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TITLE PAGE

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

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

Authors: Elyse R. Thakur[1,2]*, Mais Khasawneh[3,4]*, Professor Paul Moayyedi[5], Christopher J. Black[3,4]†, Professor Alexander C. Ford[3,4]†.

*Joint first author

†Joint last author

[1]Section of Gastroenterology, Wake Forest University School of Medicine, Winston-Salem, NC, USA.

[2]Division of Gastroenterology and Hepatology, Atrium Health, Charlotte, NC, USA.

[3]Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK.

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

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

Abbreviations:

CBT	cognitive behavioural therapy
CI	confidence interval
CINeMA	Confidence in Network Meta-Analysis
DGBI	disorder of gut-brain interaction

GDH	gut-directed hypnotherapy
IBS	irritable bowel syndrome
IBS-C	IBS with constipation
IBS-D	IBS with diarrhoea
IBS-M	IBS with mixed bowel habits
RCT	randomised controlled trial
RR	relative risk

Correspondence: Professor Alex Ford

Leeds Gastroenterology Institute

Room 125

4th Floor

Bexley Wing

St. James's University Hospital

Beckett Street

Leeds

United Kingdom

LS9 7TF

Email: alexf12399@yahoo.com

Telephone: +441132684963

ORCID ID: 0000-0001-6371-4359

Twitter: @alex_ford12399

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SUMMARY

Background: Irritable bowel syndrome (IBS) management guidelines recommend that behavioural therapies, particularly brain-gut behaviour therapies, should be considered as a treatment. Some, such as IBS-specific cognitive behavioural therapy (CBT) or gut-directed hypnotherapy (GDH), have specific techniques and, therefore, are in their own class of brain-gut behaviour therapy, while others, such as stress management or relaxation training, are common or universal techniques that are present in most classes of brain-gut behaviour therapy. In addition, there are other behavioural therapies and/or treatment options, including digital therapies, which are not classed as brain-gut behaviour therapies. The relative efficacy of all these is unclear.

Methods: We performed a network meta-analysis. We searched the medical literature through to 23rd April 2025 to identify randomised controlled trials (RCTs) comparing the efficacy of behavioural therapies for adults with IBS with each other, or a control intervention. We judged efficacy using dichotomous assessments of improvement in global IBS symptoms. We pooled data with a random effects model, with efficacy of each intervention reported as pooled relative risks (RRs) with 95% confidence intervals (CIs). We ranked behavioural therapies according to their P-score, which is the mean extent of certainty that one treatment is better than another, averaged over all competing behavioural therapies.

Findings: We identified 67 eligible RCTs, containing 7441 participants. After completion of treatment, and compared with waiting list control, behavioural therapies with the largest numbers of trials, and patients recruited, demonstrating efficacy included minimal contact CBT (RR = 0.55; 95% CI 0.39-0.76, P-score 0.78; two RCTs, 511 patients), telephone disease self-management (RR = 0.57; 95% CI 0.41-0.80, P-score 0.75; two trials, 746 patients), dynamic psychotherapy (RR = 0.59; 95% CI 0.43-0.80, P-score 0.72; three RCTs, 303 patients), CBT (RR = 0.65; 95% CI 0.53-0.80, P-score 0.64; nine trials, 1150 patients), disease self-management (RR = 0.68; 95% CI 0.50-0.92, P-score

0.58; three RCTs, 375 patients), internet-based minimal contact CBT (RR = 0.77; 95% CI 0.61-0.96, P-score 0.43; five RCTs, 705 patients), and GDH (RR = 0.79; 95% CI 0.66-0.95, P-score 0.39; 12 trials, 1507 patients), and. After completion of treatment, among trials recruiting only patients with refractory symptoms, telephone disease self-management and contingency management were both superior to attention-placebo control and routine care, and group CBT, internet-based minimal contact disease self-management, and dynamic psychotherapy were all superior to routine care.

Interpretation: Several behavioural therapies are efficacious for global symptoms in IBS, although the most evidence exists for those classed as brain-gut behaviour therapies. Due in part to evidence of publication bias and the fact that no RCTs were at low risk of bias across all domains, certainty in the evidence for all direct and indirect comparisons across the network were rated as either low or very low confidence. There are inherent issues with applying existing approaches to evaluating quality and rigour in pharmacological trials that impact risk of bias assessment of RCTs of behavioural therapies.

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RESEARCH IN CONTEXT

Evidence before this study

Behavioural therapies, including brain-gut behaviour therapies, are short-term, clinician-administered, interventions aimed at improving the symptoms of irritable bowel syndrome (IBS). It is now 5 years since our network meta-analysis examining their efficacy in IBS. A comprehensive search of the medical literature using MEDLINE, EMBASE, EMBASE Classic, PsychINFO, and the Cochrane central register of controlled trials from inception to 23rd April 2025, and including foreign language articles, identified multiple randomised controlled trials (RCTs) of behavioural therapies in IBS published since the conduct of the prior network meta-analysis. In addition, the classification of such therapies has been updated following recommendations from the Rome Foundation. Some, such as IBS-specific cognitive behavioural therapy (CBT) or gut-directed hypnotherapy (GDH), have specific techniques and, therefore, are in their own class of brain-gut behaviour therapy. Others, such as stress management or relaxation training, are common or universal techniques that are present in most classes of brain-gut behaviour therapy. Accessing behavioural therapies may be difficult but digital-based applications are increasingly available. There have been recent RCTs of these, but they are not administered by a clinician, non-personalised and, technically, are not a form of brain-gut behaviour therapy, so may have limitations in their utility. Finally, some previously published trials were excluded from the prior network as they did not report dichotomous symptom endpoints. Together, these issues provided the rationale for this updated systematic review and network meta-analysis examining the efficacy of behavioural therapies for global symptoms in IBS. We aimed to examine whether inclusion of trials of behavioural therapies studied more recently, updates in the classification system used for behavioural therapies, and imputation of dichotomous endpoints from RCTs excluded previously, changed the conclusions of our previous network meta-analysis.

Added value of this study

We did a contemporaneous systematic review and network meta-analysis of RCTs of behavioural therapies, compared with either a control intervention, including waiting list control, attention-placebo control, education and support, dietary and lifestyle advice, or routine care, or compared with any other behavioural therapy, in adult patients with IBS. We identified 67 eligible trials, including 7441 patients. Twenty-six of these were included since the last version of the network meta-analysis, including 3298 patients. In terms of effect on global symptoms immediately after treatment cessation, several therapies were more efficacious than a waiting list control. Minimal contact disease self-management, cognitive therapy, and digital gut-directed hypnotherapy (GDH), ranked first, second, and third respectively. In this analysis, efficacious behavioural therapies with the largest numbers of trials, or patients recruited, included minimal contact CBT, telephone disease self-management, dynamic psychotherapy, CBT, disease self-management, internet-based minimal contact CBT, and GDH. Minimal contact CBT and telephone disease self-management were superior to several other active interventions, and minimal contact CBT, telephone disease self-management, and dynamic psychotherapy were all superior to four of the seven possible control interventions. In terms of treatment class, other forms of behavioural therapy (specifically contingency management), and forms of disease self-management, CBT, dynamic psychotherapy/emotional processing, multicomponent behavioural therapy and stress management, both common techniques, contextually-based CBT, mindfulness training, and GDH were all superior to waiting list control. Forms of CBT were superior to forms of relaxation therapy or training, a common technique, and self-guided therapies. In patients with refractory symptoms, none of the individual active interventions were superior to waiting list control, although telephone disease self-management and contingency management were both superior to attention-placebo control and routine care, and group CBT, internet-based minimal contact disease self-management, and dynamic psychotherapy were all superior to routine care. Forms of disease self-management, dynamic psychotherapy/emotional

processing, and CBT were all superior to routine care in patients with refractory symptoms. Adverse events were reported inconsistently, precluding pooling of data.

Implications of all the available evidence

This systematic review and network meta-analysis demonstrates that, in terms of behavioural therapies for IBS, the most evidence for efficacy for global symptoms exists for forms of CBT, disease self-management, dynamic psychotherapy, and GDH. There was little evidence for efficacy of behavioural therapies that are not viewed as brain-gut behaviour therapies although, in this regard, forms of stress management, a common technique, were superior to waiting list control and digital GDH appeared promising in two large RCTs. Due, in part, to the inherent issues with applying existing approaches to evaluating quality and rigour in pharmacological trials that impact risk of bias assessment of RCTs of behavioural therapies, as well as evidence of possible publication bias, all direct and indirect comparisons across the network were rated as either low or very low confidence.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic disorder of gut-brain interaction (DGBI),[1,2] which affects 5% of people globally.[3] It is characterised by abdominal pain in association with a change in either stool frequency or form.[4] Because the pathophysiology is incompletely understood,[5] there is no cure and IBS can be difficult to manage. This means it has broad implications for society due to its impact on health services,[6] ability to work and participate in social activities,[7] and quality of life.[8] Studies have shown that impairments in quality of life in people with IBS are of a similar magnitude to that seen in patients with organic disorders of the gastrointestinal tract, such as inflammatory bowel disease,[9] and worse than those seen in people living with heart failure or a stroke.[8]

First-line approaches for IBS include dietary and lifestyle advice,[10,11] with second-line treatment usually consisting of the use of drugs, such as antispasmodics,[12] gut-brain neuromodulators,[13] drugs acting on 5-hydroxytryptamine or opioid receptors,[14] or secretagogues,[15] according to predominant symptom. However, most of these drugs act peripherally, yet IBS is conceptualised as a DGBI,[16] and there is increasing evidence that bi-directional brain-gut axis effects are involved in its pathophysiology.[17,18] Beyond first- and second-line treatments, management guidelines for IBS recommend the use of behavioural therapies, specifically brain-gut behaviour therapies.[19-21] These gastrointestinal-focused behavioural interventions target brain-gut dysregulation, and are beneficial in some patients.[22] They may improve global symptoms in IBS because of their peripheral effects on pain perception, visceral hypersensitivity, and gastrointestinal motility,[23-27] although some of their benefit may be mediated by an effect on mood.[28]

Our prior systematic review and network meta-analysis has summarised the evidence for which of these treatments may be efficacious in IBS.[29] However, despite some confirmation of their proposed benefits, there were limitations of the evidence base. These included the numerous different individual treatments and treatment classes, variations in the method of delivery, and the fact that there were few head-to-head randomised controlled trials (RCTs) of different behavioural treatments.

There were also methodological issues, such as difficulties in blinding participants to treatment and what constitutes an appropriate placebo control. Furthermore, in our prior network meta-analysis we did not classify interventions based on whether they were viewed as being a true brain-gut behaviour therapy.[29,30] This is an important distinction because brain-gut behaviour therapies consist of tailored treatment packages, as opposed to separating out common techniques. In addition, accessing behavioural therapies in routine care may be difficult,[31] and although alternatives such as digital-based applications are increasingly available, they are not administered by a clinician, not personalised, and not a form of brain-gut behaviour therapy and, therefore, may have limitations in their utility, but this requires study.

As it has been 5 years since our previous network meta-analysis studying the efficacy of behavioural therapies in IBS,[29] we updated this. We included behavioural therapies that are viewed as brain-gut behaviour therapies, as well as other behavioural therapies. Network meta-analysis allows estimation of the relative efficacy of the active interventions studied, as well any control interventions, and indirect, as well as direct, comparisons to be made across different RCTs. The latter increases the number of participants' data available for analysis. Knowledge of the most efficacious behavioural therapies, overall, is important to guide future treatment recommendations in this field.

METHODS

Search Strategy and Study Selection

We searched MEDLINE (1st January 1946 to 23rd April 2025), EMBASE, EMBASE Classic (1st January 1947 to 23rd April 2025), PsychINFO (1st January 1806 to 23rd April 2025), and the Cochrane central register of controlled trials to identify potential trials. We also identified studies published only in abstract form from conference proceedings (Digestive Disease Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2001 and 2024. Finally, we used the bibliographies of all obtained articles to perform a recursive search. The search strategy is provided in the web appendix page 2.

Eligible RCTs examined the efficacy of behavioural therapies for IBS in adult participants (≥18 years) including the first period of cross-over trials, prior to cross-over to the second treatment (see web appendix page 3). Trials had to compare behavioural therapies (see web appendix page 4) with each other, or with a control intervention. The control intervention could consist of any of waiting list control, where patients were left on a waiting list to receive the active intervention after the trial had ended, attention-placebo control, where a credible inactive intervention with an expectation of benefit was applied, forms of education and support, dietary and 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 had to be followed up for ≥4 weeks, and trials had to report global assessment of IBS symptom resolution or improvement after completion of therapy, preferably patient-reported, but if this was not recorded then as documented by the investigator. Where studies included patients with IBS among patients with other DGBI, we attempted to contact the original investigators to obtain further information only for participants with IBS. This was an update of our prior network meta-analysis,[29] with the study

protocol published on the PROSPERO international prospective register of systematic reviews (registration number CRD 42020163246).

Two investigators (MK and ACF) conducted the literature search independently from each other using medical subject heading and free text terms. There were no language restrictions. Two investigators (CJB or MK, 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. We assessed eligibility independently, according to our pre-defined criteria. We translated foreign language papers, where required, with assistance from the original investigators. We resolved disagreements between investigators by discussion.

We categorised behavioural therapies based on the type of intervention, specifically whether they fitted a class of brain-gut behaviour therapy, according to a Rome Foundation Working Team report.[32] These included forms of disease self-management, forms of dynamic psychotherapy or emotional processing interventions, forms of gut-directed hypnotherapy (GDH), forms of IBS-specific cognitive-behavioural therapy (CBT), including cognitive therapy and forms of contextually-based CBT, or forms of mindfulness training (see web appendix page 4). Where interventions did not fit into a single class of brain-gut behaviour therapy, we identified whether they were a common technique, i.e., a universal approach present in nearly all classes of brain-gut behaviour therapies, such as relaxation therapy or training, multicomponent behavioural therapy, or stress management. Interventions that were neither a brain-gut behaviour therapy, nor did they include a common technique, included self-guided forms of behavioural therapy, forms of hypnotherapy that were not gut-directed, forms of integrated treatment, or forms of digital therapy. For the purposes of this study, we did not classify contingency management as a BGBT and categorised it as its own form of behavioural therapy.

We also categorised treatments that were provided via a therapist based on the method of delivery, which included face-to-face individual delivery, face-to-face group delivery, telephone

delivery, face-to-face minimal contact delivery, or internet-based minimal contact delivery. Wherever referred to in the text, behavioural therapies are delivered face-to-face and on an individual basis, unless otherwise stated.

Outcome Assessment

The primary outcome assessed was the efficacy of all behavioural therapies and control interventions in IBS, in terms of effect on global IBS symptoms 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 behavioural therapies in IBS at 6 months post-randomisation. Secondary outcomes included treatment-emergent adverse events (total numbers, as well as adverse events leading to study withdrawal, and individual adverse events, if reported).

Data Extraction

Two investigators (CJB or MK, 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 improved or unimproved). For studies that reported a dichotomous assessment of response to therapy according to these endpoints, for example a 50-point decrease in the IBS-SSS or a 50% or more improvement in global symptom score, we extracted these data from the article. Where studies reported mean individual symptom severity scores at baseline together with follow-up mean symptom severity scores and follow-up standard deviation for these endpoints for each intervention arm, we imputed dichotomous responder and non-responder data using methodology described previously by Furukawa *et al.*,[33,34] and accounting for the minimum possible severity score if this was above zero in the scoring system used. For example, a 50% or more improvement in global symptom score on the IBS-SSS is derived from the formula: number of participants in each treatment arm at final follow-up x normal standard distribution. The normal

standard distribution corresponds to: (50% of the baseline mean score – follow-up mean score) / follow-up standard deviation. We contacted first and senior authors of studies to provide additional information for individual trials, where required.

We also extracted the following data for each eligible trial, where available: country of origin, setting (primary, secondary, or tertiary care-based), type of behavioural therapy used, including duration of therapy and number of sessions, criteria used to define IBS, primary outcome measure used to define symptom improvement or resolution following therapy, duration of follow-up, proportion of female patients, proportion of patients according to predominant bowel habit (IBS with constipation (IBS-C), diarrhoea (IBS-D), or mixed bowel habits (IBS-M)), and whether trials recruited only patients with symptoms that had been refractory to standard medical therapy. We also recorded the handling of the control arm for trials of behavioural therapies, as we pooled these separately in the analysis to assess their relative efficacy. Data were extracted as intention-to-treat analyses, with all dropouts assumed to be treatment failures (i.e., no response to the behavioural therapy or the comparator), wherever trial reporting allowed this. If this was not reported in the original article, we performed an analysis on all patients with reported evaluable data.

Quality Assessment and Risk of Bias

We used the Cochrane risk of bias tool to assess quality and risk of bias at the study level.[35] Two investigators (CJB or MK, and ACF) performed this independently with disagreements resolved by discussion. We recorded the method 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

The network meta-analysis was performed using the frequentist model, with the statistical package "netmeta" (version 2.9-0, https://cran.r-project.org/web/packages/netmeta/index.html) in R (version 4.4.2). We reported the study according to the PRISMA extension statement for network meta-analyses,[36] to explore direct and indirect treatment comparisons of the efficacy and safety of each intervention. Network meta-analysis results usually give a more precise estimate, compared with results from standard, pairwise analyses,[37,38] and allows the ranking of interventions to inform clinical decision-making.[39]

We examined the symmetry and geometry of the evidence by producing a network plot with node size corresponding to number of study subjects, and connection size corresponding to number of studies using Stata version 18 (Stata Corp., College Station, TX, USA). We used "netmeta" to produce comparison adjusted funnel plots exploring publication bias or other small study effects, for all available comparisons. These are scatterplots of effect size versus precision, measured via the inverse of the standard error. Symmetry around the effect estimate line indicates absence of publication bias, or small study effects.[40] We applied Egger testing to these,[41] where there were 10 or more RCTs, in line with recommendations.[42] We summarised the effect of each comparison tested as a pooled relative risk (RR) with 95% confidence intervals (CIs), using a random effects model as a conservative estimate. We used a RR of failure to achieve each of the endpoints of interest, where if the RR was less than 1 and the 95% CI did not cross 1, there was a significant benefit of one behavioural therapy over another. This approach is likely to be the most consistent across individual trials, compared with a RR of cure or improvement, or using the odds ratio, for some meta-analyses.[43]

Many meta-analyses use the I^2 statistic to measure heterogeneity.[44] This is easy to interpret and does not vary with the number of trials. However, the I^2 value tends to increase with the number

of included patients in the meta-analysis.[45] Therefore, we assessed global statistical heterogeneity using the τ^2 measure from the "netmeta" statistical package. Estimates of τ^2 greater than 0.04, 0.16, and 0.36 represent low, moderate, and high levels of heterogeneity, respectively.[46] We checked the correlation between direct and indirect evidence across the network via consistency modelling,[47] generating network heat plots. These have grey squares representing the size of the contribution of the direct estimate of one study design in columns, compared with the network estimate in rows.[48] The coloured squares around these represent the change in inconsistency between direct and indirect evidence in a network estimate in the row after relaxing the consistency assumption for the effect of one design in the column. Blue squares indicate that the direct evidence of the design in the column supports the indirect evidence in the row, yellow squares indicate no major inconsistency but some degree of disparity between direct and indirect evidence, and red squares are "hotspots" of inconsistency between direct and indirect evidence.

We ranked all behavioural therapies and all 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. They measure the mean extent of certainty that one intervention is better than another, averaged over all competing interventions.[49] Higher scores indicate a greater probability that the intervention is ranked as best,[49] but the magnitude of the P-score should be considered, as well as the treatment rank. The mean P-score value is always 0.5 so, if individual interventions cluster around this value, they are likely to be of similar efficacy. However, it is also important to take the RR and corresponding 95% CI for each comparison into account when interpreting the results, rather than using only rankings.[50] In our primary analyses, we pooled data for the risk of being symptomatic at the final point of follow-up for all included RCTs using an intention-to-treat analysis. We also performed analyses restricted to trials that recruited only patients with refractory symptoms, and performing analyses examining efficacy with longer term follow-up

out to 6-months post-randomisation. Finally, we performed similar analyses according to treatment class (e.g., IBS-specific CBT or GDH), irrespective of the mode of delivery.

For our primary analysis of global IBS symptoms at the final point of follow-up, we used the Confidence in Network Meta-Analysis (CINeMA) framework to evaluate confidence in the indirect and direct treatment estimates from the network,[51] which is endorsed by the Cochrane Collaboration. This includes the Risk of Bias from Missing Evidence in Network Meta Analysis tool for evaluation of reporting bias.[52]

Role of the funding source

We received no funding for this network meta-analysis. All authors had full access to all data and accepted responsibility to submit for publication.

RESULTS

The search strategy generated 3159 citations, 129 of which we retrieved for further assessment as they appeared to be relevant (Figure 1). Of these, 64 were excluded, leaving 65 eligible articles,[53-117] reporting 67 separate RCTs. These included 7441 patients, 5002 of whom received a behavioural therapy and 2439 a control intervention (see web appendix pages 5 to 6). Twenty-six trials were included since the last version of the network meta-analysis, including 3298 patients. Agreement between investigators for trial eligibility was excellent (Kappa statistic = 0.89). Adverse events were not reported in sufficient detail to allow any meaningful pooling of data. Detailed characteristics of individual RCTs, including the comparisons made, are provided in the web appendix pages 7 to 12. Risk of bias items for all included trials are reported in the web appendix pages 13 to 14. In terms of risk of bias, 39 RCTs reported the method of randomisation used,[65,66,68-70,73,74,76-78,80,83-85,87-98,100,102-109,113,115,117] and 26 described how treatment allocation was concealed.[65,68-70,76,79,83-85,87,89-91,93,95-97,100,102-105,107-109,117] Due to the nature of the interventions used, double-blinding was difficult, although two trials reported they were double-blind,[97,111] and another nine trials stated specifically that investigators were blinded to treatment assignment.[62,68-70,88,93,96,102,103] No RCT was at low risk of bias across all domains. Twenty-one trials stated that they only recruited patients with symptoms that had been refractory to medical therapy.[54,56,62,65,69,71,73,74,76,86,91,93,97,100,102,103,106,108-110]

Efficacy for Global IBS Symptoms at First Point of Follow-up Post-treatment

In total, 67 RCTs provided data for likelihood of remaining symptomatic at the first point of follow-up post-treatment, with 49 providing this as extractable dichotomous data and data imputed for the other 18 trials.[66,75-77,83,86,89,90,92,95,97,99,101,104,110,112,114,115] The network plot is provided in the web appendix pages 23 to 24. When data were pooled, there was minimal heterogeneity ($\tau^2 = 0.026$), but the funnel plot appeared asymmetrical when comparing active therapies with waiting list control (Egger test, $p = 0.0052$), suggesting publication bias or other small study effects (see web appendix

pages 25 to 26), although not when comparing active therapies with routine care (Egger test, p = 0.81). Of all the behavioural therapies studied, minimal contact disease self-management ranked first (RR of global IBS symptoms not improving = 0.31; 95% CI 0.15 to 0.64, P-score 0.96) (Figure 2), meaning that the probability that this was the most efficacious therapy was 96%, but based on only one RCT recruiting 64 patients.[85] Cognitive therapy ranked second (RR = 0.43; 95% CI 0.25 to 0.71, P-score 0.89) in three trials recruiting 88 patients,[60,61,64] and digital GDH third (RR = 0.42; 95% CI 0.20 to 0.88, P-score 0.86) in two trials recruiting 622 patients.[111,113] 95% CIs around the estimates for all these therapies were wide. Other behavioural therapies with the largest numbers of trials, or patients recruited, and with evidence for efficacy, included minimal contact CBT (RR = 0.55; 95% CI 0.39 to 0.76, P-score 0.78) in two RCTs including 511 patients,[80,102] telephone disease self-management (RR = 0.57; 95% CI 0.41 to 0.80, P-score 0.75) in two trials including 746 patients,[82,103] dynamic psychotherapy (RR = 0.59; 95% CI 0.43 to 0.80, P-score 0.72) in three RCTs including 303 patients,[56,69,116] CBT (RR = 0.65; 95% CI 0.53 to 0.80, P-score 0.64) in nine trials including 1150 patients,[55,66,68,70,74,80,87,99,102] disease self-management (RR = 0.68; 95% CI 0.50 to 0.92, P-score 0.58) in three RCTs including 375 patients,[72,82,98] internet-based minimal contact CBT (RR = 0.77; 95% CI 0.61 to 0.96, P-score 0.43) in five RCTs including 705 patients,[81,84,89,90,95] and GDH (RR = 0.79; 95% CI 0.66 to 0.95, P-score 0.39) in 12 trials including 1507 patients.[54,63,65,73,76,91,97,104,106,109,110] The network heat plot had no red “hotspots” of inconsistency (see web appendix pages 27 to 29).

Among active treatments and behavioural therapies with the largest numbers of trials, or patients recruited, digital GDH was superior to self-guided CBT (web appendix 2). Minimal contact CBT was superior to GDH, relaxation therapy or training, group GDH, and self-guided CBT. Telephone disease self-management was superior to relaxation therapy or training and self-guided CBT. Both dynamic psychotherapy and CBT were superior to self-guided CBT. None of the active treatments were superior to all seven control interventions although, again, among active treatments and behavioural therapies with the largest numbers of trials, and patients recruited, minimal contact

CBT, telephone disease self-management, and dynamic psychotherapy were all superior to attention-placebo control, education and support, and routine care, in addition to waiting list control. Using the CINeMA framework to rate confidence in the results for this endpoint for all 990 comparisons, whether contributing direct evidence or else made indirectly, confidence was rated as either low or very low. This was largely driven by high risk of within study bias, risks of reporting bias favouring active interventions for some comparisons, particularly those using waiting list control or routine care, and risks of imprecision, where clinically important effects were observed in both directions due to the size of the confidence interval for a comparison. We have not presented these results due to the size of the table required, but they are available from the authors on request.

When we examined the efficacy of behavioural therapies according to treatment class, there were 62 trials providing data for the analysis, including 6042 patients.[53,55-94,96-105,107,108,110,112-117] Three RCTs were excluded because they only compared two forms of GDH with each other,[54,106,109] one because it only compared two forms of digital therapy with each other,[111] and one because it only compared two forms of CBT with each other.[95] The network plot is provided in the web appendix page 30. When data were pooled, there was minimal heterogeneity ($\tau^2 = 0.031$), but evidence of publication bias, or other small study effects, (Egger test, $p < 0.0001$) when comparing active therapies with waiting list control (see web appendix pages 31 to 32), but not active therapies with routine care (Egger test, $p = 0.81$). Compared with waiting list control, a specific form of behavioural therapy, contingency management, studied in two trials including only 130 patients,[62,75] ranked first (RR of global IBS symptoms not improving = 0.54; 95% CI 0.33 to 0.87, P-score 0.90) (Figure 3). However, the 95% CIs were wide. Forms of disease self-management ranked second (RR = 0.66; 95% CI 0.51 to 0.85, P-score 0.79), in five RCTs recruiting 429 patients, [72,82,85,98,103] and forms of CBT third (RR = 0.67; 95% CI 0.58 to 0.77, P-score 0.79), in 19 trials including 1986 patients.[55,60,61,64,66,68,70,71,74,77,80,81,84,87,89,90,99,102,108] Forms of dynamic psychotherapy/emotional processing (RR = 0.69; 95% CI 0.52 to 0.90, P-score 0.73), forms of multicomponent behavioural

therapy (RR = 0.70; 95% CI 0.51 to 0.98, P-score 0.68), forms of contextually-based CBT (RR = 0.73; 95% CI 0.55 to 0.96, P-score 0.64), forms of mindfulness training (RR = 0.74; 95% CI 0.58 to 0.94, P-score 0.62), forms of stress management (RR = 0.74; 95% CI 0.59 to 0.94, P-score 0.61) and forms of GDH (RR = 0.80; 95% CI 0.67 to 0.95, P-score 0.51) were also superior to waiting list control. The network heat plot had no red "hotspots" of inconsistency (see web appendix pages 33 to 34).

After direct and indirect comparison, contingency management was superior to forms of self-guided therapy, and forms of CBT were superior to forms of self-guided therapy and forms of relaxation therapy or training, but there were no other significant differences between active interventions (see web appendix pages 15 to 16). Contingency management was also superior to attention-placebo control, education and support, enhanced education, and routine care. Forms of disease self-management were also superior to education and support and routine care. Forms of CBT were superior to attention-placebo control, education and support, and routine care. Finally, forms of dynamic psychotherapy/emotional processing, forms of multicomponent behavioural therapy, forms of contextually-based CBT, forms of mindfulness training, forms of stress management, forms of GDH, and forms of relaxation therapy or training were also superior to routine care.

Efficacy for Global IBS Symptoms at First Point of Follow-up Post-treatment in Patients with Refractory Symptoms

The network plot for the 21 RCTs that stated that they only recruited 2956 patients with refractory IBS is provided in the web appendix page 35.[54,56,62,65,69,71,73,74,76,86,91,93,97,100,102,103,106,108-110] When data were pooled, there was minimal heterogeneity ($\tau^2 = 0.032$), and no evidence of publication bias (Egger test, p = 0.65) when comparing active interventions with routine care (see web appendix pages 36 to 37). Compared with waiting list control, telephone disease self-

management ranked first (RR of global IBS symptoms not improving = 0.58; 95% CI 0.29 to 1.15, P-score 0.83) (see web appendix page 38), based on one RCT including 558 patients.[103] However, none of the active interventions were superior to waiting list control. After direct and indirect comparison, no behavioural therapy was significantly more efficacious than any of the other active therapies (see web appendix pages 17 to 18). None of the active treatments were superior to education and support. Telephone disease self-management and contingency management were both superior to attention-placebo control and routine care. Group CBT, internet-based minimal contact disease self-management, and dynamic psychotherapy were all superior to routine care.

Eighteen trials examined the efficacy of behavioural therapies according to treatment class in 2244 patients with refractory symptoms.[56,62,65,69,71,73,74,76,86,91,93,97,100,102,103,108,110] Three other RCTs were excluded because they only compared two forms of GDH with each other.[54,106,109] When data were pooled, there was minimal heterogeneity ($\tau^2 = 0.029$). There were too few trials making direct comparisons of active therapies with any of the control interventions to assess for publication bias. Compared with waiting list control, other forms of behavioural therapy, specifically contingency management, ranked first in one trial of 90 patients (RR = 0.55; 95% CI 0.25 to 1.21, P-score 0.86) (see web appendix page 39).[62] However, none of the active interventions were superior to waiting list control. After direct and indirect comparison, contingency management was superior to attention-placebo control and routine care, and forms of disease self-management, dynamic psychotherapy/emotional processing, and CBT were all superior to routine care (see web appendix page 19).

Efficacy for Global IBS Symptoms at 6-month Follow-up

Fourteen trials reported symptom data out to 6 months post-randomisation,[57,72,79,82,85,87-89,94,95,98,102,103,109] but three of these RCTs could not be included in the network as they made no comparison with any of the other therapies or control interventions.[89,95,109] The remaining 11 RCTs

formed two separate networks, the first consisting of seven RCTs including 1137 patients,[57,72,79,82,85,98,103] and the second consisting of four trials including 711 patients.[87,88,94,102] There were insufficient RCTs to assess for publication bias or other small study effects in either of these networks. In the first network, when data were pooled, there was low heterogeneity ($\tau^2 = 0.074$). Compared with routine care, stress management ranked first (RR of global IBS symptoms not improving = 0.34; 95% CI 0.13 to 0.86, P-score 0.88) in only one trial including 35 patients,[57] and 95% CIs were wide (see web appendix page 40). Minimal contact disease self-management ranked second (RR = 0.38; 95% CI 0.14 to 0.97, P-score 0.83) in only one RCT including 64 patients,[85] and again 95% CIs were wide. Telephone disease self-management ranked third (RR = 0.65; 95% CI 0.44 to 0.95, P-score 0.57) in two trials including 746 patients.[82,103] No other active treatment was superior to routine care, and after direct and indirect comparison no behavioural therapy was significantly more efficacious than any of the other active therapies (see web appendix page 20). In the second network, there was no heterogeneity ($\tau^2 = 0.0$). In this analysis, compared with waiting list control, minimal contact CBT ranked first (RR of global IBS symptoms not improving = 0.55; 95% CI 0.30 to 1.02, P-score 0.94) in one trial including 436 patients (see web appendix page 41),[102] but none of the active interventions were superior to waiting list control. After direct and indirect comparison, minimal contact CBT was superior to education and support, but no behavioural therapy was significantly more efficacious than any of the other active therapies (see web appendix page 21).

Of the 14 trials reporting symptom data out to 6 months post-randomisation by treatment class,[57,72,79,82,85,87-89,94,95,98,102,103] two could not be included in the network as one only compared two forms of CBT,[95] and the other two forms of GDH.[109] Therefore, data from 12 RCTs, and 2043 patients, were included. When data were pooled, there was minimal heterogeneity ($\tau^2 = 0.035$). There were too few trials making direct comparisons of active interventions with any of the control interventions to assess for publication bias. Compared with waiting list control, forms of CBT ranked first (RR = 0.56 95% CI 0.24 to 1.31, P-score 0.91), in three trials including 741 patients,[87,89,102] but

none of the active interventions were superior to waiting list control (see web appendix page 42). After direct and indirect comparison, forms of CBT were superior to forms of relaxation therapy or training and to routine care (see web appendix page 22). Forms of stress management and disease self-management were also superior to routine care. There were no other significant differences between active or control interventions.

DISCUSSION

We updated our previous systematic review and network meta-analysis examining efficacy of behavioural therapies for global symptoms in IBS.[29] We included 26 trials since the last version, some of which were published after the last search date and others we included in this update due to our ability to impute dichotomous responder data. In terms of effect on global symptoms immediately after treatment cessation, minimal contact disease self-management, cognitive therapy, and digital GDH ranked first, second, and third respectively. In this analysis, efficacious behavioural therapies with the largest numbers of trials, or patients recruited, included minimal contact CBT, telephone disease self-management, dynamic psychotherapy, CBT, disease self-management, internet-based minimal contact CBT, and GDH, all of which are classed as brain-gut behaviour therapies. Confidence in the results for this analysis was rated as either low or very low. Except for digital GDH, in two large RCTs,[111,113] and contingency management, in two small trials,[62,75] there was little evidence of efficacy for interventions not considered to be classes of brain-gut behaviour therapy or common techniques. In terms of treatment class, a specific form of behavioural therapy, contingency management, forms of disease self-management, CBT, dynamic psychotherapy/emotional processing, multicomponent behavioural therapy, contextually-based CBT, mindfulness training, stress management, and GDH were all superior to waiting list control. For refractory symptoms, no active intervention was superior to waiting list control, although telephone disease self-management and contingency management were both superior to attention-placebo control and routine care, and group CBT, internet-based minimal contact disease self-management, and dynamic psychotherapy were all superior to routine care. In terms of treatment class, forms of disease self-management, dynamic psychotherapy/emotional processing, and CBT were all superior to routine care for refractory symptoms. Longer-term, stress management, minimal contact disease self-management, and telephone disease self-management were superior to routine care, and minimal contact CBT was superior to education and support 6 months after treatment cessation. Forms of

CBT were superior to forms of relaxation therapy or training and to routine care, and forms of stress management or disease self-management were both superior to routine care 6-months post-treatment. However, for treatments found to be efficacious, P-scores were, for the most part, similar suggesting the ranking should not be applied prescriptively to judge relative efficacy. Finally, adverse events were reported inconsistently, precluding pooling of data.

The network allowed us to make indirect comparisons between over 7000 participants in these 67 RCTs, with trials conducted in a wide variety of settings, and countries, recruiting patients with IBS irrespective of bowel habit, and the majority not restricting recruitment to those with refractory symptoms. This suggests our results are likely to be generalisable to many patients with IBS. We imputed dichotomous responder data from trials that were unable to be included in the previous network meta-analysis. We utilised an intention-to-treat analysis, assuming all trial dropouts were symptomatic at the last point of follow-up and performed subgroup analyses only in trials recruiting patients with refractory symptoms or reporting data out to 6 months after the completion of treatment. Finally, we produced network heat plots, where possible, and did not identify inconsistency in any of our analyses.

Limitations of the network meta-analysis include variability between individual trials, in terms of the design. This includes the behavioural therapies used, the population studied, the setting, the way the interventions were applied, the duration of follow-up, and the endpoint used to define symptom response. Although we performed subgroup analyses examining the efficacy of behavioural therapies according to overall treatment class, based on the Rome Foundation working team report,[32] whether recruitment was restricted to patients with refractory symptoms, and only in RCTs reporting efficacy at 6 months after the end of the intervention, these may not address underlying differences between trials adequately. As an example, most RCTs of GDH and/or group GDH stated specifically that they recruited patients with refractory symptoms and, therefore, the efficacy of these treatments may have been underestimated. In addition, the Rome Foundation

working team report was based on expert opinion,[32] and there may be alternative viewpoints as to what constitutes a brain-gut behaviour therapy. Finally, most RCTs were conducted in North American or European populations, although there were 10 trials from Asia or the Middle East. Nevertheless, extrapolation of our results to other populations may be inappropriate.

Although there was minimal or low heterogeneity observed in all our analyses, there was evidence of publication bias and risk of bias of individual trials was high due to the inability of most trials to blind participants to the assigned treatment, although two trials were double-blind,[97,111] and another nine trials were investigator-blinded.[62,68-70,88,93,96,102,103] It is, therefore, likely that the efficacy of some behavioural therapies has been overestimated, and confidence in the results of our main analysis was either low or very low for all comparisons. However, it is important to point out that there are inherent issues with applying existing approaches to evaluating quality and rigour in pharmacological trials that impact risk of bias assessment of RCTs of behavioural therapies. A recent Rome Foundation working team report highlighted that the use of approaches to evaluating quality in RCTs, such as assessment of double-blinding or use of a placebo-control, shortchange the proper evaluation of trials of behavioural therapies, as they fail to capture the specific elements of scientific rigour that define the conduct of RCTs of behavioural therapies.[118] Instead, the report recommended that confidence should be established by measuring and establishing mechanistic pathways for the behavioural therapy and demonstrating superiority over an active comparator that controls for potential effects of attention and expectancy. Nevertheless, the report also highlighted that these recommendations were aspirational and may not be reflected in current and near-future studies due to funding and other constraints.

Our study demonstrates that the most evidence for efficacy for behavioural therapies for global IBS symptoms exists for those interventions considered to be brain-gut behaviour therapies. There was also some evidence for the efficacy of stress management, and multicomponent behavioural therapy, consisting primarily of relaxation training, which are both common techniques.

However, these findings came from small RCTs.[53,57,58,62,75] Other efficacious approaches not considered to be brain-gut behaviour therapies included digital GDH and contingency management. Evidence for digital GDH came from two RCTs,[111,113] containing over 600 patients, and digital GDH was compared with a control intervention of enhanced education, which contained elements of CBT, in one trial. In contrast, RCTs of contingency management were small.[62,75] Other than digital GDH, no digital therapy was superior to waiting list control in our analyses. In terms of treatment class, we found forms of CBT and GDH to have the largest evidence base for efficacy, which further supports these as being the most robust behavioural interventions for IBS. However, other approaches were also beneficial, most of which were brain-gut behaviour therapies or common techniques. Although management guidelines suggest that patients with refractory symptoms are the population in whom behavioural therapies should be deployed,[19-21] there were relatively few RCTs restricting their recruitment to such patients. Nevertheless, in our analyses of these trials, contingency management, a form of behavioural therapy in its own class, and forms of disease self-management, dynamic psychotherapy/emotional processing, and CBT were all superior to routine care, although none were superior to waiting list control. Finally, data on the longer-term efficacy of behavioural therapies was reported by only 14 RCTs, some of which could not be included in the network due to the lack of a common comparator with other trials. In these analyses, forms of CBT, stress management, and disease self-management were superior to routine care.

Across all our analyses, there were some behavioural therapies that were significantly more efficacious than other active therapies. However, these were almost all treatments that were studied in only a single RCT or in two or three smaller trials. None of the active treatments were superior to all seven of the possible control interventions although, in our main analysis, among active treatments and behavioural therapies with the largest numbers of trials, and patients recruited, minimal contact CBT, telephone disease self-management, and dynamic psychotherapy were all superior to waiting list control, attention-placebo control, education and support, and routine care. It

remains uncertain for whom different behavioural therapies are most efficacious. Some of the RCTs included in this network meta-analysis are large, and it would be possible to perform *post hoc* analysis to try to identify predictors of response, as has been done for a large RCT of amitriptyline in IBS.[119] To date, we are aware of few such examples in trials of behavioural therapies. In a RCT of GDH versus short-course GDH, higher levels of non-gastrointestinal symptom reporting, higher symptom severity, and lower depression scores predicted response to GDH, although there was no inactive control intervention in this trial.[120] In an RCT of CBT or minimal contact CBT versus education, response rates were higher with active treatment in patients with lower levels of anxiety.[121] Such analyses of other trials would enable the refinement of recommendations made in management guidelines.

Although there was limited evidence for the efficacy of digital techniques, alternative delivery methods, such as group, internet, or minimal contact approaches, as opposed to relying solely on individual face-to-face methods, appeared suitable for some therapies. Delivery method is important, as it may represent a barrier to providing care, due to the requirement to travel, time constraints of individual face-to-face delivery, and costs. These alternative methods may also permit the use of behavioural therapies earlier in the treatment pathway, rather than being restricted to those patients who have not benefitted from first- or second-line treatments. The latter is supported by the fact that only a few behavioural therapies were efficacious in patients with refractory symptoms. Although brain-gut behaviour therapies have been integrated in gastroenterology settings, future trials should study the use of these interventions in primary care settings. This may reduce the symptom burden of IBS in the community, as has been seen in an RCT of amitriptyline in IBS in primary care,[13] leading to other positive effects, including reductions in healthcare costs. There is also evidence from one trial that integration of behavioural therapies into outpatient care of patients with DGBI improves symptoms, mood scores, and quality of life, and reduces management costs, compared with standard care.[122]

Taken together, the benefit of brain-gut behaviour therapies for IBS is evident. However, the existing literature has several methodological limitations. To strengthen the current evidence base, future efforts should prioritise the development of rigorous RCTs that incorporate optimal control conditions, standardised protocols for outcome reporting, and clearly defined therapeutic targets. Consistent with our prior network meta-analysis,[29] reporting of adverse events in trials of behavioural therapies remains weak. More consistent recording of such outcomes will help to demonstrate the safety of these approaches. There is also a critical need for larger trials that assess long-term efficacy and identify patient subgroups who are most likely to benefit from specific therapeutic interventions. We may then be able to predict patients in whom particular behavioural therapies are the most efficacious, including those with or without refractory symptoms. Finally, as a means of improving access and availability, both internet-based and digital approaches to delivering behavioural therapies have been studied in recent years. However, it is imperative that we consider efficacy in terms of the mode of delivery for both clinician-administered internet-based brain-gut behaviour therapies and digital approaches, which are not considered to be brain-gut behaviour therapies, and differentiate the impact of common techniques, including the patient-provider relationship. In addition, it will be important to consider the impact of treatment dose in future studies to identify efficient and effective treatment options.

In summary, we found numerous behavioural therapies to be efficacious for global symptoms in IBS. Most of these were treatments considered to be brain-gut behaviour therapies, with evidence for other types of therapy restricted to results from single trials or pooling several small RCTs. Despite the promise of digital approaches, in terms of improving access, only digital GDH had any evidence for efficacy. Nevertheless, our analysis provides support for alternative methods of delivery of behavioural therapies that may improve access. There was evidence for longer-term efficacy, beyond treatment cessation, for some therapies. However, the high risk of bias of all included RCTs, as well as possible publication bias, means that efficacy may have been overestimated and

confidence in the results of the network meta-analysis was low or very low. Forms of CBT and GDH had the largest evidence base, and forms of CBT, stress management, and disease self-management had some evidence for longer-term efficacy. Moving forward, RCTs should use appropriate control conditions, report adverse effects in full, and examine the influence of patient factors that predict response, and assess efficacy of behavioural therapies earlier in the disease course, before patients are refractory to medical management.

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DATA SHARING STATEMENT

Trial level data are already in the public domain, but we would consider reasonable requests to share the trial level data we extracted or imputed with others. No other data are available.

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FIGURE LEGENDS

Figure 1. Flow Diagram of Assessment of Studies Identified in the Systematic Review.

Figure 2. Forest Plot for Failure to Achieve an Improvement in Global IBS Symptoms with Behavioural Therapies* at First Point of Follow-up Post-treatment.

*All therapies delivered face-to-face on an individual basis, unless otherwise stated; active interventions that are not brain-gut behaviour therapies include digital gut-directed hypnotherapy, contingency management, digital relaxation therapy or training, stress management, Ericksonian hypnotherapy, multicomponent behavioural therapy, group integrative therapy, individualised hypnotherapy, digital CBT, internet-based minimal contact relaxation therapy or training, relaxation therapy or training, group relaxation therapy or training, group stress management, internet-based minimal contact stress-management, self-guided CBT, and digital stress management.

CBT; cognitive behavioural therapy, GDH; gut-directed hypnotherapy.

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

Figure 3. Forest Plot for Failure to Achieve an Improvement in Global IBS Symptoms with Behavioural Therapies* at First Point of Follow-up Post-treatment According to Treatment Class.

*Active interventions that are not brain-gut behaviour therapies include other forms of behavioural therapy (contingency management), forms of multicomponent behavioural therapy, forms of stress management, forms of integrated treatment, forms of digital therapy, forms of relaxation therapy or training, and forms of self-guided therapy.

CBT; cognitive behavioural therapy, GDH; gut-directed hypnotherapy.

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