TITLE PAGE

Title: Effect of Brain-gut Behavioral Treatments on Abdominal Pain in Irritable Bowel Syndrome: Systematic Review and Network Meta-analysis.

Short title: Brain-gut Behavioral Treatments for Abdominal Pain in IBS: Network Meta-analysis.

Authors: Vivek C. Goodoory[1,2]*, Mais Khasawneh[1,2]*, Elyse R. Thakur[3,4], Hazel A. Everitt[5], Gregory D. Gudleski[6], Jeffrey M. Lackner[6], Rona Moss-Morris[7], Magnus Simren[8], Dipesh H. Vasant[9,10], Paul Moayyedi[11], Christopher J. Black[1,2]†, Alexander C. Ford[1,2]†.

*Joint first author

†Joint last author

[1]Leeds Gastroenterology Institute, Leeds Teaching Hospitals NHS Trust, Leeds, UK.

[2]Leeds Institute of Medical Research at St. James's, University of Leeds, Leeds, UK.

[3]Department of Psychiatry & Behavioral Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA.

[4]Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX, USA.

[5]Primary Care Research Centre, Faculty of Medicine, University of Southampton, Southampton, UK.

[6]Division of Behavioral Medicine, Department of Medicine, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA.

[7]Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

[8]Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

[9]Neurogastroenterology Unit, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, UK.

[10]Division of Diabetes, Endocrinology and Gastroenterology, University of Manchester, Manchester, UK.

[11]Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada.

Grant support: None

Abbreviations:

AGA	American Gastroenterology Association
BGBT	brain-gut behavioral treatment
CBT	cognitive behavioral therapy
CI	confidence interval
DGBI	disorder of gut-brain interaction
FDA	Food and Drug Administration
IBS	irritable bowel syndrome
IBS-C	IBS with constipation
IBS-D	IBS with diarrhea
IBS-M	IBS with mixed stool pattern
RCT	randomized controlled trial
RR	relative risk
SNRI	serotonin norepinephrine reuptake inhibitor
TCA	tricyclic antidepressant

Correspondence: Professor Alex Ford

Leeds Gastroenterology Institute

Room 125

4th Floor

Bexley Wing

St. James's University Hospital

Beckett Street

Leeds

United Kingdom

LS9 7TF

Email: alexf12399@yahoo.com

Telephone: +441132684963

ORCID ID: 0000-0001-6371-4359

Twitter: @alex_ford12399

Disclosures: VCG: none. MK: none. ERT: speakers fees and advisory board honorariums for Mahana Therapeutics and Salix Pharmaceuticals. HAE is a beneficiary of a license agreement signed between King's College London and Mahana Therapeutics and received honorariums for consultancy to Mahana Therapeutics. GDG: none. JML: none. RMM reports fees from training in CBT for irritable bowel syndrome intervention for Central and Northwest London NHS Foundation Trust and University of East Anglia. She is a beneficiary of a license agreement signed between King's College London and Mahana Therapeutics and received honorariums for consultancy to Mahana Therapeutics. MS: none. DHV: none. PM: none. CJB: none. ACF: none.

Specific author contributions: Study concept and design: VCG, MK, ERT, PM, CJB and ACF conceived and drafted the study. VCG, MK, PM, CJB, and ACF analyzed, and interpreted the data. ACF and ERT drafted the manuscript. All authors have approved the final draft of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Guarantor: ACF is guarantor.

Writing assistance: None.

Word count: 6360

ABSTRACT

Objectives: Some brain-gut behavioral treatments (BGBTs) are beneficial for global symptoms in irritable bowel syndrome (IBS). US management guidelines suggest their use in patients with persistent abdominal pain but their specific effect on this symptom has not been assessed systematically.

Design: We searched the literature through 16th December 2023 for randomized controlled trials (RCTs) assessing efficacy of BGBTs for adults with IBS, compared with each other, or a control intervention. Trials provided an assessment of abdominal pain resolution or improvement at treatment completion. We extracted data as intention-to-treat analyses, assuming dropouts to be treatment failures and reporting pooled relative risks (RRs) of abdominal pain not improving with 95% confidence intervals (CIs), ranking therapies according to P-score.

Results: We identified 42 eligible RCTs, containing 5220 participants. After treatment completion, the BGBTs with the largest numbers of trials, and patients recruited, demonstrating efficacy for abdominal pain, specifically, included self-guided/minimal contact cognitive behavioral therapy (CBT) (RR = 0.71; 95% CI 0.54-0.95, P-score 0.58), face-to-face multicomponent behavioral therapy (RR = 0.72; 95% CI 0.54-0.97, P score 0.56), and face-to-face gut-directed hypnotherapy (RR = 0.77; 95% CI 0.61-0.96, P-score 0.49). Among trials recruiting only patients with refractory global IBS symptoms, group CBT was more efficacious than routine care for abdominal pain, but no other significant differences were detected. No trials were low risk of bias across all domains and there was evidence of funnel plot asymmetry.

Conclusions: Several BGBTs, including self-guided/minimal contact CBT, face-to-face multicomponent behavioral therapy, and face-to-face gut-directed hypnotherapy may be efficacious for abdominal pain in IBS, although none were superior to another.

Key words: abdominal pain; hypnosis; cognitive behavior therapy; evidence-based practice

INTRODUCTION

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction (DGBI),[1] and one of the most common conditions seen by gastroenterologists.[2] It affects between 5% and 10% of people globally,[3] and is characterized by abdominal pain in association with a change in stool frequency or form.[4] The pathophysiology is multifactorial and incompletely understood,[5] meaning it can be difficult to manage clinically, but the role of the gut-brain axis in its etiology is increasingly recognized as important. IBS impacts quality of life and ability to work and socialize.[6, 7] Direct costs to the health service are substantial, estimated at more than $10 billion in the US.[8]

Although most novel drug therapies for IBS target predominant stool pattern,[9, 10] recent evidence suggests there are subgroups of patients with IBS beyond those based on stool pattern alone.[11-13] In these alternative classification systems, one-in-five patients report abdominal pain as their predominant gastrointestinal symptom.[4] Current US management guidelines for IBS also recognize abdominal pain may be a persistent feature for some patients.[14, 15] Suggested treatments for abdominal pain in the American Gastroenterology Association (AGA) Clinical Decision Support Tool for IBS include antispasmodics or peppermint oil and, if persistent, gut-brain neuromodulators, such as tricyclic antidepressants (TCAs) or serotonin norepinephrine reuptake inhibitors (SNRIs), or brain-gut behavioral treatments (BGBTs), including cognitive behavioral therapy (CBT) or gut-directed hypnotherapy.[16] BGBTs have been defined as clinician-administered, short-term, non-pharmacologic interventions that prioritize the remediation of gastrointestinal symptoms over improvement of psychological comorbidity, although the latter is also possible.[17]

Although antispasmodic drugs appeared efficacious for abdominal pain in a meta-analysis,[18] results of individual randomized controlled trials (RCTs) were inconsistent. In another meta-analysis peppermint oil was beneficial for abdominal pain,[19] but efficacy was modest and more rigorously designed RCTs did not show any benefit. TCAs demonstrated a benefit for abdominal pain in a meta-analysis,[18] but based on four trials containing less than 200 patients. A definitive trial of

amitriptyline, published subsequently, has confirmed the drug to be superior to placebo for abdominal pain.[20] To our knowledge, there has been only one 12-week RCT of an SNRI assessing abdominal pain in IBS in 34 patients.[21] In this trial, venlafaxine led to significantly reduced abdominal pain frequency, compared with placebo. Given the overlap between predominant abdominal pain and psychological symptoms,[11, 12] and the role of the gut-brain axis in IBS, BGBTs seem a rational treatment choice because they not only have effects within the CNS, but also peripheral effects on pain perception and visceral hypersensitivity.[22-25] A prior network meta-analysis demonstrated several BGBTs were superior to a control in IBS,[26] but this was based on global symptom improvement in 38 of the 41 eligible trials. Less is known about the extent to which BGBTs impact abdominal pain, specifically, in IBS.

Given BGBTs are suggested by the AGA Clinical Decision Support Tool for IBS for patients with persistent abdominal pain,[16] assessment of their efficacy in this regard is warranted to support current, and inform future, management guidelines for IBS. We, therefore, undertook a network meta-analysis to assess efficacy of BGBTs for abdominal pain in IBS, rather than global symptoms, to estimate relative efficacy of the active interventions studied, as well as the control interventions, in all patients recruited to individual trials, as well as in those with refractory global symptoms. Network meta-analysis allows indirect, as well as direct, comparisons to be made across different RCTs, increases the number of participants' data available for analysis, and produces a credible ranking system of the likely efficacy of different psychological therapies, and control interventions, even when there are no trials making direct comparisons.

METHODS

Search Strategy and Study Selection

We searched MEDLINE (1st January 1947 to 16th December 2023), EMBASE, EMBASE Classic (1st January 1947 to 16th December 2023), PsychINFO (1st January 1806 to 16th December 2023), and the Cochrane central register of controlled trials to identify potential studies. We searched conference proceedings (Digestive Disease Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2001 and 2023 to identify studies published only in abstract form. Finally, we used the bibliographies of all articles to perform a recursive search.

Eligible RCTs examined the effect of BGBTs (Supplementary Table 1) on abdominal pain, specifically, in adults (≥16 years) with IBS. We included the first period of cross-over trials prior to cross-over to the second treatment (Table 1). The diagnosis of IBS could be based on either a physician's opinion or accepted symptom-based diagnostic criteria. Trials compared BGBTs with each other, or with a control. Eligible control interventions included any of waiting list "attention" control, where patients were left on a waiting list to receive the active intervention after the trial had ended, education and/or support, dietary and/or lifestyle advice, or routine care. Minimum duration of therapy and follow-up was ≥4 weeks. Trials had to report abdominal pain resolution or improvement as a dichotomous endpoint, preferably patient-reported, but if this was not recorded then as documented by the investigator, or mean abdominal pain scores, after completion of therapy. Where studies included patients with IBS among patients with other DGBI or did not report dichotomous or continuous data but were otherwise eligible, we contacted original investigators to obtain further information. We published the study protocol on the PROSPERO international prospective register of systematic reviews (registration number CRD42023466440). Ethical approval was not required.

We conducted a literature search, with the search strategy provided in the Supplementary Materials. We applied no language restrictions, with foreign language articles translated, if required. Two investigators (VCG or MK and ACF) evaluated all abstracts identified for eligibility, independently from each other. We obtained all potentially relevant papers, evaluating them in more detail, using pre-designed forms, to assess eligibility independently, according to the pre-defined criteria, with any disagreements between investigators resolved by discussion.

Outcome Assessment

The primary outcome assessed was efficacy of all BGBTs and control interventions in IBS, in terms of effect on abdominal pain after completion of treatment. Secondary outcomes included adverse events during therapy (total numbers, as well as adverse events leading to study withdrawal, and individual adverse events), if reported.

Data Extraction

We extracted all data independently. This was done by two investigators (VCG or MK and ACF) onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as a dichotomous outcome (abdominal pain unimproved). Otherwise, if mean abdominal pain scores at baseline and after completion of treatment were available, along with a SD, we imputed dichotomous responder and non-responder data, according to the methodology described by Furukawa *et al*.[27] A 30% improvement in abdominal pain score is determined from the formula: number of participants in each treatment arm at final follow-up x normal SD. The latter corresponds to (70% of the baseline mean abdominal pain score – follow-up mean abdominal pain score) / follow-up SD.

We also extracted the following data for each trial, where available: country, setting (primary, secondary, or tertiary care-based), whether concomitant IBS medications were allowed, type of

BGBT used, including duration of therapy and number of sessions, method of delivery, IBS criteria used, primary outcome measure utilized to define abdominal pain improvement or resolution following therapy and the instrument used to assess this, proportion of female patients, proportion of patients according to predominant stool pattern (IBS with constipation (IBS-C), diarrhea (IBS-D), or mixed stool pattern (IBS-M)), and whether trials recruited only patients whose global IBS symptoms were refractory to standard medical therapy. The BGBT used was assessed by a practicing gastrointestinal psychologist (ERT), based on the approach that it was felt to align with most closely. Hence, for some BGBTs, the therapy reported in the original study was reclassified for the purposes of this meta-analysis. We recorded the control interventions used, as we pooled these separately in the analysis to assess their relative efficacy. We extracted data as intention-to-treat analyses at the first point of follow-up after completion of treatment, with all dropouts assumed to be treatment failures (*i.e.*, abdominal pain unimproved at follow-up), wherever trial reporting allowed.

Quality Assessment and Risk of Bias

We performed risk of bias assessment at the study level. This was done by two investigators (VCG or MK and ACF) independently. We used the Cochrane risk of bias tool.[28] We resolved disagreements by discussion. We recorded the methods used to generate the randomization schedule and conceal treatment allocation, as well as whether blinding was implemented for participants, personnel, and outcomes assessment, whether there was evidence of incomplete outcomes data, and whether there was evidence of selective reporting of outcomes.

Data Synthesis and Statistical Analysis

We used the frequentist model to perform a network meta-analysis, with “netmeta” (version 0.9-0, https://cran.r-project.org/web/packages/netmeta/index.html) in R (version 4.0.1). We reported the network meta-analysis according to the PRISMA extension statement for network meta-

analyses.[29] Network meta-analysis results can give more precise estimates, compared with results from standard, pairwise analyses,[30, 31] and allow ranking of treatments to inform decisions.[32]

We produced a network plot with node and connection size corresponding to the number of study subjects and number of studies, respectively to examine the symmetry and geometry of the evidence, using Stata version 14 (Stata Corp., College Station, TX, USA). We produced comparison-adjusted funnel plots to explore publication bias or other small study effects, for all available comparisons, where sufficient numbers of studies existed,[33] using R (version 4.0.1). This is a scatterplot of effect size versus precision, measured via the inverse of the standard error. Symmetry around the effect estimate line indicates absence of publication bias, or small study effects.[34] We summarized efficacy of each active and control intervention tested with a pooled relative risk (RR) and 95% confidence interval (CI), using a random effects model as a conservative estimate. We used an RR of abdominal pain remaining unimproved at the first point of follow-up post-treatment; if the RR is less than 1 and the 95% CI does not cross 1 there is a significant benefit of one intervention over another.

Many meta-analyses use the I^2 statistic to measure heterogeneity.[35] Although this statistic is easy to interpret and does not vary with the number of studies, its value does increase with the number of patients included in the meta-analysis.[36] We, therefore, assessed global statistical heterogeneity across all comparisons using the τ^2 measure. Measures of τ^2 of 0.04, 0.16, and 0.36 are considered to represent low, moderate, and high heterogeneity, respectively.[37] We assessed inconsistency in the network analysis by comparing direct and indirect evidence, where available, by splitting the network estimates into the contribution of direct and indirect evidence, and looking for any statistically significant differences.

We ranked both active treatments and control interventions according to their respective P-score, which is a value between 0 and 1. P-scores are based on the point estimates and standard errors of the network estimates, and measure mean extent of certainty that one intervention is better

than another, averaged over all competing interventions.[38] The higher the score the greater the probability of the intervention being ranked as best.[38] However, magnitude, as well as rank, of the P-score should be considered. As the mean value of the P-score is always 0.5, individual treatments clustering around this value are likely to be of similar efficacy. Nevertheless, when interpreting the results, it is also important to take the RR and corresponding 95% CI for each comparison into account, rather than relying on rankings alone.[39] Due to the sparseness of information derived from direct comparisons for some active interventions, we performed a sensitivity analysis where only trials that had direct connections of active interventions to the four control interventions were included. Given the multitude of therapies studied and the fact that, in the US, BGBTs are suggested in patients with persistent abdominal pain,[16] we conducted subgroup analyses, where trials were grouped according to the type of BGBT studied, rather than how it was delivered, and also where only trials recruiting patients with refractory global IBS symptoms were included.

For our primary outcome of the effect of BGBTs on abdominal pain after completion of treatment, we used the Confidence in Network Meta-Analysis (CINeMA) framework to evaluate confidence in the direct and indirect treatment estimates from the network,[40, 41] which is endorsed by the Cochrane Collaboration. This includes the Risk of Bias from Missing Evidence in Network Meta-Analysis tool for evaluating reporting bias.[42]

RESULTS

Our search strategy generated 3134 citations, 123 articles of which we retrieved for further assessment as they appeared relevant (Supplementary Figure 1). Of these, 83 were excluded, leaving 40 eligible articles.[s1-s40] These contained 42 separate RCTs, comprising 5220 participants, 3726 of whom received a BGBT and 1494 a control intervention, as described in Supplementary Table 2. All were fully published. The agreement between investigators for trial eligibility was excellent (Kappa statistic = 0.89). We obtained abdominal pain data from authors of 12 RCTs.[s1-s3,, s9, s10, s12, s15, s16, s18, s30, s39, s40] Four trials that reported using digital CBT were re-classified as it was felt the BGBT utilized aligned more closely with digital acceptance and commitment therapy.[s1, s23, s24, s39] Adverse events were reported in insufficient detail in most trials, meaning data could not be pooled. Detailed characteristics of individual RCTs, including comparisons made, are provided in Supplementary Table 3 and risk of bias items in Supplementary Table 4. Only eight trials required a minimum abdominal pain threshold as part of their entry criteria.[s7, s12, s20, s26-s28, s30, s37] None of the trials were low risk of bias across all domains, although blinding as to whether a BGBT was received or not would be extremely difficult for both patients and therapists. Eight RCTs were judged as low risk of bias across all other domains.[s6, s10, s16, s23, s28, s39, s40] Efficacy by type of BGBT is provided in the Supplementary Materials.

Efficacy in Terms of Effect on Abdominal Pain at First Point of Follow-up Post-treatment

Thirteen RCTs provided dichotomous data for likelihood of abdominal pain being unimproved at completion of therapy,[s2, s5, s9, s12, s14-17, s20, s22, s24, s31, s37] and for the other 29 trials we imputed data. The network plot is provided in Figure 1. When data were pooled, there was minimal heterogeneity ($\tau^2 = 0.0332$). Funnel plot examination according to control intervention used suggested evidence of publication bias for trials comparing BGBTs with either routine care or waiting list control (Supplementary Figures 2 and 3), but there were too few studies comparing

efficacy with education/support or dietary/lifestyle advice to assess this. The netsplit analysis revealed significant differences between the direct and indirect treatment effect estimates only for face-to-face CBT versus routine care and versus waiting list control (Supplementary Table 5). Of all the BGBTs studied, digital gut-directed hypnotherapy was ranked first (RR of abdominal pain remaining unimproved = 0.19; 95% CI 0.09 to 0.43, P-score 0.99) (Figure 2a), but based on only one trial containing 188 patients assigned to active therapy.[s37] Digital relaxation therapy or training performed similarly (RR = 0.22; 95% CI 0.11 to 0.44, P-score 0.97), based on only two trials containing 230 patients assigned to active therapy.[s37, s38] Face-to-face stress management, mindfulness meditation training, and group CBT were also more efficacious than waiting list control (RR = 0.52; 95% CI 0.29 to 0.95, P-score 0.79, RR = 0.55; 95% CI 0.31 to 0.99, P-score = 0.75, and RR = 0.61; 95% CI 0.40 to 0.92, P-score 0.72) but only in two trials containing 31 patients,[s19, s33] one RCT containing 36 patients,[s13] and three trials containing 80 patients receiving active therapy,[s17, s21, s32] respectively. 95% CIs around the estimates for all these therapies were wide. The BGBTs with the largest numbers of trials and/or patients recruited, with evidence for efficacy for abdominal pain, included self-guided or minimal contact CBT (RR = 0.71; 95% CI 0.54 to 0.95, P-score 0.58), face-to-face multicomponent behavioral therapy (RR = 0.72; 95% CI 0.54 to 0.97, P score 0.56), and face-to-face gut-directed hypnotherapy (RR = 0.77; 95% CI 0.61 to 0.96, P-score 0.49). Among control interventions, dietary and/or lifestyle advice was ranked last (P-score 0.12), followed by waiting list control (P-score 0.14).

On indirect comparison, digital gut-directed hypnotherapy was superior to all other BGBTs, except digital relaxation therapy or training, and digital relaxation therapy or training was superior to all other BGBTs, except face-to-face stress management or emotional awareness training (Supplementary Table 6). No other BGBT was superior to any of the other active therapies. Only digital gut-directed hypnotherapy and digital relaxation therapy or training were superior to all four of the control interventions including waiting list control, education and/or support, dietary and/or

lifestyle advice, and routine care. Face-to-face stress management, group CBT, and face-to-face multicomponent behavioral therapy were all superior to both routine care and waiting list control. Using the CINeMA framework to evaluate confidence in the results of this endpoint and classifying the eight RCTs judged as low risk of bias across all domains other than blinding as being at low risk of bias,[s6, s10, s16, s23, s28, s39, s40] most direct comparisons across the network were rated as either very low or low confidence (Supplementary Table 7). Some indirect comparisons, including those related to digital gut-directed hypnotherapy, digital relaxation therapy, digital stress management, group relaxation therapy, and dietary and/or lifestyle advice, were moderate confidence.

When we performed an analysis where only trials that had direct connections of active interventions to the four control interventions were included, excluding four RCTs,[s1, s24, s37, s38] the pooled estimates of efficacy were unchanged. In this analysis face-to-face stress management, mindfulness meditation training, and emotional awareness training were ranked first (RR = 0.52; 95% CI 0.29 to 0.95, P-score 0.85), second (RR = 0.55; 95% CI 0.31 to 0.99, P-score = 0.80), and third (RR = 0.56; 95% CI 0.27 to 1.13, P-score 0.77) but only in two trials containing 31 patients,[s19, s33] one RCT containing 36 patients,[s13] and one trial containing 36 patients receiving active therapy,[s29] respectively (Figure 2b). Again, 95% CIs around the estimates for all these therapies were wide, and the BGBTs with the largest numbers of trials and/or patients recruited, with evidence for efficacy for abdominal pain, included self-guided or minimal contact CBT (RR = 0.71; 95% CI 0.54 to 0.95, P-score 0.61), face-to-face multicomponent behavioral therapy (RR = 0.72; 95% CI 0.54 to 0.97, P score 0.59), and face-to-face gut-directed hypnotherapy (RR = 0.77; 95% CI 0.61 to 0.96, P-score 0.51). On indirect comparison, no BGBT was superior to any of the other active therapies (Supplementary Table 8).

When we restricted the analysis to the 15 RCTs that stated that they only recruited patients with global IBS symptoms refractory to treatment,[s2, s3, s5, s10, s12, s15, s17-s19, s26, s30, s32, s35, s36] there was low heterogeneity between studies ($\tau^2 = 0.0560$). Contingency management ranked first (RR = 0.52;

95% CI 0.19 to 1.42, P-score 0.79) based on one RCT assigning 23 patients to active therapy,[s19] and group CBT second (RR = 0.58; 95% CI 0.30 to 1.15, P-score 0.77) (Supplementary Figure 4), based on two RCTs containing 68 patients receiving active therapy.[s17, s32] On indirect comparison, group CBT was superior to routine care (RR = 0.59; 95% CI 0.36 to 0.98) (Supplementary Table 9), but none of the other BGBTs were significantly more efficacious than each other or than any of the control interventions for the specific symptom of abdominal pain after indirect comparison.

DISCUSSION

BGBTs are suggested for persistent abdominal pain in IBS by the AGA Clinical Decision Support Tool.[16] However, to our knowledge, there has been no evidence synthesis to assess whether they are beneficial for this symptom. Our systematic review and network meta-analysis of 42 RCTs demonstrated several BGBTs were more efficacious than a control intervention of waiting list control for abdominal pain. These included digital gut-directed hypnotherapy, digital relaxation therapy or training, face-to-face stress management, mindfulness meditation training, group CBT, self-guided or minimal contact CBT, face-to-face multicomponent behavioral therapy, and face-to-face gut-directed hypnotherapy. However, the first four of these treatments were assessed in only one or two trials and, in some cases, contained small numbers of patients. After indirect comparison, digital gut-directed hypnotherapy and digital relaxation therapy or training were significantly more efficacious than almost all other active therapies, but this was only in one and two RCTs, respectively, and these estimates were based solely on indirect comparisons in the network. The BGBTs with the largest numbers of trials, and some of the largest numbers of patients recruited, with evidence for efficacy included self-guided or minimal contact CBT, face-to-face multicomponent behavioral therapy, and face-to-face gut-directed hypnotherapy. Of these three, only face-to-face multicomponent behavioral therapy was more efficacious than more than one control intervention, including both routine care and waiting list control. Most comparisons across this network were rated as either low or very low confidence. In patients with global IBS symptoms that were refractory to treatment, only group CBT appeared more efficacious than a control intervention of routine care. In terms of BGBT studied, digital acceptance and commitment therapy, CBT, and gut-directed hypnotherapy were superior to waiting list control and, in patients with refractory symptoms, CBT was superior to routine care. Regrettably, detailed adverse events were reported by few studies,[s15, s18] precluding any meaningful analysis, but underscoring the importance of this issue in the design of future trials.[43]

We were able to make indirect comparisons between over 5000 participants in the included RCTs. Because the individual trials took place across a wide variety of settings and countries, and many recruited patients with IBS with any stool pattern, results are likely to be generalizable to many patients with IBS. We used an intention-to-treat analysis, with all trial dropouts assumed to be symptomatic. We imputed dichotomous data for 29 trials, without which they would have been ineligible for inclusion, and contacted authors of 12 studies to obtain supplementary data and further maximize number of eligible trials. When imputing data, we used a 30% or more improvement in abdominal pain after treatment, approximating the Food and Drug Administration (FDA)-recommended endpoint for drug trials in IBS.[44] As four trials provided data for this endpoint as a dichotomous outcome,[s2, s15, s16, s37] this means for 33 of 42 included trials we used this outcome measure. Heterogeneity was minimal or low in all analyses. We conducted subgroup analysis of trials according to BGBT studied, and those that only recruited patients with global IBS symptoms refractory to treatment, to approximate an assessment of whether current suggestions to use BGBTs for persistent abdominal pain are evidence-based.[16]

There were differences between individual trials, in terms of the population studied, study setting, the interventions themselves (e.g., the protocols used by different individual studies assessing the same intervention) and the way they were applied, the duration of follow-up and, in nine trials, the endpoint used to define symptom improvement.[s5, s9, s12, s14, s17, s20, s22, s24, s31] Due to the high variability in treatment interventions and small sample sizes in many of the RCTs, there is limited generalizability of the data to all BGBTs. Moreover, several of the interventions were only studied in one or two trials, recruiting small numbers of patients, and most included IBS of all subtypes. This makes it difficult to draw definitive conclusions and determine which of the therapies are most efficacious, and in which patients. The netsplit analysis revealed evidence of inconsistency between the direct and indirect treatment evidence for face-to-face CBT versus routine care and versus waiting list control. There was evidence of funnel plot asymmetry in our main analysis, suggesting

publication bias or other small study effects. The efficacy of BGBTs may, therefore, have been overestimated. “Unpacking” validated questionnaires to impute only abdominal pain data may limit interpretation of the results, as the psychometric properties of some of these as measures of abdominal pain varies. On this note, the binary outcome of a 30% or more improvement in abdominal pain may be viewed as an over-simplification of treatment response and, in trials that are often small and only powered for the primary endpoint, means that these trials will be underpowered for this endpoint. This together with our use of an intention-to-treat analysis could have underestimated efficacy. However, the fact that only one trial used the Rome IV criteria,[s37] which mandate the presence of abdominal pain for the diagnosis of IBS, means that some individuals in the included RCTs may have had relatively mild pain severity at baseline. This could have affected the proportions of individuals meeting the 30% or more threshold for improvement we stipulated. Although we identified 42 trials, the number of patients receiving each individual therapy was lower than the numbers assigned to most licensed drugs whose effects on abdominal pain have been studied in other network meta-analyses.[9, 10] As most RCTs were conducted in Western populations, with two trials conducted in Japan,[s5, s32] two in Iran,[s29, s38] and one in Israel,[s6] our findings are not necessarily generalizable to other populations. In addition, no RCTs were judged as being at low risk of bias across all domains, because blinding the patient or therapist to treatment assignation would be almost impossible in trials of BGBTs. Only two RCTs were described as being double-blind,[s30, s37] although neither trial stated how this was done. Eight RCTs were judged as being low risk of bias across all other domains.[s6, s10, s16, s23, s28, s39, s40] Lack of blinding is less of an issue where trials do not used subjective endpoints, but this is not the case in trials in IBS. Efforts to mitigate potential bias due to lack of blinding by assessing pre-treatment expectancy of efficacy and credibility, as recommended by others,[45] was done by 10 of the included trials.[s1, s8, s13-s15, s17, s21, s24, s27] Finally, although we conducted a subgroup analysis including only trials that stated they recruited patients with refractory

symptoms, how this was defined may differ between individual RCTs, which may limit generalizability, and this is only a proxy measure for persistent abdominal pain.

The current study reveals evidence for a benefit of some BGBTs for abdominal pain, specifically, which is a cardinal symptom of IBS. The mechanism likely involves targeting cognitive and affective drivers of IBS through stress-sensitive pathways that regulate the gut-brain axis and modulate visceral pain.[46] However, there was little evidence for benefit for abdominal pain in patients whose global IBS symptoms are judged as being refractory to medical treatment. This suggests restricting their use to patients with persistent abdominal pain may be inappropriate. Beyond gastrointestinal symptom presentation, BGBTs are most appropriate for patients who have accepted their diagnosis, understand the gut-brain connection and the role of stress, have deficits in coping and/or present with maladaptive behaviors associated with gastrointestinal symptoms, and have the time, interest, and motivation to invest in behavior change. Other factors, including severe psychopathology, disordered eating, trauma, or lack of insight or motivation, may make patients inappropriate for BGBTs depending on severity and the therapist's skill level or expertise.[17] We also found that digitally delivered treatments may be beneficial for abdominal pain in IBS. Other than digital gut-directed hypnotherapy and digital relaxation therapy, for which estimates were based solely on indirect comparisons, no single BGBT was significantly more efficacious than any other active therapy, although it is uncertain whether this is due to insufficient numbers of trials, comparable outcomes, or other factors.[47, 48] Indeed, it important to understand patient characteristics, including pain, when considering appropriate digital therapeutic options. It has been suggested that patients with severe pain, or multiple somatic, extra-intestinal symptoms, may benefit most from gut-directed hypnotherapy, as opposed to patients with skills deficits and maladaptive behaviors who may benefit from CBT.[48]

Very few trials used currently accepted endpoints to assess the effect of BGBTs on abdominal pain. Future RCTs could consider assessing this in patients with IBS with persistent

abdominal pain according to accepted FDA-recommended endpoints. Given there was little evidence of a benefit in patients with refractory global IBS symptoms, this should also be examined in future studies. The trials we identified in this network meta-analysis utilized a variety of delivery methods for the therapies of interest and some, such as digital, telehealth, or home-based methods appeared promising. These delivery methods may be particularly welcome, as digital therapeutics improve access and reduce costs,[48] and many patients with IBS experience interference in their social activities and may, therefore, find it difficult to attend appointments in-person.[7] However, these latter findings needs to be replicated by others, and none of the included trials compared digitally delivered BGBTs with therapist-delivered ones directly. The comparable efficacy of most BGBTs across different approaches and delivery systems underscores the importance of conducting more detailed research that identifies specific subgroups of patients for whom these treatments are more effective.[49] Additionally, factors beyond efficacy including rapidity of response, cost effectiveness, accessibility, durability, time scale, safety profile, and breadth and scope of treatment gains, including improvement in quality of life and abdominal pain, may inform treatment selection to deliver optimal responses. All of this will assist in informing future management guidelines for IBS.

In summary, we found several BGBTs to be efficacious for abdominal pain, specifically, in IBS including self-guided or minimal contact CBT, face-to-face multicomponent behavioral therapy, face-to-face gut-directed hypnotherapy, digital gut-directed hypnotherapy, digital relaxation therapy or training, face-to-face stress management, mindfulness meditation training, and group CBT. Self-guided or minimal contact CBT, face-to-face multicomponent behavioral therapy, and face-to-face gut-directed hypnotherapy had the largest numbers of trials and patients. However, certainty in the evidence was mostly low to very low. Future RCTs should examine the impact of administering BGBTs in a way that allows better understanding of their benefit in specific groups of patients, particularly those in whom persistent abdominal pain is the main issue.[12, 13] Exploration of whether adapting protocols for some of the BGBTs studied could serve as a more targeted approach for

patients in whom abdominal pain is the predominant symptom would also be worthwhile. Investigators should also consider relevant adverse events, such as worsening of symptoms or deterioration of mood, which may affect efficacy, as well as which control condition to select, given the minimal differences between active treatment and either education and/or support or routine care in most of our analyses.

ACKNOWLEDGEMENTS

We are grateful to Brjann Ljotsson and Jenny Lovdahl for providing extra information and data from their studies.

REFERENCES

1. Drossman DA, Hasler WL. Rome IV-functional GI disorders: Disorders of gut-brain interaction. Gastroenterology 2016;150:1257-61.

2. Shivaji UN, Ford AC. Prevalence of functional gastrointestinal disorders among consecutive new patient referrals to a gastroenterology clinic. Frontline Gastroenterology 2014;5:266-271.

3. Oka P, Parr H, Barberio B, et al. Global prevalence of irritable bowel syndrome according to Rome III or IV criteria: A systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020;5:908-917.

4. Mearin F, Lacy BE, Chang L, et al. Bowel disorders. Gastroenterology 2016;150:1393-1407.

5. Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. Lancet Gastroenterol Hepatol 2016;1:133-146.

6. Goodoory VC, Guthrie EA, Ng CE, et al. Factors associated with lower disease-specific and generic health-related quality of life in Rome IV irritable bowel syndrome. Aliment Pharmacol Ther 2023;57:323-334.

7. Goodoory VC, Ng CE, Black CJ, et al. Impact of Rome IV irritable bowel syndrome on work and activities of daily living. Aliment Pharmacol Ther 2022;56:844-856.

8. Peery AF, Crockett SD, Murphy CC, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: Update 2018. Gastroenterology 2019;156:254-272.e11.

9. Black CJ, Burr NE, Camilleri M, et al. Efficacy of pharmacological therapies in patients with IBS with diarrhoea or mixed stool pattern: Systematic review and network meta-analysis. Gut 2020;69:74-82.

10. Black CJ, Burr NE, Quigley EMM, et al. Efficacy of secretagogues in patients with irritable bowel syndrome with constipation: Systematic review and network meta-analysis. Gastroenterology 2018;155:1753-1763.

11. Polster A, Van Oudenhove L, Jones M, et al. Mixture model analysis identifies irritable bowel syndrome subgroups characterised by specific profiles of gastrointestinal, extraintestinal somatic and psychological symptoms. Aliment Pharmacol Ther 2017;46:529-539.

12. Black CJ, Yiannakou Y, Guthrie EA, et al. A novel method to classify and subgroup patients with IBS based on gastrointestinal symptoms and psychological profiles. Am J Gastroenterol 2021;116:372-381.

13. Black CJ, Ng CE, Goodoory VC, et al. Novel symptom subgroups in individuals with irritable bowel syndrome predict disease impact and burden. Clin Gastroenterol Hepatol 2024;22:386-396.

14. Chang L, Sultan S, Lembo A, et al. AGA Clinical Practice Guideline on the pharmacological management of irritable bowel syndrome with constipation. Gastroenterology 2022;163:118-136.

15. Lembo A, Sultan S, Chang L, et al. AGA Clinical Practice Guideline on the pharmacological management of irritable bowel syndrome with diarrhea. Gastroenterology 2022;163:137-151.

16. Chang L, Lembo A, Sultan S. Spotlight: IBS treatment. Gastroenterology 2022;163:153.

17. Keefer L, Ballou SK, Drossman DA, et al. A Rome Working Team Report on brain-gut behavior therapies for disorders of gut-brain interaction. Gastroenterology 2022;162:300-315.

18. Black CJ, Yuan Y, Selinger CP, et al. Efficacy of soluble fibre, antispasmodic drugs, and gut-brain neuromodulators in irritable bowel syndrome: A systematic review and network meta-analysis. Lancet Gastroenterol Hepatol 2020;5:117-131.

19. Ingrosso MR, Ianiro G, Nee J, et al. Systematic review and meta-analysis: Efficacy of peppermint oil in irritable bowel syndrome. Aliment Pharmacol Ther 2022;56:932-941.

20. Ford AC, Wright-Hughes A, Alderson SL, et al. Amitriptyline at low-dose and titrated for irritable bowel syndrome as second-line treatment in primary care (ATLANTIS): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2023;402:1773-1785.

21. Sharbafchi MR, Afshar H, Adhamian P, et al. Effects of venlafaxine on gastrointestinal symptoms, depression, anxiety, stress, and quality of life in patients with the moderate-to-severe irritable bowel syndrome. J Res Med Sci. Volume 25, 2020:115.

22. Lowen MB, Mayer EA, Sjoberg M, et al. Effect of hypnotherapy and educational intervention on brain response to visceral stimulus in the irritable bowel syndrome. Aliment Pharmacol Ther 2013;37:1184-1197.

23. Simren M, Ringstrom G, Bjornsson ES, et al. Treatment with hypnotherapy reduces the sensory and motor component of the gastrocolonic response in irritable bowel syndrome. Psychosom Med 2004;66:233-238.

24. Lea R, Houghton LA, Calvert EL, et al. Gut-focused hypnotherapy normalizes disordered rectal sensitivity in patients with irritable bowel syndrome. Aliment Pharmacol Ther 2003;17:635-42.

25. Houghton LA, Calvert EL, Jackson NA, et al. Visceral sensation and emotion: A study using hypnosis. Gut 2002;51:701-4.

26. Black CJ, Thakur ER, Houghton LA, et al. Efficacy of psychological therapies for irritable bowel syndrome: Systematic review and network meta-analysis. Gut 2020;69:1441-1451.

27. Furukawa TA, Cipriani A, Barbui C, et al. Imputing response rates from means and standard deviations in meta-analyses. Int Clin Psychopharmacol 2005;20:49-52.

28. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions: Version 5.1.0 [updated March 2011]. http://handbook-5-1.cochrane.org/ 2011.

29. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. Ann Intern Med 2015;162:777-84.

30. Salanti G, Higgins JP, Ades AE, et al. Evaluation of networks of randomized trials. Stat Methods Med Res 2008;17:279-301.

31. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: Many names, many benefits, many concerns for the next generation evidence synthesis tool. Res Synth Methods 2012;3:80-97.

32. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: An overview and tutorial. J Clin Epidemiol 2011;64:163-71.

33. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.

34. Chaimani A, Higgins JP, Mavridis D, et al. Graphical tools for network meta-analysis in STATA. PLoS One 2013;8:e76654.

35. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-560.

36. Rucker G, Schwarzer G, Carpenter JR, et al. Undue reliance on I(2) in assessing heterogeneity may mislead. BMC Med Res Methodol 2008;8:79.

37. da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: Principles and pitfalls. Eur Heart J 2014;35:3336-45.

38. Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol 2015;15:58.

39. Morton SC, Murad MH, O'Connor E, et al. AHRQ methods for effective health care. Quantitative synthesis-an update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US), 2018.

40. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. PLoS Med 2020;17:e1003082.

41. Papakonstantinou T, Nikolakopoulou A, Higgins JPT, et al. CINeMA: Software for semiautomated assessment of the confidence in the results of network meta-analysis. Campbell Systematic Reviews 2020;16:e1080.

42. Chiocchia V, Nikolakopoulou A, Higgins JPT, et al. ROB-MEN: A tool to assess risk of bias due to missing evidence in network meta-analysis. BMC Med 2021;19:304.

43. Palermo TM, Slack K, Loren D, et al. Measuring and reporting adverse events in clinical trials of psychological treatments for chronic pain. Pain 2020;161:713-717.

44. Food and Drug Administration. Guidance for industry: Irritable bowel syndrome - clinical evaluation of drugs for treatment. https://www.fda.gov/media/78622/download. 2012.

45. Munder T, Barth J. Cochrane's risk of bias tool in the context of psychotherapy outcome research. Psychother Res 2018;28:347-355.

46. Lacy BE, Pimentel M, Brenner DM, et al. ACG Clinical Guideline: Management of irritable bowel syndrome. Am J Gastroenterol 2021;116:17-44.

47. Lackner JM, Mesmer C, Morley S, et al. Psychological treatments for irritable bowel syndrome: A systematic review and meta-analysis. J Consult Clin Psychol 2004;72:1100-1113.

48. Brenner DM, Ladewski AM, Kinsinger SW. Development and current state of digital therapeutics for irritable bowel syndrome. Clin Gastroenterol Hepatol 2024;22:222-234.

49. Lackner JM, Jaccard J. Factors associated with efficacy of cognitive behavior therapy vs education for patients with irritable bowel syndrome. Clin Gastroenterol Hepatol 2019;17:1500-1508.e3.

Table 1. Eligibility Criteria.

Randomized controlled trials
Adults (participants aged ≥16 years)
Diagnosis of IBS based on either a clinician's opinion, or meeting specific diagnostic criteria*, supplemented by negative investigations where trials deemed this necessary.
Compared BGBTs with each other or with a control intervention, including waiting list control, education and/or support, dietary and/or lifestyle advice, or routine care.
Minimum duration of therapy 4 weeks.
Minimum duration of follow-up 4 weeks
Dichotomous assessment of response to therapy in terms of effect on abdominal pain, or continuous data in the form of effect on abdominal pain scores, following therapy.†

*Manning criteria, Kruis score, Rome I, II, III, or IV criteria.

†Preferably patient-reported, but if this was not available then as assessed by a physician.

FIGURE LEGENDS

Figure 1. Network Plot for Failure to Achieve an Improvement in Abdominal Pain Post-treatment.

Note: Circle (node) size is proportional to the number of study participants assigned to receive each intervention. The line width (connection size) corresponds to the number of studies comparing the individual treatments.

Figure 2a. Forest Plot for Failure to Achieve an Improvement in Abdominal Pain Post-treatment.

Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

Figure 2b. Forest Plot for Failure to Achieve an Improvement in Abdominal Pain Post-treatment Including Only Trials with A Direct Connection to the Four Control Interventions.

Note: The P-score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.