory bowel disease.

to the Cochrane Handbook by two or more reviewers (PZ and HZ).[37] Any disagreements will be resolved by a third reviewer (YZ).

Measures of treatment effect

All eligible data will be synthesised and analysed using RevMan V.5.4. The binary outcome data (adverse events) will be handled by applying the risk ratio with 95% CIs. For continuous outcome data (BAI, BDI, HAM-A, HAM-D, HADS, IBDQ, C reactive protein, CDAI, CAI), if the measurement method and units are the same, the weighted mean difference with 95% CIs will be used. However, if the continuous variable has different units of measures or large differences in means, the standard mean difference with 95% CIs will be calculated.

Unit of analysis issues

The unit of analysis will be implemented according to the summary outcome data.

Dealing with missing data

The missing data or incomplete data will be supplemented by contacting the relevant authors of the study as far as possible. An ITT analysis will be preferentially used for all outcomes (ie, all randomised patients will be included in the analysis).[44] If the data cannot be obtained, only the available data will be analysed. If feasible, the missing data will be disposed of with a sensitivity analysis.

Assessment of heterogeneity

Heterogeneity will be evaluated using the X^2 test in the forest plot. Moreover, the total variation of the included studies will be assessed using the I^2 test. If the I^2 value is 0%–40%, it will be expressed as insignificant heterogeneity. If the I^2 value is 30%–60%, it will be indicated with moderate heterogeneity. If the I^2 value is 50%–90%, it will be indicated with abundant heterogeneity. If the I^2 value is 75%–100%, it will be represented with considerable heterogeneity.[45]

Assessment of reporting biases

A funnel plot will be used to reflect the publication bias when the number of RCTs exceeds 10 in the meta-analysis. The heterogeneity of the funnel plot will be identified by the Begg's and Egger's tests. Moreover, $p<0.05$ will imply an important reporting bias.[46]

Data synthesis

Data synthesis will be performed by importing clinical data into RevMan software (V.5.4). The random-effects model will be selected to pool and analyse the data. However, if I^2 is >75%, the meta-analysis will not be performed. In the case of $I^2 \geq 40\%$, the potential source of heterogeneity will be comprehended by subgroup analysis.

Subgroup analysis and investigation of heterogeneity

If the number of studies is sufficient and there is large heterogeneity between studies, a subgroup analysis will be performed to interpret the reasons for heterogeneity according to the types of acupuncture (manual acupuncture, electroacupuncture, body acupuncture), types of control (sham/placebo acupuncture, conventional

therapy, waiting list/no treatment), duration of treatment, age and sex.

Sensitivity analysis

Sensitivity analysis will be performed to examine the stability of the primary outcome based on the following factors: methodological quality (eg, whether sequence generation, allocation concealment, blinding of patients, acupuncture operators and outcome evaluators were fully performed) and sample size. If the results are inconsistent with the previous results, they will be discussed and interpreted.

Quality of the evidence

The Grading of Recommendations Assessment, Development and Evaluations (GRADE) system approach will be used to evaluate the quality of evidence for primary outcomes by two reviewers (Z-DG and KY).[47] The four grades of 'high', 'moderate', 'low' and 'very low' will be used to describe the quality of evidence. The evaluation for quality of evidence includes the following items: risk of bias, inconsistency, indirectness, imprecision, publication bias, large effect and dose–response.[48] The results of GRADE will be submitted in the summary of the finding table.

Patient and public involvement

No patient participation.

Ethics and dissemination

It is not necessary for the meta-analysis to provide ethical approval due to patient privacy without involvement. The results of the meta-analysis will be presented in a peer-reviewed journal or related conference.

DISCUSSION

Acupuncture is considered playing an effective role in improving emotional disorders in patients with IBD. Nevertheless, no systematic review related to this theme has been published. This meta-analysis will provide a more convincing judgement on acupuncture for IBD with emotional disorders. This study comprises four parts: identification, inclusion studies, data extraction and data synthesis. A potential limitation of this protocol may have an effect on the results. The diverse types of acupuncture may cause a large risk of heterogeneity.

Author affiliations
[1]Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China
[2]Department of Orthopedics, First Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China
[3]Rehabilitation Medicine Center and Institute of Rehabilitation Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan, China
[4]Key Laboratory of Rehabilitation Medicine in Sichuan Province, Chengdu, Sichuan, China
[5]Emergency Department, The First People's Hospital of Longquanyi District, Chengdu, Sichuan, China

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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ORCID iDs
Yuan-Fang Zhou http://orcid.org/0000-0002-5848-6432
Gui-Long Zhang http://orcid.org/0000-0002-1770-3656
Ning Sun http://orcid.org/0000-0002-1064-5705
Rui-Rui Sun http://orcid.org/0000-0003-0555-2042
Fan-Rong Liang http://orcid.org/0000-0001-8518-9268

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