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FUNCTIONAL GI DISEASE

Effect of Brain-Gut Behavioral Treatments on Abdominal Pain in Irritable Bowel Syndrome: Systematic Review and Network Meta-Analysis

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e1. Learning Objective: Upon completion of this CME activity, successful learners will be able to understand the efficacy of brain-gut behavioral treatments for abdominal pain in irritable bowel syndrome.

See editorial on page 843.

BACKGROUND & AIMS: Some brain-gut behavioral treatments (BGBTs) are beneficial for global symptoms in irritable bowel syndrome (IBS). United States management guidelines suggest their use in patients with persistent abdominal pain, but their specific effect on this symptom has not been assessed systematically. **METHODS:** We searched the literature through December 16, 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 the P score. **RESULTS:** We identified 42 eligible randomized controlled trials comprising 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 was superior to another.

Keywords: Abdominal Pain; Hypnosis; Cognitive Behavior Therapy; Evidence-Based Practice.

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction,[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 IBS 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

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Abbreviations used in this paper: AGA, American Gastroenterology Association; BGBT, brain-gut behavioral treatment; CBT, cognitive behavioral therapy; CI, confidence interval; IBS, irritable bowel syndrome; RCT, randomized controlled trial; RR, relative risk; SD, standard deviation; TCA, tricyclic antidepressant.

Most current article

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

United States management guidelines suggest the use of brain-gut behavioral treatments for persistent abdominal pain in irritable bowel syndrome (IBS), but their efficacy in this regard is uncertain.

NEW FINDINGS

In network meta-analysis, brain-gut behavioral treatments demonstrating efficacy for abdominal pain, specifically, included self-guided or minimal contact cognitive behavioral therapy, face-to-face multicomponent behavioral therapy, and face-to-face gut-directed hypnotherapy.

LIMITATIONS

There was evidence of possible publication bias, and few trials were powered to report effect on abdominal pain in IBS as a primary or secondary end point.

CLINICAL RESEARCH RELEVANCE

Several brain-gut behavioral treatments, including self-guided or minimal contact cognitive behavioral therapy, face-to-face multicomponent behavioral therapy, and face-to-face gut-directed hypnotherapy, may be efficacious for abdominal pain in IBS. However, none was superior to another.

BASIC RESEARCH RELEVANCE

Not applicable.

costs to the health service are substantial, estimated at >$10 billion in the United States.[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, 1 in 5 patients report abdominal pain as their predominant gastrointestinal symptom.[4] Current United States 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, 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, nonpharmacologic 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. Another meta-analysis found 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 was based on 4 trials containing <200 patients. A definitive trial of amitriptyline, published subsequently, has confirmed the drug is superior to placebo for abdominal pain.[20] To our knowledge, there has been only one 12-week RCT of a serotonin norepinephrine reuptake inhibitor 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 have effects not only within the central nervous system but also peripherally 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 the efficacy of BGBTs for abdominal pain in IBS, rather than global symptoms, to estimate relative efficacy of the active interventions studied and 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 (January 1, 1947, to December 16, 2023), EMBASE, EMBASE Classic (January 1, 1947, to December 16, 2023), PsychINFO (January 1, 1806, to December 16, 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 before cross-over to the second treatment (Table 1). The diagnosis of IBS could be based on 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

Table 1. Eligibility Criteria

Randomized controlled trials
Adults (participants aged $\geq$16 years)
Diagnosis of IBS based on a clinician's opinion or meeting specific diagnostic criteria,[a] supplemented by negative investigations where trials deemed this necessary.
Compared BGBTs with each other or with a control intervention, including waiting list control, education or support, or both, dietary or lifestyle advice, or both, 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, after therapy.[b]

[a]Manning criteria, Kruis score, Rome I, II, III, or IV criteria.
[b]Preferably patient-reported, but if this was not available, then as assessed by a physician.

after the trial had ended, education or support, or both, dietary or lifestyle advice, or both, or routine care. Minimum duration of therapy and follow-up was $\geq$4 weeks. Trials had to report abdominal pain resolution or improvement as a dichotomous end point, 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 disorder of gut-brain interaction 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 (V.C.G. or M.K. and A.C.F.) evaluated all abstracts identified for eligibility, independently from each other. We obtained all potentially relevant papers, evaluating them in more detail, using predesigned forms, to assess eligibility independently according to the predefined 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 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 2 investigators (V.C.G. or M.K. and A.C.F.) onto an Excel spreadsheet (XP Professional Edition; Microsoft Corp, Redmond, WA) 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 standard deviation (SD), we imputed dichotomous responder and nonresponder data according to the methodology described by Furukawa et al.[27] A 30% improvement in an abdominal pain score is determined from the formula: number of participants in each treatment arm at final follow-up $\times$ 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 used to define abdominal pain improvement or resolution after therapy and the instrument used to assess this, proportion of female patients, proportion of patients according to predominant stool pattern (IBS with constipation, diarrhea, or mixed stool pattern), 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 (E.R.T.), 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 because 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 (ie, 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 2 investigators (V.C.G. or M.K. and A.C.F.) independently. We used the Cochrane Risk of Bias tool.[28] Disagreements were resolved 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" 0.9-0 (https://cran.r-project.org/web/packages/netmeta/index.html) in R 4.0.1 software. We reported the network meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 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 14 software (StataCorp, College Station, TX). Comparison-adjusted funnel plots were produced to explore publication bias or other small study effects, for all available comparisons, where sufficient numbers of studies existed,[33] using R 4.0.1. This is a scatterplot of effect size vs 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 after treatment; if the RR is <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 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. Because 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, taking the RR and corresponding 95% CI for each comparison into account is also important rather than relying on rankings alone.[39] Owing 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 4 control interventions were included. Given the multitude of therapies studied and that in the United States, 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 because they appeared relevant (Supplementary Figure 1). Of these, 83 were excluded, leaving 40 eligible articles.[e1–e40] 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 (κ statistic = 0.89). We obtained abdominal pain data from authors of 12 RCTs.[e1–e3,e9,e10,e12,e15,e16,e18,e30,e39,e40] Four trials that reported using digital CBT were reclassified because we believed the BGBT used aligned more closely with digital acceptance and commitment therapy.[e1,e23,e24,e39] 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 8 trials required a minimum abdominal pain threshold as part of their entry criteria.[e7,e12,e20,e26–e28,e30,e37] None of the trials were low risk of bias across all domains, although blinding on 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.[e6,e10,e16,e23,e28,e39,e40] Efficacy by type of BGBT is provided in the Supplementary Materials.

Efficacy in Effect on Abdominal Pain at First Point of Follow-up After Treatment

Thirteen RCTs provided dichotomous data for likelihood of abdominal pain being unimproved at completion of therapy,[e2,e5,e9,e12,e14–e17,e20,e22,e24,e31,e37] and we imputed data for the other 29 trials. The network plot is provided in Figure 1. When data were pooled, there was minimal heterogeneity (τ^2 = 0.0332). Funnel plot examination according to the control intervention used suggested evidence of

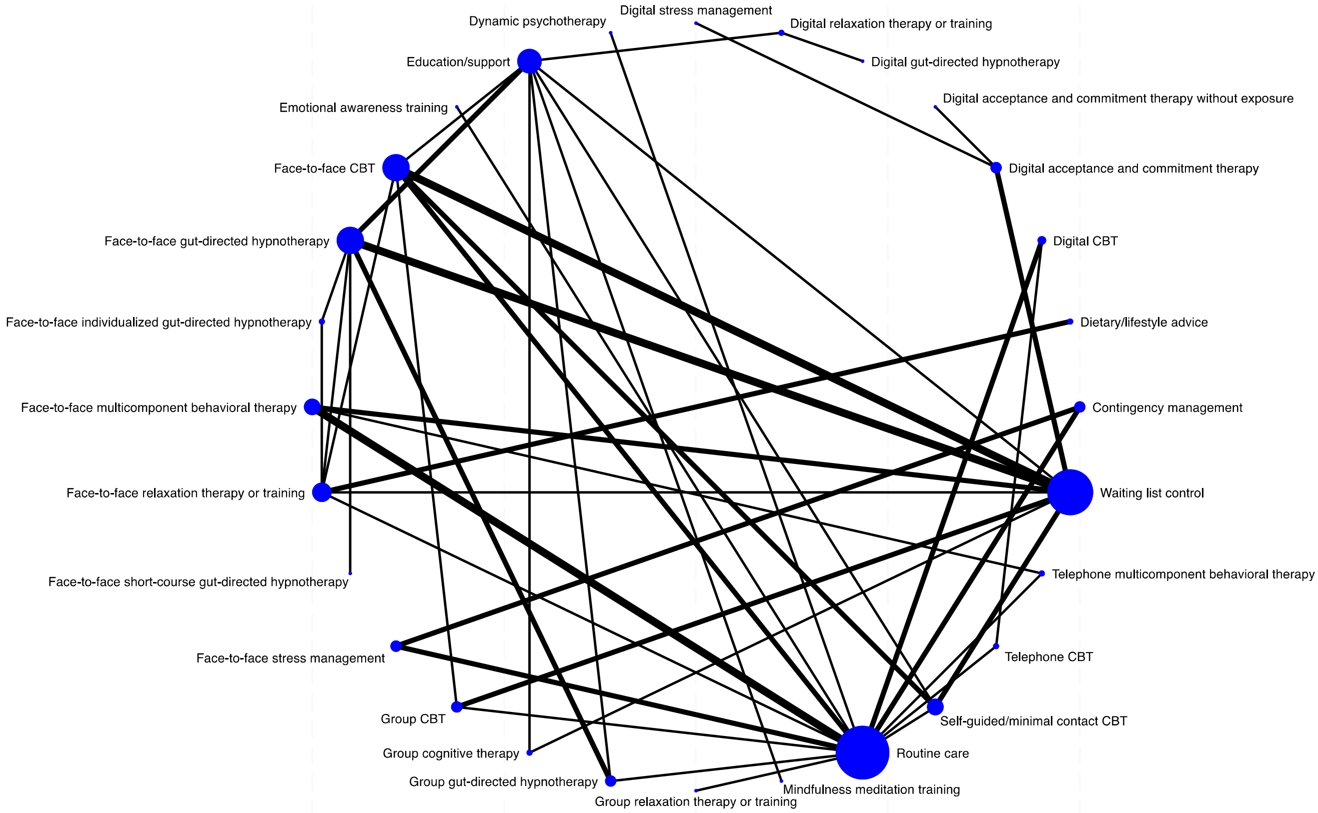

Figure 1. Network plot for failure to achieve an improvement in abdominal pain after treatment. *Circle* (node) size is proportional to the number of study participants assigned to receive each intervention. The *line* width (connection size) corresponds to the number of studies comparing the individual treatments.

publication bias for trials comparing BGBTs with 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 vs routine care and vs 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–

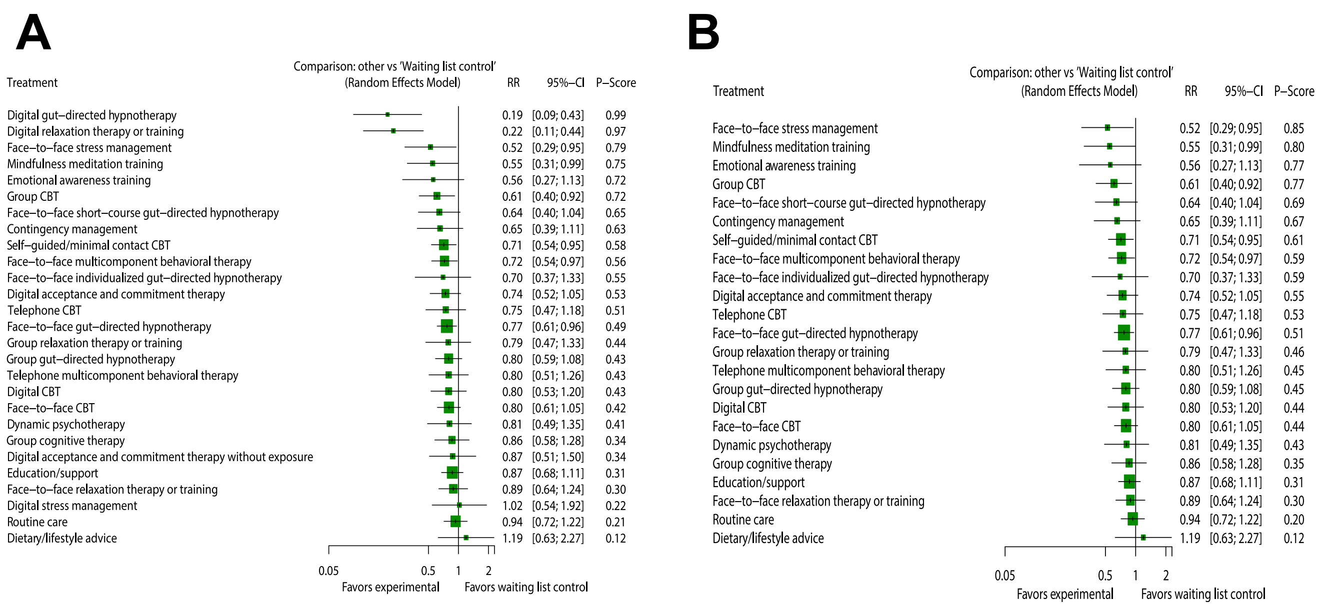

Figure 2. Forest plots for failure to achieve an improvement in abdominal pain (*A*) after treatment and (*B*) after treatment including only trials with a direct connection to the 4 control interventions. The P score is the probability of each treatment being ranked as best in the network analysis. A higher score equates to a greater probability of being ranked first.

0.43; P-score, 0.99) (Figure 2A), but based on only 1 trial containing 188 patients assigned to active therapy.[e37] Digital relaxation therapy or training performed similarly (RR, 0.22; 95% CI, 0.11–0.44; P score, 0.97), based on only 2 trials containing 230 patients assigned to active therapy.[e37,e38] Also more efficacious than waiting list control were face-to-face stress management (RR, 0.52; 95% CI, 0.29–0.95; P-score, 0.79) mindfulness meditation training (RR, 0.55; 95% CI, 0.31–0.99; P-score, 0.75), and group CBT (RR, 0.61; 95% CI, 0.40–0.92; P-score, 0.72) but only in 2 trials containing 31 patients,[e19,e33] 1 RCT containing 36 patients,[e13] and 3 trials containing 80 patients receiving active therapy.[e17,e21,e32] The 95% CIs around the estimates for all these therapies were wide. The BGBTs with the largest numbers of trials or patients recruited, with evidence for efficacy for abdominal pain, included self-guided or minimal contact 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 control interventions, dietary 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 4 of the control interventions, including waiting list control, education or support, dietary 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 8 RCTs judged as low risk of bias across all domains other than blinding as being at low risk of bias,[e6,e10,e16,e23,e28,e39,e40] 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 or lifestyle advice, were moderate confidence.

When we performed an analysis where only trials that had direct connections of active interventions to the 4 control interventions were included, excluding 4 RCTs,[e1,e24,e37,e38] 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, 0.29–0.95; P-score, 0.85), second (RR, 0.55; 95% CI, 0.31–0.99; P-score, 0.80), and third (RR, 0.56; 95% CI, 0.27–1.13; P-score, 0.77) but only in 2 trials containing 31 patients,[e19,e33] 1 RCT containing 36 patients,[e13] and 1 trial containing 36 patients receiving active therapy,[e29] respectively (Figure 2B). Again, 95% CIs around the estimates for all these therapies were wide, and the BGBTs with the largest numbers of trials or patients recruited, with evidence for efficacy for abdominal pain, included self-guided or minimal contact CBT (RR, 0.71; 95% CI, 0.54–0.95; P-score, 0.61), face-to-face multicomponent behavioral therapy (RR, 0.72; 95% CI, 0.54–0.97; P score, 0.59), and face-to-face gut-directed hypnotherapy (RR, 0.77; 95% CI, 0.61–0.96; 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,[e2,e3,e5,e10,e12,e15,e17–e19,e26,e30,e32,e35,e36] there was low heterogeneity between studies ($\tau^2 = 0.0560$). Contingency management ranked first (RR, 0.52; 95% CI, 0.19–1.42; P-score, 0.79) based on 1 RCT assigning 23 patients to active therapy,[e19] and group CBT second (RR, 0.58; 95% CI, 0.30–1.15; P-score, 0.77) (Supplementary Figure 4), based on 2 RCTs containing 68 patients receiving active therapy.[e17,e32] On indirect comparison, group CBT was superior to routine care (RR, 0.59; 95% CI, 0.36–0.98) (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 4 of these treatments were assessed in only 1 or 2 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 1 and 2 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 3, only face-to-face multicomponent behavioral therapy was more efficacious than more than 1 control intervention, including both routine care and waiting list control. Most comparisons across this network were rated as 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 BGBTs 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,[e15,e18] 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 >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% improvement in abdominal pain after treatment, approximating the United States Food and Drug Administration-recommended end point for drug trials in IBS.[44] Because 4 trials provided data for this end point as a dichotomous outcome,[e2,e15,e16,e37] this means we used this outcome measure for 33 of 42 included trials. 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 the population studied, study setting, the interventions themselves (eg, the protocols used by different individual studies assessing the same intervention) and the way they were applied, the duration of follow-up and, in 9 trials, the end point used to define symptom improvement.[e5,e9,e12,e14,e17,e20,e22,e24,e31] Owing 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 1 or 2 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 vs routine care and vs 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, because the psychometric properties of some of these as measures of abdominal pain vary. On this note, the binary outcome of a ≥30% improvement in abdominal pain may be viewed as an oversimplification of treatment response and, in trials that are often small and only powered for the primary end point, means that these trials will be underpowered for this end point. This, together with our use of an intention-to-treat analysis, could have underestimated efficacy. However, only 1 trial used the Rome IV criteria,[e37] which mandate the presence of abdominal pain for the diagnosis of IBS, which 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% 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] Because most RCTs were conducted in Western populations, with 2 trials conducted in Japan,[e5,e32] 2 in Iran,[e29,e38] and 1 in Israel,[e6] 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 2 RCTs were described as being double-blind,[e30,e37] although neither trial stated how this was done. Eight RCTs were judged as being low risk of bias across all other domains.[e6,e10,e16,e23,e28,e39,e40] Lack of blinding is less of an issue where trials do not use subjective end points, but this is not the case in trials in IBS. Efforts to mitigate potential bias due to lack of blinding by assessing pretreatment expectancy of efficacy and credibility, as recommended by others,[45] was done by 10 of the included trials.[e1,e8,e13–e15,e17,e21,e24,e27]

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 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, extraintestinal 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 end points 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 Food and Drug Administration-recommended end points. 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 used 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, because 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 need 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.

Conclusion

In summary, we found several BGBTs were 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 support or routine care in most of our analyses.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2024.05.010.

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Data Availability
Study data will be made available to other investigators on reasonable request.

Supplementary Methods

Search Strategy

Studies on IBS were identified with the terms *irritable bowel syndrome* and *functional diseases, colon* (both as medical subject heading [MeSH] and free text terms), and *IBS*, *spastic colon*, *irritable colon*, or *functional* adj5 *bowel* (as free text terms). These were combined using the set operator ***and***, with studies identified with the terms *cognitive therapy*, *psychotherapy*, *behaviour therapy*, *relaxation therapy*, or *hypnosis* (both as MeSH terms and free text terms), and the following free text terms: *cognitive behavioral therapy*, *cognitive behavioural therapy*, *cognitive behaviour therapy*, *relaxation technique*, *stress management*, *contingency management*, *mindfulness meditation*, *dynamic psychotherapy*, *behavioral therapy*, *behavioural therapy*, *behavior therapy*, *hypnotherapy*, *mesmerism*, or *imagery*.

Supplementary Results

Efficacy by Type of Brain-Gut Behavioral Treatment in Effect on Abdominal Pain at First Point of Follow-up After treatment

Three trials compared different delivery methods of the same type of BGBT without any comparison with a control intervention and were, therefore, excluded from this analysis,[e1–e3] leaving 39 eligible RCTs.[e4–e40] Heterogeneity between studies was low ($\tau^2 = 0.0439$). Of all the BGBTs studied, emotional awareness training ranked first (RR, 0.56; 95% CI, 0.27–1.17; P score, 0.80) (Supplementary Figure 5), but based on only 1 trial containing 36 patients assigned to active therapy.[e29] Digital acceptance and commitment therapy was ranked second (RR, 0.65; 95% CI, 0.46–0.92; P score, 0.75), based on 3 trials comprising 171 patients assigned to active therapy.[e23,e24,e39] Also efficacious for abdominal pain were CBT (RR, 0.75; 95% CI, 0.59–0.94; P score, 0.61) and gut-directed hypnotherapy (RR, 0.77; 95% CI, 0.61–0.97; P score, 0.55) and in 12 trials containing 955 patients,[e7,e11,e14–e18,e21,e25,e32,e4,e40] and 8 trials containing 686 patients receiving active therapy,[e10,e22,e26,e30,e35–e37] respectively. None of the other therapies were more efficacious than any of the control interventions. After indirect comparison, CBT was superior to both routine care and waiting list control, but there were no other significant between-group differences (Supplementary Table 10).When we restricted the analysis to the 13 RCTs that stated that they only recruited patients with global IBS symptoms refractory to treatment,[e5,e10,e12,e15,e17–e19,e26,e30,e32,e35,e36] there was low heterogeneity between studies ($\tau^2 = 0.0324$). Contingency management was ranked first (RR, 0.54; 95% CI, 0.24–1.21; P score, 0.85) (Supplementary Figure 6), based on 1 RCT assigning 23 patients to active therapy.[e19] However, none of the different types of BGBT studied were more efficacious for abdominal pain. After indirect comparison, CBT was superior to dietary/lifestyle advice (RR, 0.75; 95% CI, 0.57–0.98) (Supplementary Table 11), and contingency management was superior to dietary/lifestyle advice (RR, 0.18; 95% CI, 0.03–0.96), but no other significant differences were detected.

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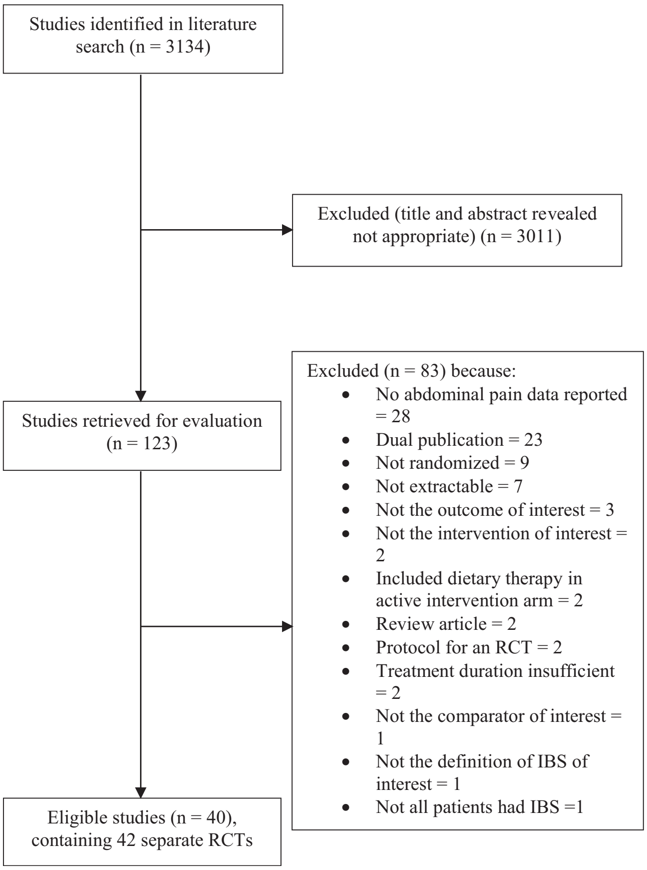
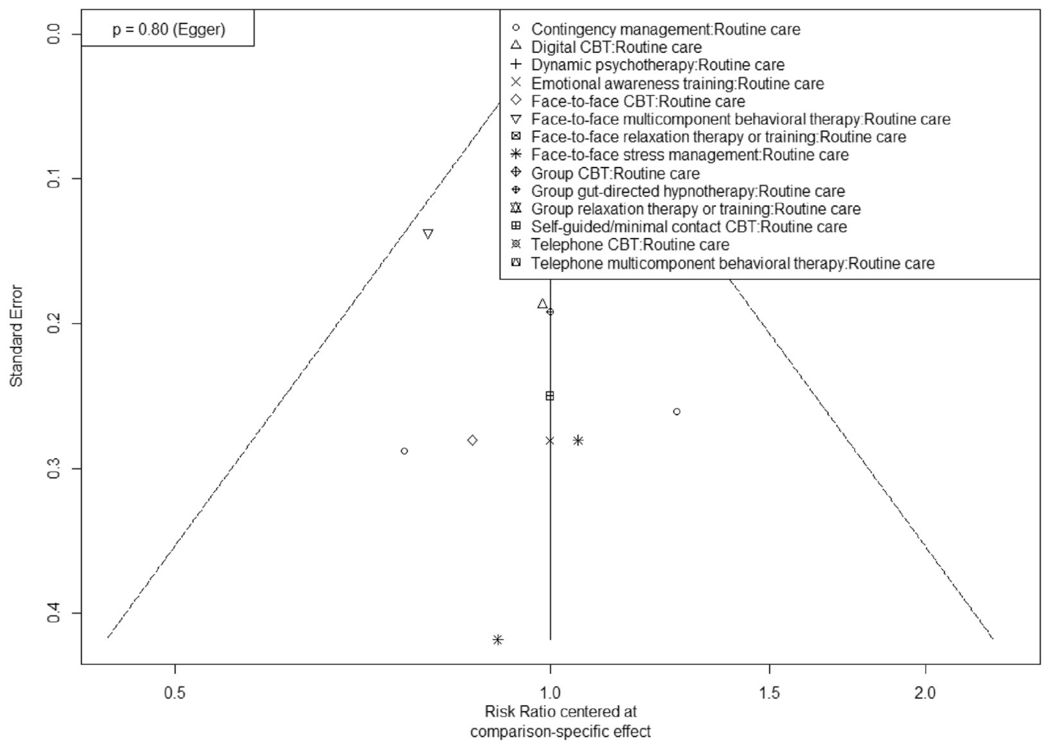
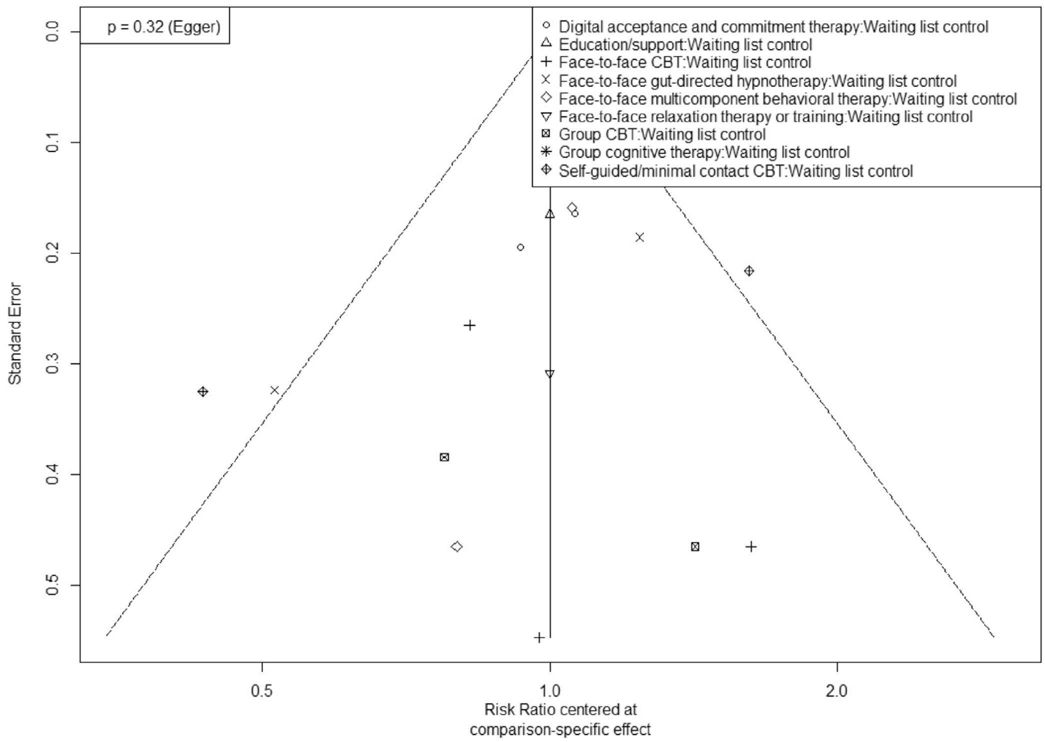


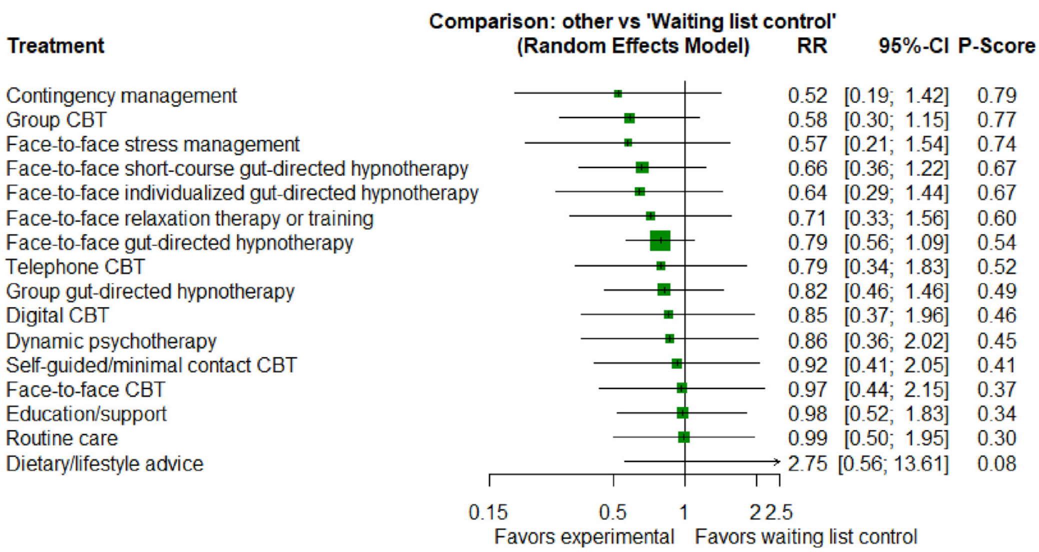
Supplementary Figure 1. Flow diagram of assessment of studies identified in the systematic review.



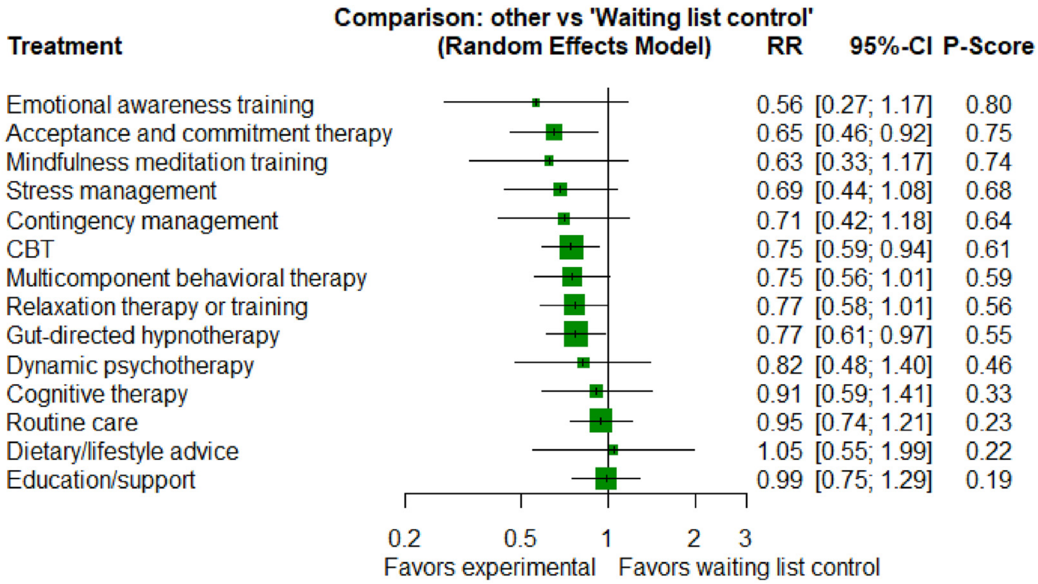
Supplementary Figure 2. Funnel plot for failure to achieve an improvement in abdominal pain at the first point of follow-up after treatment: trials comparing with routine care. The *horizontal axis* represents the difference between the comparison-specific and study-specific effect sizes.



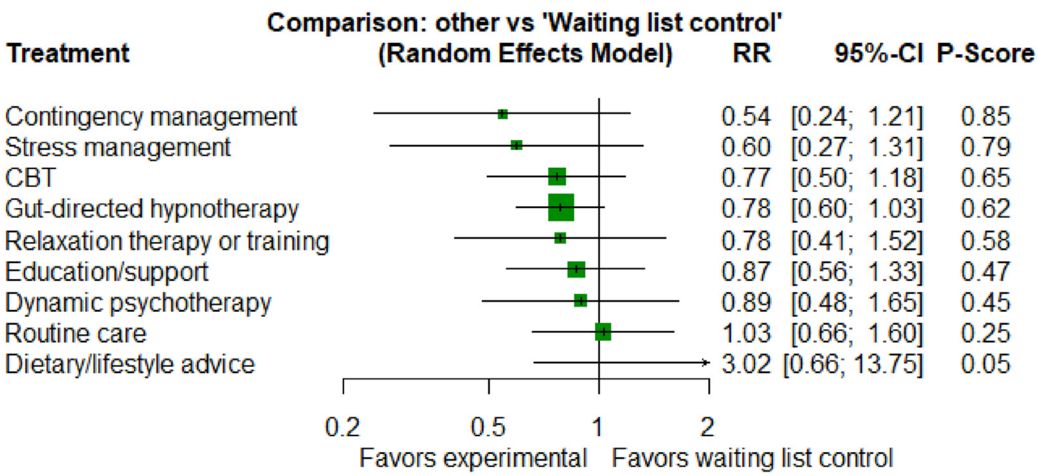
Supplementary Figure 3. Funnel plot for failure to achieve an improvement in abdominal pain at the first point of follow-up after treatment: trials comparing with waiting list control. The *horizontal axis* represents the difference between the comparison-specific and study-specific effect sizes.



Supplementary Figure 4. Forest plot for failure to achieve an improvement in abdominal pain after treatment: trials recruiting only patients with global IBS symptoms refractory to treatment. 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.



Supplementary Figure 5. Forest plot for failure to achieve an improvement in abdominal pain after treatment by type of BGBT. 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.



Supplementary Figure 6. Forest plot for failure to achieve an improvement in abdominal pain after treatment by type of BGBT: trials recruiting only patients with global IBS symptoms refractory to treatment. 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.