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TITLE PAGE

Title: Efficacy of Psychological Therapies for Irritable Bowel Syndrome: Systematic Review and Network Meta-analysis.

Short title: Psychological Therapies for Irritable Bowel Syndrome: Network Meta-analysis.

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Abbreviations:

	CNS	central nervous system
	CBT	cognitive behavioural therapy

CI	confidence interval
IBS	irritable bowel syndrome
IBS-C	IBS with constipation
IBS-D	IBS with diarrhoea
IBS-M	IBS with mixed stool pattern
MeSH	medical subject heading
NICE	National Institute for Health and Care Excellence
RCT	randomised controlled trial
RR	relative risk

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ABSTRACT

Objectives: National guidelines for the management of irritable bowel syndrome (IBS) recommend that psychological therapies should be considered, but their relative efficacy is unknown, because there have been few head-to-head trials. We performed a systematic review and network meta-analysis to try to resolve this uncertainty.

Design: We searched the medical literature through January 2020 for randomised controlled trials (RCTs) assessing efficacy of psychological therapies for adults with IBS, compared with each other, or a control intervention. Trials reported a dichotomous assessment of symptom status after completion of therapy. We pooled data using a random effects model. Efficacy was reported as a pooled relative risk (RR) of remaining symptomatic, with a 95% confidence interval (CI) to summarise efficacy of each comparison tested, and ranked by therapy according to P-score.

Results: We identified 41 eligible RCTs, containing 4072 participants. After completion of therapy, the psychological interventions with the largest numbers of trials, and patients recruited, demonstrating efficacy included self-administered or minimal contact cognitive behavioural therapy (CBT) (RR = 0.61; 95% CI 0.45-0.83, P-score 0.66), face-to-face CBT (RR = 0.62; 95% CI 0.48-0.80, P score 0.65), and gut-directed hypnotherapy (RR = 0.67; 95% CI 0.49-0.91, P-score 0.57). After completion of therapy, among trials recruiting only patients with refractory symptoms, group CBT and gut-directed hypnotherapy were more efficacious than either education and/or support or routine care, and CBT via the telephone, contingency management, CBT via the internet, and dynamic psychotherapy were all superior to routine care. Risk of bias of trials was high, with evidence of funnel plot asymmetry; the efficacy of psychological therapies is therefore likely to have been overestimated.

Conclusions: Several psychological therapies are efficacious for IBS, although none were superior to another. CBT-based interventions and gut-directed hypnotherapy had the largest evidence base and were the most efficacious long-term.

STUDY HIGHLIGHTS

What is already known about this subject

- Irritable bowel syndrome affects 10% of the population.
- Many patients with IBS have symptoms that are refractory to available medical therapies and exhibit psychological co-morbidity.
- Trial-based meta-analyses demonstrate that psychological therapies may be beneficial in IBS, and national management guidelines suggest they should be used in patients with refractory symptoms, but their relative efficacy is unknown, as there have been few head-to-head trials.

What are the new findings

- Of the active interventions that were superior to a control, self-administered or minimal contact CBT, face-to-face CBT, and gut-directed hypnotherapy had the most evidence for efficacy, although all trials were at high risk of bias.
- In terms of control interventions, education and/or support was ranked first; studies that use other control interventions as their comparator may therefore overestimate the efficacy of psychological therapies in IBS.
- Self-administered or minimal contact CBT, stress management, CBT via the telephone, CBT via the internet, gut-directed hypnotherapy, and group gut-directed hypnotherapy all had evidence of longer-term efficacy.

How might it impact on clinical practice in the foreseeable future

- Although guidelines recommend the use of these therapies in patients with refractory symptoms, evidence to support this is sparse.

- Future trials should consider studying the effect of earlier intervention with these therapies in the disease course.

INTRODUCTION

Irritable bowel syndrome (IBS), a chronic gastrointestinal condition, affects as many as 10% of people. [1] Historically, IBS has been defined as a functional bowel disorder, but more recently it has been recognised as a disorder of gut-brain interaction. [2] IBS is characterised by abdominal pain in association with a change in stool frequency, and/or form. [3] The pathophysiology is multifactorial, and includes disturbed gastrointestinal motility, visceral hypersensitivity, and altered central nervous system (CNS) processing; however, the mechanisms by which these processes interact are poorly understood. [4] Thus, IBS is difficult to manage clinically and, as a result, this chronic episodic condition [5] impacts considerably on social functioning and quality of life. [6, 7] The degree of quality of life impairment among patients with IBS is similar to that observed in patients with organic disorders of the gastrointestinal tract, such as inflammatory bowel disease. [8] As a result, economic burden and healthcare utilisation are substantial. A burden of illness study in the USA reported that IBS was associated with annual direct costs of almost $1 billion, as well as another $50 million in indirect costs. [9]

There are limitations as to how IBS can best be managed medically. Numerous licensed and unlicensed drugs have been tested in randomised controlled trials (RCTs) in patients with IBS, which have demonstrated efficacy. These include soluble fibre, such as ispaghula, [10] antispasmodic drugs, [11, 12] gut-brain neuromodulators, such as tricyclic antidepressants and pregabalin, [13, 14] drugs acting on 5-hydroxytryptamine or opioid receptors, [15, 16, 17] the minimally absorbed antibiotic rifaximin, [18] and drugs acting on ion channels in the intestinal enterocyte. [19, 20, 21] Trial-based and network meta-analyses have estimated the efficacy of these treatments relative to placebo and to each other. [22, 23, 24, 25, 26, 27, 28, 29] However, for the most part, these are of similar efficacy, and many patients are refractory to medical management. Other approaches may therefore be required.

Given that IBS has been recognised as a disorder of gut-brain interaction, [2] it is becoming increasingly understood how psychological co-morbidity may have an impact on gastrointestinal function, [30, 31, 32, 33] and vice versa, [34, 35] although cause-effect mechanisms remain unclear. Gastrointestinal-focused psychological and behavioural therapies (detailed in Supplementary Table 1) can target brain-gut dysregulation and are beneficial in some patients. [22] Although these treatments have effects within the CNS, they also have peripheral effects on pain perception, visceral hypersensitivity, and gastrointestinal motility. [36, 37, 38, 39, 40, 41] In the UK, the National Institute for Health and Care Excellence (NICE) guideline for the management of IBS recommends that physicians "consider" referral for psychological interventions, such as cognitive behavioural therapy (CBT) or gut-directed hypnotherapy, in patients not benefiting from drug treatment after 12 months, and who have refractory IBS. [42] However, this guideline makes no other recommendations, due to perceived limitations of the evidence base for efficacy at the time it was published. In addition, demonstrating outcomes of psychological therapies in routine care can be challenging, [43] which has contributed to difficulties describing the impact of such treatments, and implementing them, in clinical settings. [44, 45]

To date, limitations of the current evidence base for psychological therapies in IBS include the numerous different types of interventions studied, unknown relative efficacy of the different approaches, as there have been few head-to-head studies, and design features of RCTs, such as the difficulties of selecting an appropriate placebo control for psychological interventions, leading to the use of a waiting list control in some studies, as well as the challenges that blinding may pose. The latter may contribute to an overestimation of efficacy. In addition, whether these treatments are of greater benefit in those with refractory symptoms is unknown, which is important when considering the timing at which to offer them. We therefore conducted a network meta-analysis of psychological therapies in IBS in order to estimate the relative efficacy of the active interventions studied, as well as the control interventions. This approach allows indirect, as well as direct, comparisons to be made

across different RCTs, increasing the number of participants' data available for analysis. In addition, it allows a credible ranking system of the likely efficacy of different psychological therapies, and control interventions, to be developed, even in the absence of trials making direct comparisons. Knowledge of the most efficacious psychological therapy overall, and according to whether symptoms are refractory, may help inform future national guidelines and clinical decision-making. In addition, an examination of the optimum control intervention may assist in developing a more robust design for future RCTs of these therapies and, therefore, provide evidence of greater integrity to inform clinical care.

METHODS

Search Strategy and Study Selection

We searched MEDLINE (1947 to January 2020), EMBASE, EMBASE Classic (1947 to January 2020), PsychINFO (1806 to January 2020), and the Cochrane central register of controlled trials to identify potential studies. In order to identify studies published only in abstract form, conference proceedings (Digestive Disease Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2001 and 2019 were hand-searched. Finally, we performed a recursive search, using the bibliographies of all obtained articles.

Eligible RCTs examined the efficacy of psychological therapies for IBS in adult participants (≥18 years) including the first period of cross-over trials, prior to cross-over to the second treatment (Table 1). Trials had to compare psychological therapies with each other, or with a control intervention. The control intervention could consist of 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. Duration of therapy had to be ≥4 weeks. The diagnosis of IBS could be based on either a physician's opinion or accepted symptom-based diagnostic criteria. Subjects were required to be followed up for ≥4 weeks, and studies had to report either a global assessment of IBS symptom resolution or improvement, or abdominal pain resolution or improvement, after completion of therapy, preferably as reported by the patient, but if this was not recorded then as documented by the investigator or via questionnaire data. We also extracted endpoints at other subsequent points of follow-up in individual trials, in order to assess the longer-term efficacy of psychological therapies in IBS. Where studies included patients with IBS among patients with other functional disorders, or did not report these types of dichotomous data, but were otherwise eligible for inclusion in the systematic review, we attempted to

Table 1. Eligibility Criteria.

Randomised controlled trials
Adults (participants aged ≥18 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 psychological therapies 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 global IBS symptoms or abdominal pain 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 or questionnaire data.

contact the original investigators in order to obtain further information. The study protocol was published on the PROSPERO international prospective register of systematic reviews (registration number CRD 42020163246). Ethical approval was not required.

Two investigators (CJB and ACF) conducted the literature search independently from each other. The search strategy is provided in the Supplementary Materials. There were no language restrictions. Two investigators (CJB and ACF) evaluated all abstracts identified by the search for eligibility, again independently from each other. We obtained all potentially relevant papers, and evaluated them in more detail, using pre-designed forms, in order to assess eligibility independently, according to the pre-defined criteria. We translated foreign language papers, where required. We resolved disagreements between investigators by discussion.

Outcome Assessment

The primary outcome assessed was the efficacy of all psychological therapies and control interventions in IBS, in terms of effect on global IBS symptoms or abdominal pain after completion of therapy. In addition, because some trials reported efficacy data at other subsequent time points we were able to assess the longer-term efficacy of psychological therapies in IBS (out to 6 to 12 months post-randomisation). Secondary outcomes included adverse events occurring as a result of therapy (total numbers of adverse events, as well as adverse events leading to study withdrawal, and individual adverse events, if reported).

Data Extraction

Two investigators (CJB and ACF) extracted all data independently onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (global IBS symptoms unimproved, or abdominal pain unimproved). For all included studies, we also extracted the following data for each trial, where available: country of origin, setting

(primary, secondary, or tertiary care-based), exact type of psychological therapy used, including duration of therapy and number of sessions, IBS criteria used, primary outcome measure to define symptom improvement or resolution following therapy, duration of follow-up, proportion of female patients, proportion of patients according to predominant stool pattern (IBS with constipation (IBS-C), diarrhoea (IBS-D), or mixed stool pattern (IBS-M)), and whether trials recruited only patients whose symptoms were refractory to standard medical therapy. We also recorded the handling of the control arm for trials of psychological therapies, as we pooled these separately in the analysis in order to assess their relative efficacy. Data were extracted as intention-to-treat analyses, with all dropouts assumed to be treatment failures (*i.e.* symptomatic at final point of follow-up), wherever trial reporting allowed this.

Quality Assessment and Risk of Bias

Risk of bias assessment was performed at the study level, by two investigators (CJB and ACF) independently, using the Cochrane risk of bias tool. [46] We resolved disagreements by discussion. We recorded the methods used to generate the randomisation 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 performed a network meta-analysis using the frequentist model, with the statistical package "netmeta" (version 0.9-0, https://cran.r-project.org/web/packages/netmeta/index.html) in R (version 3.4.2). We reported the network meta-analysis according to the PRISMA extension statement for network meta-analyses. [47] Network meta-analysis results usually give a more precise

estimate, compared with results from standard, pairwise analyses, [48, 49] and can rank treatments to inform clinical decisions. [50]

We examined the symmetry and geometry of the evidence by producing a network plot with node and connection size corresponding to the number of study subjects and number of studies, respectively. We produced comparison-adjusted funnel plots to explore publication bias or other small study effects, for all available comparisons, using Stata version 14 (Stata Corp., College Station, TX, USA). This is a scatterplot of effect size versus precision, measured via the inverse of the standard error. Symmetry around the effect estimate line indicates the absence of publication bias, or small study effects. [51] We produced a pooled relative risk (RR) with a 95% confidence interval (CI) to summarise the efficacy of each active and control intervention tested, using a random effects model as a conservative estimate. We used a RR of remaining symptomatic at the final point of follow-up; where the RR is less than 1 and the 95% CI does not cross 1, there is a significant benefit of one intervention over another. As there were direct comparisons between some of the psychological therapies of interest, we were able to perform consistency modelling to check the agreement between direct and indirect evidence in some of our analyses. [52]

Many meta-analyses use the I^2 statistic to measure heterogeneity, which ranges between 0% and 100%. [53] This statistic is easy to interpret, and does not vary with the number of studies. However, the I^2 value can increase with the number of patients included in the meta-analysis. [54] We therefore assessed global statistical heterogeneity across all comparisons using the τ^2 measure from the "netmeta" statistical package. Estimates of τ^2 of approximately 0.04, 0.16, and 0.36 are considered to represent a low, moderate, and high degree of heterogeneity, respectively. [55] We assessed inconsistency in the network analysis by comparing direct and indirect evidence, where available, by producing a network heat plot. [52, 56] These plots have grey squares, which represent the size of the contribution of the direct estimate in columns, compared with the network estimate in rows. [56] The coloured squares around these represent the degree of inconsistency, with red squares

indicating “hotspots” of inconsistency. In order to investigate sources of potential inconsistency, we planned to remove studies that introduced any red “hotspots” and repeat the analyses.

We ranked both the active treatments and control interventions according to their P-score, which is a value between 0 and 1. P-scores are based solely on the point estimates and standard errors of the network estimates, and measure the mean extent of certainty that one intervention is better than another, averaged over all competing interventions. [57] Higher scores indicate a greater probability of the intervention being ranked as best, [57] but the magnitude of the P-score should be considered, as well as the rank. As the mean value of the P-score is always 0.5, individual treatments that cluster around this value are likely to be of similar efficacy. However, 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. [58] In our primary analysis, we pooled data for the risk of being symptomatic at the final point of follow-up in each study for all included RCTs using an intention-to-treat analysis, as well as restricting the analysis to trials that recruited only patients with refractory symptoms, and performing analyses examining efficacy during longer-term follow-up.

RESULTS

We updated our previous systematic review and trial-based meta-analysis. [22] The search strategy generated 2232 citations, 88 articles of which we retrieved for further assessment as they appeared to be relevant (Supplementary Figure 1). Of these, 49 were excluded, leaving 39 eligible articles. [37, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96] These contained 41 separate RCTs, comprising 4072 participants, 2616 of whom received a psychological therapy and 1456 a control intervention, allocated to active intervention or control as described in Supplementary Table 2. All but one trial was fully published. [94] Agreement between investigators for trial eligibility was excellent (Kappa statistic = 0.88). We obtained supplementary data from authors of eight of the trials. [63, 64, 71, 74, 80, 81, 82, 95] Adverse events were not reported in sufficient detail in the majority of trials to allow any meaningful pooling of data. Detailed characteristics of individual RCTs, including the comparisons made, are provided in Supplementary Table 3. Risk of bias items for all included trials are reported in Supplementary Table 4. Efficacy analyses at 6 and 12 months are provided in the Supplementary Materials.

Efficacy at First Point of Follow-up Post-treatment

All 41 RCTs provided dichotomous data for likelihood of remaining symptomatic at the first point of follow-up post-treatment. [37, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96] The network plot is provided in Figure 1. When data were pooled, there was moderate heterogeneity ($\tau^2 = 0.058$), but the funnel plot appeared symmetrical (Supplementary Figure 2). However, there was clear evidence of funnel plot asymmetry when pooling the trial-based data, suggesting publication bias or other small study effects (Supplementary Figure 3). Of all the psychological therapies studied, contingency management was ranked first (RR of remaining symptomatic = 0.39; 95% CI 0.19 to 0.84, P-score

0.89) (Figure 2), but based on only one small RCT. [88] Group CBT and CBT via the telephone performed similarly, but based on only two small trials for group CBT, [85, 90] and one trial for CBT via the telephone, [87] although the latter included 558 patients. [87] 95% CIs around the estimates for all these therapies were wide. The psychological interventions with the largest numbers of trials, and patients recruited, included self-administered or minimal contact CBT (RR = 0.61; 95% CI 0.45 to 0.83, P-score 0.66), face-to-face CBT (RR = 0.62; 95% CI 0.48 to 0.80, P score 0.65), and gut-directed hypnotherapy (RR = 0.67; 95% CI 0.49 to 0.91, P-score 0.57). Among control interventions, dietary and/or lifestyle advice was ranked last (P-score 0.08), followed by waiting list control (P-score 0.13). The network heat plot had no red "hotspots" of inconsistency (Supplementary Figure 4).

No psychological therapy was significantly more efficacious than any of the other active therapies, on either direct or indirect comparison (Table 2). Contingency management, CBT via the telephone, self-administered or minimal contact CBT, and face-to-face CBT were all more efficacious than any of the four control interventions. Group CBT, stress management and dynamic psychotherapy were also more efficacious than routine care, waiting list control, or dietary and/or lifestyle advice, but not education and/or support. Gut-directed hypnotherapy was more efficacious than education and/or support or waiting list control, but not routine care or dietary and/or lifestyle advice. Finally, face-to-face multicomponent psychological therapy was more efficacious than routine care or waiting list control, but not education and/or support or dietary and/or lifestyle advice.

When we restricted the analysis to the 13 RCTs that stated that they only recruited patients with refractory IBS, [37, 66, 73, 76, 77, 81, 85, 86, 87, 88, 94, 95] there was very little observed heterogeneity between studies ($\tau^2 = 0.022$). Group CBT was ranked first (RR of remaining symptomatic = 0.05; 95% CI 0.00 to 0.85, P-score 0.96) (Supplementary Figure 5), but based on only one small RCT, and 95% CIs were again wide. No psychological therapy was significantly more efficacious than any of the other active therapies, on either direct or indirect comparison

Table 2. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve an Improvement in Global IBS Symptoms at First Point of Follow-up Post-treatment.

CM	N/A	N/A	0.63 (0.29; 1.37)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.45 (0.22; 0.92)	N/A	N/A
0.95 (0.32; 2.82)	**Group CBT**	N/A	N/A	N/A	N/A	0.83 (0.31; 2.25)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.40 (0.18; 0.90)	N/A
0.79 (0.34; 1.86)	0.83 (0.33; 2.14)	**Phone CBT**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.80 (0.47; 1.35)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.46 (0.28; 0.77)	N/A	N/A
0.73 (0.35; 1.53)	0.76 (0.29; 2.01)	0.92 (0.46; 1.84)	**SM**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.57 (0.34; 0.94)	N/A	N/A
0.68 (0.30; 1.53)	0.71 (0.28; 1.79)	0.86 (0.46; 1.61)	0.94 (0.49; 1.78)	**DPT**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.61 (0.41; 0.91)	N/A	N/A
0.65 (0.30; 1.42)	0.68 (0.29; 1.57)	0.82 (0.46; 1.45)	0.89 (0.48; 1.65)	0.95 (0.56; 1.63)	**S-A/MC CBT**	0.91 (0.58; 1.42)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.70 (0.41; 1.19)	0.33 (0.15; 0.71)	0.73 (0.48; 1.09)	N/A
0.63 (0.30; 1.35)	0.66 (0.30; 1.49)	0.80 (0.46; 1.37)	0.87 (0.49; 1.55)	0.93 (0.57; 1.52)	0.98 (0.70; 1.36)	**F-t-F CBT**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.90 (0.53; 1.51)	N/A	0.73 (0.53; 1.00)	0.89 (0.59; 1.33)	0.40 (0.27; 0.58)	N/A
0.64 (0.25; 1.60)	0.67 (0.26; 1.73)	0.80 (0.38; 1.69)	0.88 (0.40; 1.91)	0.94 (0.46; 1.92)	0.98 (0.53; 1.82)	1.01 (0.56; 1.81)	**ACT**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.72 (0.40; 1.32)	N/A	N/A	0.62 (0.36; 1.05)	N/A
0.59 (0.27; 1.30)	0.62 (0.27; 1.44)	0.75 (0.42; 1.34)	0.81 (0.44; 1.51)	0.87 (0.51; 1.50)	0.91 (0.62; 1.36)	0.94 (0.67; 1.32)	0.93 (0.50; 1.72)	**HT**	N/A	N/A	N/A	N/A	0.84 (0.56; 1.24)	N/A	N/A	N/A	0.71 (0.51; 1.00)	N/A	0.76 (0.48; 1.20)	N/A
0.59 (0.28; 1.28)	0.62 (0.27; 1.46)	0.75 (0.43; 1.31)	0.82 (0.45; 1.47)	0.87 (0.53; 1.45)	0.92 (0.60; 1.40)	0.94 (0.65; 1.36)	0.93 (0.50; 1.74)	1.00 (0.66; 1.53)	**F-t-F MPT**	N/A	0.96 (0.57; 1.63)	N/A	N/A	N/A	N/A	N/A	N/A	0.72 (0.50; 1.06)	0.63 (0.41; 0.97)	N/A
0.56 (0.25; 1.23)	0.58 (0.25; 1.39)	0.70 (0.43; 1.15)	0.77 (0.41; 1.43)	0.82 (0.47; 1.42)	0.86 (0.54; 1.36)	0.88 (0.58; 1.34)	0.87 (0.46; 1.67)	0.94 (0.59; 1.50)	0.94 (0.60; 1.47)	**Internet CBT**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.58 (0.35; 0.96)	0.89 (0.55; 1.46)	N/A
0.55 (0.24; 1.28)	0.58 (0.23; 1.47)	0.69 (0.35; 1.35)	0.76 (0.38; 1.50)	0.81 (0.43; 1.50)	0.85 (0.48; 1.51)	0.87 (0.51; 1.48)	0.86 (0.41; 1.81)	0.93 (0.52; 1.65)	0.93 (0.57; 1.50)	0.99 (0.55; 1.78)	**Phone MPT**	N/A	N/A	N/A	N/A	N/A	N/A	0.78 (0.47; 1.29)	N/A	N/A
0.53 (0.21; 1.35)	0.55 (0.20; 1.56)	0.66 (0.30; 1.46)	0.72 (0.32; 1.61)	0.77 (0.37; 1.62)	0.81 (0.39; 1.67)	0.83 (0.42; 1.65)	0.82 (0.35; 1.96)	0.89 (0.43; 1.83)	0.88 (0.44; 1.78)	0.94 (0.46; 1.96)	0.96 (0.44; 2.09)	**Group MPT**	N/A	N/A	N/A	N/A	N/A	0.79 (0.42; 1.47)	N/A	N/A
0.51 (0.23; 1.13)	0.53 (0.22; 1.27)	0.64 (0.35; 1.17)	0.70 (0.37; 1.32)	0.75 (0.43; 1.31)	0.79 (0.50; 1.23)	0.80 (0.54; 1.19)	0.80 (0.42; 1.53)	0.86 (0.61; 1.21)	0.86 (0.54; 1.36)	0.91 (0.55; 1.51)	0.93 (0.51; 1.68)	0.97 (0.46; 2.02)	**Group HT**	N/A	N/A	N/A	0.89 (0.54; 1.44)	0.71 (0.39; 1.30)	N/A	N/A
0.50 (0.21; 1.18)	0.52 (0.21; 1.29)	0.63 (0.32; 1.23)	0.69 (0.34; 1.39)	0.73 (0.39; 1.39)	0.77 (0.46; 1.29)	0.79 (0.49; 1.28)	0.78 (0.39; 1.55)	0.84 (0.51; 1.40)	0.84 (0.49; 1.43)	0.90 (0.51; 1.58)	0.91 (0.47; 1.77)	0.95 (0.43; 2.12)	0.98 (0.57; 1.70)	**MM**	N/A	N/A	0.57 (0.27; 1.19)	N/A	0.97 (0.58; 1.64)	N/A
0.49 (0.23; 1.05)	0.51 (0.22; 1.19)	0.61 (0.35; 1.07)	0.67 (0.37; 1.20)	0.72 (0.43; 1.19)	0.75 (0.50; 1.14)	0.77 (0.55; 1.08)	0.77 (0.41; 1.43)	0.82 (0.54; 1.25)	0.82 (0.55; 1.23)	0.88 (0.56; 1.37)	0.89 (0.51; 1.54)	0.93 (0.46; 1.86)	0.96 (0.61; 1.51)	0.98 (0.57; 1.66)	**RT**	N/A	N/A	1.00 (0.70; 1.42)	0.70 (0.41; 1.19)	0.66 (0.40; 1.09)
0.46 (0.15; 1.39)	0.48 (0.16; 1.49)	0.58 (0.22; 1.51)	0.63 (0.24; 1.70)	0.68 (0.27; 1.73)	0.71 (0.30; 1.68)	0.73 (0.31; 1.69)	0.72 (0.40; 1.32)	0.78 (0.33; 1.84)	0.78 (0.33; 1.85)	0.83 (0.34; 2.01)	0.84 (0.32; 2.18)	0.88 (0.31; 2.52)	0.91 (0.37; 2.21)	0.92 (0.37; 2.30)	0.95 (0.40; 2.25)	**Internet SM**	N/A	N/A	N/A	N/A
0.43 (0.20; 0.94)	0.46 (0.20; 1.04)	0.55 (0.31; 0.96)	0.60 (0.33; 1.08)	0.64 (0.38; 1.07)	0.67 (0.48; 0.94)	0.69 (0.53; 0.89)	0.68 (0.37; 1.23)	0.73 (0.55; 0.97)	0.73 (0.49; 1.08)	0.78 (0.50; 1.21)	0.79 (0.45; 1.37)	0.83 (0.41; 1.67)	0.85 (0.60; 1.21)	0.87 (0.55; 1.38)	0.89 (0.61; 1.30)	0.94 (0.40; 2.19)	**E/S**	N/A	0.83 (0.45; 1.53)	N/A
0.41 (0.21; 0.83)	0.43 (0.19; 0.99)	0.52 (0.32; 0.84)	0.57 (0.34; 0.94)	0.61 (0.41; 0.91)	0.64 (0.45; 0.91)	0.65 (0.49; 0.87)	0.65 (0.36; 1.18)	0.70 (0.48; 1.00)	0.69 (0.51; 0.95)	0.74 (0.51; 1.08)	0.75 (0.47; 1.20)	0.79 (0.42; 1.47)	0.81 (0.55; 1.20)	0.83 (0.50; 1.36)	0.85 (0.63; 1.15)	0.89 (0.38; 2.09)	0.95 (0.69; 1.32)	**RC**	N/A	N/A

0.39 (0.19; 0.84)	0.41 (0.19; 0.91)	0.50 (0.29; 0.84)	0.54 (0.31; 0.96)	0.58 (0.36; 0.94)	0.61 (0.45; 0.83)	0.62 (0.48; 0.80)	0.62 (0.36; 1.05)	0.67 (0.49; 0.91)	0.66 (0.48; 0.92)	0.71 (0.49; 1.03)	0.72 (0.43; 1.20)	0.75 (0.38; 1.49)	0.78 (0.53; 1.13)	0.79 (0.51; 1.22)	0.81 (0.58; 1.12)	0.85 (0.38; 1.91)	0.91 (0.69; 1.19)	0.96 (0.73; 1.26)	**WLC**	N/A
0.32 (0.13; 0.80)	0.34 (0.13; 0.90)	0.40 (0.19; 0.86)	0.44 (0.20; 0.96)	0.47 (0.23; 0.96)	0.50 (0.26; 0.95)	0.51 (0.28; 0.93)	0.50 (0.23; 1.12)	0.54 (0.28; 1.04)	0.54 (0.28; 1.03)	0.58 (0.29; 1.13)	0.58 (0.28; 1.23)	0.61 (0.26; 1.44)	0.63 (0.32; 1.24)	0.64 (0.31; 1.34)	0.66 (0.40; 1.09)	0.70 (0.25; 1.90)	0.74 (0.39; 1.39)	0.78 (0.43; 1.40)	0.81 (0.45; 1.49)	**D/L**

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The treatment in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Direct comparisons are provided above the strategy labels, and indirect comparisons are below.

ACT; acceptance and commitment therapy, CBT; cognitive behavioural therapy, CM; contingency management; D/L; dietary and/or lifestyle advice, DPT; dynamic psychotherapy, E/S; education and/or support, F-t-F; face-to-face, HT; hypnotherapy, MM; mindfulness meditation, MPT; multicomponent psychological therapy, N/A; not applicable, no RCTs making direct comparisons, RC; routine care, RT; relaxation therapy, S-A/MC; self-administered/minimal contact, SM; stress management; WLC; waiting list control.

(Supplementary Table 5). Group CBT and gut-directed hypnotherapy were both more efficacious than education and/or support or routine care, and CBT via the telephone, contingency management, CBT via the internet, and dynamic psychotherapy were all superior to routine care.

DISCUSSION

This systematic review and network meta-analysis has demonstrated that several psychological therapies were more efficacious than a control intervention, in terms of their effect on IBS symptoms. These included contingency management, group CBT, CBT via the telephone, stress management, dynamic psychotherapy, self-administered or minimal contact CBT, face-to-face CBT, gut-directed hypnotherapy, and face-to-face multicomponent psychological therapy, although no psychological therapy was significantly more efficacious than any of the other active therapies. However, in some instances there were only one or two trials, recruiting small numbers of patients. The psychological interventions with the largest numbers of trials, and patients recruited, with evidence for efficacy included self-administered or minimal contact CBT, face-to-face CBT, and gut-directed hypnotherapy. In addition, efficacy depended on the control intervention; only contingency management, CBT via the telephone, self-administered or minimal contact CBT, face-to-face CBT, and gut-directed hypnotherapy were more efficacious than the top ranked control intervention, which was education and/or support. We also studied the efficacy of psychological therapies in patients with refractory symptoms. Only group CBT and gut-directed hypnotherapy were more efficacious than both the control interventions studied in this patient group, which were either education and/or support or routine care, although CBT via the telephone, contingency management, CBT via the internet, and dynamic psychotherapy were all superior to routine care. Psychological therapies with the best evidence for longer-term efficacy in this network meta-analysis included self-administered or minimal contact CBT, stress management, CBT via the telephone, CBT via the internet, gut-directed hypnotherapy, and group gut-directed hypnotherapy. At 12 months, CBT via the telephone was ranked first, and was superior to both education and/or support and routine care. Finally, adverse events were reported poorly, precluding any meaningful analysis.

The network allowed us to make indirect comparisons between over 4000 participants in these 41 RCTs. The trials themselves took place in a wide variety of settings, and countries, and

recruited patients with IBS irrespective of predominant stool pattern, meaning the results are likely to be generalisable to many patients with IBS. We used an intention-to-treat analysis, with all trial dropouts assumed to be symptomatic. We extracted data during longer-term follow-up, out to 6 and 12 months, wherever these data were reported, and contacted authors of studies in order to obtain supplementary data and maximise number of trials eligible for inclusion. We also conducted a subgroup analysis including only trials that recruited patients with refractory symptoms, in order to assess whether current recommendations to consider the use of these treatments in this patient group are evidence-based. Finally, we produced network heat plots, where possible, and did not identify inconsistency in any of our analyses.

Weaknesses include the fact that there were differences between individual trials, in terms of the population studied, study setting, the way the interventions were applied, the duration of follow-up, and the endpoint used to define symptom response, meaning it may not be appropriate to combine data from them in a meta-analysis. There was moderate heterogeneity observed in our main analysis. Individual trials recruited unselected patients, meaning that it is impossible to say whether any of these therapies are more likely to be efficacious in patients with a particular predominant stool pattern. The fact that the presence of psychological co-morbidity was not screened for routinely in these trials, or examined as a predictor of response, also makes it difficult to know whether mood is a modifier of the effect of these therapies. Although a large number of trials, and patients, were included the variety of psychological interventions studied means that the number of patients receiving each of these individual therapies was much lower than the numbers assigned to many of the available pharmacological therapies in a series of recent network meta-analyses. [25, 26, 27, 29] As the majority of studies were conducted in Western populations, with only one RCT conducted in Japan and one trial from Israel, [62, 63] our findings cannot be extrapolated to other populations. In addition, all of the included RCTs were at high risk of bias, due to the nature of the intervention studied, which meant that blinding of participants was not possible, although nine trials stated

specifically that investigators were blinded to treatment allocation. [63, 64, 77, 79, 81, 82, 86, 87, 88] Assessing risk of bias, in terms of whether blinding is employed, using the Cochrane risk of bias tool in trials of psychological therapies has been the subject of recent discussions, due to the impossibility of blinding therapists and patients. [97] It has been suggested that, instead, it may be preferable to address this issue by evaluating patients' treatment expectations and therapists' enthusiasm for the treatment. Lastly, although there was no evidence of funnel plot asymmetry in the network meta-analysis, the trial-based analysis revealed possible publication bias or other small study effects. It is therefore highly likely that the efficacy of psychological therapies has been overestimated.

Our study confirmed prior findings that psychological therapies are more efficacious than control interventions. Similar to our previous systematic review and trial-based meta-analysis, [22] we found CBT and gut-directed hypnotherapy to have the largest evidence base. However, we found that CBT can be efficacious when administered in various forms, including via the telephone, group, or self-administered/minimal contact, which differed from earlier findings. We also found other types of interventions, such as stress management, that previously demonstrated no benefit, to be beneficial in our study. Other interventions, such as face-to-face dynamic psychotherapy and multicomponent psychological therapy remain beneficial. However, data on these types of psychological therapies are limited; these findings therefore need to be interpreted more cautiously. In addition, although previous reviews have demonstrated the short and long-term efficacy of psychological therapies for IBS, [98] regardless of delivery method (in person or online), our study demonstrated that CBT via telephone appeared to be the most beneficial in the long-term.

Across studies, no single psychological therapy has been shown to be significantly more efficacious than any other active therapies; however, it remains unclear if this is because of insufficient data, non-specific factors, or equivalent outcomes. [99] Historically, adverse events have also been poorly reported among RCTs, [22] which remained a concern in our study. We did, however, restrict our analysis to examine the efficacy of psychological therapies only in patients with

refractory symptoms, which to our knowledge has not been done before. This is particularly relevant given that current clinical guidelines hinge on this population as the basis for which to focus care. [42]

Our study provides evidence to support the long-term benefit of psychological therapies, particularly CBT-based interventions and gut-directed hypnotherapy, in the management of IBS. These are relatively short-term treatments, and likely to be cost-effective within this time frame. [100] However, future investigations should focus on strengthening this evidence and identify for whom different psychological therapy approaches are most efficacious. This may help to refine clinical guidelines and provide evidence as to how to address the full spectrum of clinical needs seen in patients with IBS. Our study also strengthens previous research by providing some support for alternative methods of delivery of psychological therapies, particularly for CBT, as opposed to relying solely on traditional face-to-face methods. This is important when considering barriers to care, including travel distance, time limitations, and financial constraints, and may provide patients and providers with practical alternatives to care, which will become more feasible in the next generation of technology-based healthcare delivery. It could also permit the use of such therapies at an earlier stage in the treatment algorithm, rather than being restricted to those with refractory and persistent symptoms.

Although policy makers have previously considered psychological therapies to be most beneficial for patients with refractory symptoms and focused on making recommendations for this population, [42] our study demonstrated little evidence to support this. Future RCTs should examine the impact of administering psychological therapies earlier in the disease course, to better understand their benefit across the spectrum of disease severity. Offering psychological therapies as a complement to usual medical management may reduce disease burden and have positive downstream effects, such as a reduction of unnecessary healthcare utilisation and added healthcare costs. This has been seen in RCTs in other disorders, such as chronic tension headache, [101] and real-world

evidence from outpatient gastroenterology services suggests that integration of psychological care in this setting reduced future healthcare usage and costs, [102] as well as improving mood and quality of life. [103]

Lastly, although the benefit of psychological therapies for IBS patients has become increasingly clear, the current evidence base remains limited by several methodological shortcomings. To strengthen this, and enhance the next phase of psychological therapies research, it is critical to do more rigorous investigations examining promising treatments with well-designed RCTs. In doing so, investigators need to select optimal control conditions carefully. Our findings suggest that education and/or support controls should be the gold standard, as compared with other controls, such as waiting list, which may overestimate the efficacy of psychological therapies in IBS and provide more threats to internal validity. [104] Control interventions need to be real and possess some intrinsic value to the patients, in order to ensure that any response to the psychological therapy is not simply a placebo response. We also found that there was insufficient data to examine adverse events in our study. This is not surprising. In general, the reporting of adverse events in RCTs of psychological interventions has been identified as weak. [105] The complexities of psychological therapy trials may make it more challenging to report such events; however, there have been increasing efforts to do so, [106] in an effort to provide more clarity and meaningful interpretations of findings. In future RCTs of psychological therapy in IBS, investigators should consider relevant adverse events, such as treatment failure, worsened gastrointestinal symptoms, elevated levels of gastrointestinal-related distress, self-harm, or suicidal ideation, which may impact outcomes and hinder research findings.

In summary, we found several psychological therapies to be efficacious for IBS including contingency management, group CBT, CBT via the telephone, stress management, dynamic psychotherapy, self-administered or minimal contact CBT, face-to-face CBT, gut-directed hypnotherapy, and face-to-face multicomponent psychological therapy. However, no single active

therapy was superior to another active therapy, and the high risk of bias of all included RCTs, as well as possible publication bias, mean that efficacy has likely been overestimated. CBT-based interventions and gut-directed hypnotherapy had the largest evidence base and were the most efficacious long-term. Future RCTs should carefully select control conditions, consider the impact of adverse effects on outcomes, and examine the influence of psychological therapy earlier in the disease course to address clinical needs, before patients are refractory to medical management. Addressing these gaps in the current literature, will help policy makers refine clinical guidelines, so healthcare providers can more efficiently and effectively address patients' needs in frontline practice settings.

CONTRIBUTOR AND GUARANTOR INFORMATION

Guarantor: ACF is guarantor. He accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Specific author contributions: Study concept and design: CJB, ERT, LAH, EMMQ, PM, and ACF conceived and drafted the study. CJB, ERT, PM, and ACF analysed, 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.

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COMPETING INTERESTS DECLARATION

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

TRANSPARENCY STATEMENT

The lead author (ACF, the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been

omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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None.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

We did not involve patients or the public in this work. We will disseminate our findings in lay terms via the national charity for people living with digestive diseases, “Guts UK”, and the national charity for people living with IBS, the IBS Network.

DATA SHARING

No additional data available.

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FIGURE LEGENDS

Figure 1. Network Plot for Failure to Achieve an Improvement in IBS Symptoms at First Point of Follow-up 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 2. Forest Plot for Failure to Achieve an Improvement in IBS Symptoms at First Point of Follow-up 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.