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TITLE PAGE

Title: Efficacy of Gut-brain Neuromodulators and Brain-gut Behaviour Therapies for Irritable Bowel Syndrome: Systematic Review and Network Meta-analysis.

Short title: Gut-brain Neuromodulators and Brain-gut Behaviour Therapies for Irritable Bowel Syndrome: Network Meta-analysis.

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Abbreviations:

CBT	cognitive behavioural therapy
CI	confidence interval
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
SNRI	serotonin and norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant

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ABSTRACT

Background: Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction, with some recommended treatments targeting brain-gut axis dysfunction.

Objective: To compare relative efficacy of gut-brain neuromodulators and brain-gut behaviour therapies in IBS.

Design: Network meta-analysis searching the medical literature to 8th February 2026 for randomised controlled trials (RCTs) of gut-brain neuromodulators or brain-gut behaviour therapies in adults with IBS. In our main analysis, we judged efficacy using dichotomous endpoints of improvement in either global IBS symptoms or abdominal pain. We pooled data with a random effects model, with efficacy reported as a pooled relative risk (RR) with 95% confidence intervals (CIs). We ranked treatments according to P-score; the mean extent of certainty that one treatment is better than another, averaged over all competing treatments.

Results: We identified 68 eligible RCTs (6694 participants). Compared with waiting list control, in 66 trials (6542 patients), serotonin and norepinephrine reuptake inhibitors (SNRIs) ranked first in six trials (387 patients) (RR of global IBS symptoms or abdominal pain not improving = 0.49; 95% CI 0.32-0.75, P-score 0.95), meaning the probability that this was the most efficacious treatment was 95%. However, no trials were low risk of bias. Tricyclic antidepressants (TCAs) ranked second in 15 trials (1519 patients) (RR = 0.60; 95% CI 0.43-0.85, P-score 0.79), and forms of dynamic psychotherapy/emotional processing third (RR = 0.62; 95% CI 0.44-0.87, P-score 0.75). Forms of cognitive behavioural therapy, forms of disease self-management, selective serotonin reuptake inhibitors, and forms of gut-directed hypnotherapy (GDH) were also superior to waiting list control.

Conclusion: Several gut-brain neuromodulators, especially TCAs, and brain-gut behaviour therapies, particularly forms of dynamic psychotherapy/emotional processing, CBT, disease self-management, and GDH, are efficacious for IBS. However, there was possible publication bias in some analyses, and overall certainty in the evidence was low or very low for most comparisons.

What is already known on this topic

- Beyond first-line approaches and drugs directed towards abnormalities in bowel habit, management guidelines for irritable bowel syndrome (IBS) recommend the use of low-dose antidepressants or brain-gut behaviour therapies.

What this study adds

- Although there have been prior pairwise and network meta-analyses of randomised controlled trials (RCTs) examining the efficacy of these treatments separately in IBS, no network meta-analysis has compared their efficacy.
- This is feasible, because there are individual RCTs comparing gut-brain neuromodulators with brain-gut behaviour therapies directly, and RCTs comparing more than one type of gut-brain neuromodulator or comparing more than one class of brain-gut behaviour therapy directly.
- In the network meta-analysis, serotonin and norepinephrine reuptake inhibitors ranked first, mainly in high risk of bias trials, tricyclic antidepressants second, and forms of dynamic psychotherapy/emotional processing third.
- Forms of cognitive behavioural therapy, forms of disease self-management, selective serotonin reuptake inhibitors, and forms of gut-directed hypnotherapy were also superior to waiting list control.

How this study might affect research, practice or policy

- This network meta-analysis provides useful information that may guide current clinical practice and influence updates to management guidelines for IBS, as well as highlighting future research priorities.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic bowel disorder, hypothesised to arise because of abnormal gut-brain interaction.[1, 2] The prevalence of IBS is between 3% and 5% in most countries.[3] The cardinal symptoms are abdominal pain in association with either abnormal stool frequency or form.[4] Because there is no cure for IBS, it has a considerable impact on society, arising from the costs associated with managing it,[5] and individuals, due to its effects on social functioning, ability to work,[6] and quality of life.[7]

IBS management guidelines recommend lifestyle and dietary advice as first-line treatments, alongside drugs, including laxatives, anti-diarrhoeals, or antispasmodics.[8-11] Beyond this, drugs acting on 5-hydroxytryptamine receptors or secretagogues are recommended, depending on whether diarrhoea or constipation is the predominant symptom reported by the individual. However, as already discussed, IBS is conceptualised as a disorder of gut-brain interaction.[12] Beyond first-line approaches and drugs directed towards abnormalities in bowel habit, the use of low-dose antidepressants or brain-gut behaviour therapies is recommended.[8-11] At lower doses, antidepressants are acting as gut-brain neuromodulators,[13] whereas brain-gut behaviour therapies are gastrointestinal-focused therapies targeting modifiable factors implicated in gut-brain dysregulation.[14] Both are beneficial for a subset of patients with IBS for global symptoms and abdominal pain, specifically.[15-17] The latter is important, given that abdominal pain may be the most troublesome symptom for many patients with IBS,[18] rather than abnormal bowel habit.

Although there have been multiple pairwise and network meta-analyses of gut-brain neuromodulators or brain-gut behaviour therapies in IBS, there have been no network meta-analyses comparing their relative efficacy. However, this is feasible because there are individual randomised controlled trials (RCTs) that have compared gut-brain neuromodulators with brain-gut behaviour therapies directly,[19, 20] and RCTs comparing more than one type of gut-brain neuromodulator, or more than one class of brain-gut behaviour therapy, directly.[21-26] We, therefore, conducted a

network meta-analysis of gut-brain neuromodulators and brain-gut behaviour therapies in IBS to assess their relative efficacy. This approach allows indirect, as well as direct, comparisons to be made across different RCTs, increasing the number of participants' data available for analysis. Knowledge of the relative efficacy of these two different interventions in IBS may help inform both current clinical decision-making and future management guidelines.

METHODS

Search Strategy and Study Selection

The study protocol was published on the PROSPERO international prospective register of systematic reviews (registration number CRD420261324267; available at https://www.crd.york.ac.uk/PROSPERO/view/CRD420261324267). The search strategy is provided in the Supplementary Methods.

Eligible RCTs examined the efficacy of gut-brain neuromodulators and/or brain-gut behaviour therapies for IBS in adults (≥18 years) including the first period of cross-over trials, prior to cross-over to the second treatment (Supplementary Table 1). Trials compared gut-brain neuromodulators and brain-gut behaviour therapies with each other, or with a control. The control intervention could consist of any of placebo, 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, education and support, dietary and lifestyle advice, or routine care. Duration of therapy had to be ≥4 weeks. To avoid extreme results from single trials of a therapy, there had to be a minimum of two RCTs of each intervention. Hence, there were fewer RCTs than in our previous meta-analyses of these treatments.[15, 17] Gut-brain neuromodulators encompassed alpha-2-delta ligand agents, such as pregabalin or gabapentin, antipsychotic drugs, including sulpiride or levosulpiride, azapirones, such as buspirone or tandospirone, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tetracyclic antidepressants, including mirtazapine, or tricyclic antidepressants (TCAs). Brain-gut behaviour therapies were defined according to the Rome Working Team report,[14] including forms of cognitive behavioural therapy (CBT), forms of contextually-based CBT, forms of disease self-management, forms of dynamic psychotherapy or emotional processing, forms of gut-directed hypnotherapy (GDH), or forms of mindfulness training.

The diagnosis of IBS could be based on a physician's opinion or accepted symptom-based diagnostic criteria, including the Manning criteria,[27] the Kruis scoring system,[28] or the Rome I, II, III, or IV criteria.[4, 29-31] Trials reported assessment of either global IBS symptom resolution or improvement or abdominal pain resolution or improvement after completion of therapy. Where studies included patients with IBS among those with other disorders of gut-brain interaction, we contacted original investigators to obtain further information only for participants with IBS.

Outcome Assessment

The primary outcome was the efficacy of all gut-brain neuromodulators or brain-gut behaviour therapies and control interventions in IBS according to the primary endpoint used in each individual RCT, including effect on either global IBS symptoms or abdominal pain after completion of therapy. Secondary outcomes included efficacy of all gut-brain neuromodulators or brain-gut behaviour therapies and control interventions in IBS in terms of effect on global IBS symptoms only and treatment-emergent adverse events (total numbers of treatment-emergent adverse events, as well as treatment-emergent adverse events leading to study withdrawal, and individual adverse events, if reported). We did not perform an analysis examining effect on abdominal pain only, because the network became too sparse, with no direct comparisons between brain-gut behaviour therapies and gut-brain neuromodulations.

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 or abdominal pain improved or unimproved). For studies reporting a dichotomous assessment of response to therapy according to these endpoints, for example a 50-point decrease in the IBS-SSS, a 50% or more improvement in global symptom score, or a 30% or

more improvement in abdominal pain, we extracted these data from the article. Where studies reported mean individual symptom severity scores at baseline together with both mean symptom severity scores and standard deviations at follow-up for these endpoints for each intervention arm, we imputed dichotomous responder and non-responder data using methodology described previously by Furukawa *et al*.,[32, 33] and accounting for the minimum possible severity score if this was above zero in the scoring system used. For example, the number of participants achieving 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 for each eligible trial, where available: country of origin, setting (primary, secondary, or tertiary care-based), type, dose, and duration of gut-brain neuromodulator used, type, duration, and number of sessions of brain-gut behaviour therapy used, criteria used to define IBS, primary outcome measure to define symptom improvement or resolution following therapy, proportion of female patients, and proportion of patients according to predominant bowel habit (IBS with constipation (IBS-C), diarrhoea (IBS-D), or mixed bowel habits (IBS-M)). We also recorded the handling of the control arm for trials of brain-gut behaviour 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 gut-brain neuromodulator, brain-gut behaviour 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.[34] 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, 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

Full details are provided in the Supplementary Methods.

RESULTS

The search strategy generated 8640 citations, 177 of which were retrieved for further assessment as they appeared relevant (Figure 1). Of these, 110 were excluded, leaving 67 eligible articles,[19-26, 35-93] reporting 68 separate RCTs. These included 6694 patients, 1509 receiving a gut-brain neuromodulator, 2457 a brain-gut behaviour therapy, and 2728 a control intervention, as described in the Supplementary Results and Supplementary Table 2. Among those assigned to a control intervention, 1038 received placebo, 757 routine care, 561 education and support, and 372 waiting list control. Agreement between investigators for trial eligibility was excellent (Kappa statistic = 0.92). Adverse events were not reported in RCTs of brain-gut behaviour therapies in sufficient detail to allow any meaningful pooling of data.

Detailed characteristics of individual RCTs, including comparisons made, are provided in Supplementary Table 3. Risk of bias items for all included trials are reported in Supplementary Table 4. In terms of risk of bias, 43 RCTs reported an appropriate method of randomisation,[19-25, 40, 42-46, 49-51, 54-57, 59, 60, 62-65, 68-70, 72-75, 80, 83-86, 89-91, 93] and 29 described how treatment allocation was concealed.[19-21, 24, 25, 43-46, 50, 51, 54, 55, 57, 59, 60, 63, 65, 68, 69, 72, 73, 83, 84, 86, 89-91] Nine trials of gut-brain neuromodulators were low risk of bias across all domains.[19, 21, 43, 45, 46, 54, 57, 59, 83] Due to the nature of the brain-gut behaviour therapies used, double-blinding was difficult, with no RCT at low risk of bias across all domains, although seven trials stated specifically that investigators were blinded to treatment assignment.[19, 20, 24, 63, 74, 90, 91]

Efficacy for Either Global IBS Symptoms or Abdominal Pain

When we examined efficacy with brain-gut behaviour therapies grouped by treatment class, there were 66 trials providing data for the analysis, including 6542 patients.[19-21, 24-26, 36-40, 42, 43, 45-47, 49-55, 57-59, 61-69, 71-85, 88-93] Of these, 57 RCTs reported effect on global IBS symptoms,[19-21, 24-26, 36-40, 42, 43, 45-47, 49-55, 57-59, 61-69, 71-85, 88-93] and nine reported

effect on abdominal pain. [22, 23, 35, 41, 44, 48, 56, 60, 70] Two RCTs were excluded because they only compared two forms of GDH with each other.[86, 87] The network plot is provided in Figure 2. When data were pooled, there was low heterogeneity ($\tau^2 = 0.044$), but evidence of publication bias, or other small study effects (Supplementary Figure 1) when comparing active therapies with waiting list control or placebo (Egger test, $p < 0.0001$). Compared with waiting list control, SNRIs ranked first (relative risk (RR) of global IBS symptoms or abdominal pain not improving = 0.49; 95% confidence interval (CI) 0.32 to 0.75, P-score 0.95) in six RCTs recruiting 387 patients (Figure 3),[22, 23, 70-73] meaning the probability that this was the most efficacious treatment was 95%. TCAs ranked second (RR = 0.60; 95% CI 0.43 to 0.85, P-score 0.79) in 15 trials recruiting 1519 patients,[19, 21, 22, 35-46] and forms of dynamic psychotherapy/emotional processing third (RR = 0.62; 95% CI 0.44 to 0.87, P-score 0.75) in three RCTs recruiting 389 patients.[20, 81, 82] Forms of CBT (including cognitive therapy) (RR = 0.66; 95% CI 0.56 to 0.78, P-score 0.68) in 18 trials recruiting 1927 patients,[19, 24, 26, 61-69, 77, 78, 85, 88, 89, 93] forms of disease self-management (RR = 0.66; 95% CI 0.47 to 0.92, P-score 0.67) in four RCTs recruiting 748 patients,[79, 80, 91, 92] SSRIs (RR = 0.69; 95% CI 0.48 to 0.97, P-score 0.61) in 10 trials recruiting 782 patients,[20, 21, 23, 54-60] and forms of GDH (RR = 0.73; 95% CI 0.59 to 0.90, P-score 0.53) in 10 RCTs recruiting 994 patients,[25, 47-53, 90] were also superior to waiting list control. The network heat plot suggested inconsistency between the direct and indirect evidence for the comparison between SNRIs and TCAs, but there were no other red “hotspots” (Supplementary Figure 2).

After direct and indirect comparison, SNRIs were superior to SSRIs and alpha-2-delta ligands, but there were no other significant differences between active treatments (Table 1). SNRIs and TCAs were superior to all of placebo, education and support, and routine care, in addition to waiting list control. Forms of dynamic psychotherapy/emotional processing, forms of CBT, and forms of GDH were superior to education and support and routine care, in addition to waiting list control. Forms of disease self-management were superior to routine care, in addition to waiting list

Table 1. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve an Improvement in Either Global IBS Symptoms or Abdominal Pain with Gut-brain Neuromodulators or Brain-gut Behaviour Therapies According to Treatment Class.

SNRI	0.20 (0.07; 0.54)				0.70 (0.42; 1.14)				0.67 (0.48; 0.94)			
0.82 (0.60; 1.12)	**TCA**		1.15 (0.70; 1.87)		0.09 (0.00; 1.49)				0.65 (0.55; 0.78)	0.73 (0.45; 1.19)		
0.79 (0.50; 1.27)	0.97 (0.64; 1.47)	**Forms of DP/EP**			1.12 (0.66; 1.90)						0.61 (0.42; 0.88)	0.61 (0.35; 1.09)
0.75 (0.50; 1.12)	0.91 (0.66; 1.26)	0.94 (0.67; 1.32)	**Forms of CBT**						0.72 (0.44; 1.19)	0.76 (0.59; 0.97)	0.72 (0.56; 0.92)	0.63 (0.52; 0.76)
0.75 (0.46; 1.21)	0.92 (0.60; 1.40)	0.94 (0.64; 1.40)	1.00 (0.73; 1.37)	**Forms of DS-M**							0.66 (0.52; 0.84)	
0.72 (0.53; 0.98)	0.88 (0.69; 1.13)	0.91 (0.61; 1.34)	0.96 (0.69; 1.34)	0.96 (0.64; 1.45)	**SSRI**				0.79 (0.64; 0.99)		0.66 (0.40; 1.09)	

0.68 (0.44; 1.05)	0.83 (0.58; 1.18)	0.85 (0.59; 1.24)	0.91 (0.72; 1.13)	0.90 (0.63; 1.29)	0.94 (0.65; 1.35)	**Forms of GDH**				0.79 (0.63; 0.98)	0.71 (0.41; 1.24)	0.76 (0.57; 1.01)
0.66 (0.39; 1.11)	0.81 (0.51; 1.28)	0.83 (0.53; 1.32)	0.88 (0.62; 1.27)	0.88 (0.56; 1.37)	0.92 (0.58; 1.46)	0.98 (0.67; 1.43)	**Forms of MT**			0.57 (0.28; 1.15)	0.62 (0.32; 1.19)	0.97 (0.61; 1.56)
0.59 (0.38; 0.91)	0.72 (0.49; 1.05)	0.74 (0.44; 1.24)	0.78 (0.49; 1.24)	0.78 (0.46; 1.33)	0.81 (0.55; 1.20)	0.86 (0.53; 1.41)	0.89 (0.50; 1.56)	**A-2-DL**	0.96 (0.68; 1.35)			
0.56 (0.43; 0.74)	0.69 (0.58; 0.81)	0.71 (0.48; 1.05)	0.75 (0.55; 1.02)	0.75 (0.50; 1.12)	0.78 (0.64; 0.95)	0.83 (0.59; 1.17)	0.85 (0.54; 1.34)	0.96 (0.68; 1.35)	**P**	0.89 (0.54; 1.45)		
0.54 (0.36; 0.82)	0.66 (0.48; 0.92)	0.68 (0.47; 0.98)	0.72 (0.59; 0.88)	0.72 (0.51; 1.02)	0.75 (0.53; 1.06)	0.80 (0.66; 0.96)	0.82 (0.57; 1.18)	0.92 (0.58; 1.47)	0.96 (0.70; 1.33)	**ES**		0.93 (0.65; 1.35)
0.50 (0.33; 0.76)	0.61 (0.43; 0.86)	0.63 (0.46; 0.86)	0.67 (0.54; 0.82)	0.66 (0.52; 0.84)	0.69 (0.49; 0.97)	0.74 (0.56; 0.96)	0.75 (0.52; 1.10)	0.85 (0.53; 1.37)	0.89 (0.64; 1.24)	0.92 (0.71; 1.19)	**RC**	

0.49 (0.32; 0.75)	0.60 (0.43; 0.85)	0.62 (0.44; 0.87)	0.66 (0.56; 0.78)	0.66 (0.47; 0.92)	0.69 (0.48; 0.97)	0.73 (0.59; 0.90)	0.75 (0.53; 1.06)	0.84 (0.52; 1.35)	0.88 (0.63; 1.22)	0.91 (0.75; 1.12)	0.99 (0.78; 1.26)	**WLC**

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. Boxes shaded green denote a statistically significant difference.

A-2-DL; alpha-2-delta ligands, CBT; cognitive behavioural therapy, DP/EP; dynamic psychotherapy/emotional processing, DS-M; disease self-management, ES; education and support, GDH; gut-directed hypnotherapy, MT; mindfulness training, P; placebo, RC; routine care, SNRI; serotonin norepinephrine reuptake inhibitors, SSRI; selective serotonin reuptake inhibitors, TCA; tricyclic antidepressants, WLC; waiting list control.

control. SSRIs were superior to placebo and routine care, in addition to waiting list control. Using the Confidence in Network Meta-Analysis framework to evaluate confidence in the results of this endpoint, all direct and indirect comparisons across the network for treatments that appeared to be effective in the network meta-analysis were rated as either low or very low confidence (Supplementary Table 5). Efficacy of gut-brain neuromodulators and brain-gut behaviour therapy for global IBS symptoms only, and for both global IBS symptoms or abdominal pain and for global IBS symptoms only with each brain-gut behaviour therapy considered individually, is detailed in the Supplementary Results.

DISCUSSION

This systematic review and network meta-analysis has compared the efficacy of gut-brain neuromodulators and brain-gut behaviour therapies in IBS. Overall, when effect on either global IBS symptoms or abdominal pain was studied, SNRIs ranked first and TCAs second, although forms of dynamic psychotherapy/emotional processing, forms of CBT, forms of disease self-management, forms of GDH, and SSRIs, were all superior to waiting list control. SNRIs were superior to SSRIs and alpha-2-delta ligands, but there were no other significant differences between active treatments. SNRIs and TCAs were superior to all four control interventions studied. In terms of brain-gut behaviour therapies, when considered individually, the best evidence appeared to exist for minimal contact CBT, telephone disease self-management, dynamic psychotherapy, CBT, and GDH. However, of these, only minimal contact CBT ranked higher than TCAs and none ranked higher than SNRIs. When only effect on global IBS symptoms was considered, TCAs ranked first, with forms of dynamic psychotherapy/emotional processing second, and forms of CBT third. Forms of disease self-management and forms of GDH were also superior to waiting list control. There were no significant differences between active interventions and only TCAs were superior to all four control interventions studied. When brain-gut behaviour therapies were considered individually, again the best evidence was for minimal contact CBT, telephone disease self-management, dynamic psychotherapy, CBT, GDH, and internet-based minimal contact CBT, with only minimal contact CBT ranked higher than TCAs. Finally, adverse events were reported incompletely in many RCTs of brain-gut behaviour therapies, precluding any meaningful analysis.

We were able to make indirect comparisons across the network between over 6000 participants in the included trials. Most RCTs recruited patients with IBS irrespective of predominant bowel habit and were conducted in a variety of settings, including primary care, and countries. Hence, the results of the network are likely to be generalisable to many patients with IBS. For all trials, we extracted data using an intention-to-treat analysis, wherever possible, with dropouts

assumed to be symptomatic. We conducted subgroup analyses with the efficacy of brain-gut behaviour therapies considered individually, according to treatment class. We checked for publication bias with comparison adjusted funnel plots and inconsistency in the network using network heat plots. There was evidence of publication bias, or small study effects, in all our analyses and inconsistency between the direct and indirect evidence for the comparison between SNRIs and TCAs for either global IBS symptoms or abdominal pain. The latter arose because a small head-to-head trial of SNRIs versus TCAs suggested SNRIs were superior,[22] whereas the indirect evidence did not demonstrate any difference in efficacy between the two.

Limitations of any meta-analysis arise from the published literature. Due to the nature of the brain-gut behaviour therapies under study, none were at low risk of bias, particularly because blinding was not attempted in most trials as it is challenging. This is because therapists know which intervention they are delivering, and participants may be able work this out during treatment or from freely available sources, even if they have not previously received such interventions. Consequently, assessing risk of bias, in terms of whether blinding is employed, using the Cochrane risk of bias tool in trials of brain-gut behaviour therapies has been a subject of recent debate, as this will always lead to them being judged to be at high risk of bias.[94] A preferable approach may be to instead evaluate patients' treatment expectations and therapists' enthusiasm for the treatment. Nonetheless, many trials use a waiting list control which might inflate treatment effects, via a nocebo effect, relative to using active control interventions, because participants know they are receiving no additional treatment and may, therefore, expect a poor outcome. Hence, it remains important to consider these sources of bias when interpreting the results and treatment rankings. Even among trials of gut-brain neuromodulators, only nine were low risk of bias across all domains.[19, 21, 43, 45, 46, 54, 57, 59, 83] Overall, it is possible that these issues have led to the efficacy of gut-brain neuromodulators and brain-gut behaviour therapies being overestimated.

There were differences between individual trials, in terms of the population studied, the criteria used to define IBS, the trial setting, the way the interventions were applied, the duration of follow-up, and the endpoint used to define symptom response. Such differences could challenge whether the transitivity assumption for network meta-analysis is valid. However, there was minimal to low heterogeneity observed in our main analyses and any form of evidence synthesis always necessitates a degree of compromise. Sensitivity analyses exploring important potential effect modifiers, such as whether patients were refractory to treatment, may address this, alongside appropriate interpretation of results within the context of any inherent methodological limitations of the individual trials. Unfortunately, as most trials recruited unselected patients and did not report response to treatment according to predominant bowel habit, it is not possible to make recommendations for the use any of the therapies studied in specific groups of patients. In addition, whether psychological co-morbidity is a predictor of response to any of these treatments has been a subject of debate, although in two of the largest trials of TCAs and CBT there was no consistent effect of baseline anxiety or depression scores on response to low-dose amitriptyline,[95] and response rates to CBT or minimal contact CBT were higher with active treatment in patients with lower anxiety levels.[96] The effect of gut-brain neuromodulators and brain-gut behaviour therapies on abdominal pain, specifically, could not be examined as the connections between the 41 trials in the network that reported this endpoint were lost, and it became two separate networks instead. Finally, there is the possibility that the higher ranking of SNRIs and TCAs over most brain-gut behaviour therapies under study arises from trials of gut-brain neuromodulators recruiting a population of patients with less refractory symptoms. However, although 16 RCTs of brain-gut behaviour therapies stated they recruited patients with symptoms refractory to medical treatment, only three specified that this included gut-brain neuromodulators. It could, therefore, be concluded that this is unlikely to be the major reason for the differences in ranking observed. Nevertheless, we acknowledge that in studies that do not clearly describe patients' prior treatment, they may have had

no benefit with gut-brain neuromodulators, and this may be more likely in studies in tertiary care settings. This is an important consideration for future studies.

Our study is novel, in that it compares the efficacy of gut-brain neuromodulators and brain-gut behaviour therapies with each other in IBS. In our primary analyses, when brain-gut behaviour therapies were grouped according to treatment class, SNRIs and TCAs were more highly ranked for the endpoint of either global IBS symptoms or abdominal pain and TCAs for the endpoint of global IBS symptoms only. However, these results should be viewed with some caution, given the finding of inconsistency between direct and indirect evidence for the comparison of SNRIs and TCAs. When we studied efficacy of brain-gut behaviour therapies individually, however, some of these ranked more highly than either SNRIs or TCAs. With the exception of minimal contact CBT, these were brain-gut behaviour therapies that were studied in smaller numbers of patients, and 95% CIs around the estimates were wide. Also of note is that SNRIs were efficacious when either global IBS symptoms or abdominal pain were considered together, but not for global IBS symptoms only. This could be because there were fewer RCTs of SNRIs reporting global IBS symptoms as an endpoint, or because this class of gut-brain neuromodulator exerts its beneficial effect, primarily, through pain modulation. There were only six RCTs of SNRIs, containing less than 400 patients, none of which were at low risk of bias. They were also of heterogeneous design, including two unblinded head-to-head studies of SNRIs versus SSRIs and SNRIs versus TCAs.[22, 23] Hence, larger trials of this drug class in IBS are warranted to prove their efficacy. SSRIs were also more efficacious for either global IBS symptoms or abdominal pain, but not for global symptoms only, which is in line with the findings from a recent pairwise meta-analysis.[15] Our search identified only two RCTs of alpha-2-delta ligands, which were not efficacious in any of our analyses, and only one RCT of either an azapirone or a tetracyclic antidepressant.[97, 98] Hence, these two drug classes were not included in our analysis. In terms of brain-gut behaviour therapies, the best evidence for efficacy was for forms

of dynamic psychotherapy/emotional processing, forms of CBT, forms of disease self-management, and forms of GDH, as in prior network meta-analyses.[17, 99]

This network meta-analysis provides evidence to support the benefit of several gut-brain neuromodulators and brain-gut behaviour therapies for IBS. These findings are consistent with expert consensus that these approaches can be integrated to optimise clinical care.[14] The benefits across treatment modalities for patients with IBS reinforces the need for multimodal management. However, future RCTs should determine when it is best to implement gut-brain neuromodulators and brain-gut behaviour therapies as standalone interventions, versus when they may confer additive or synergistic benefits if used in combination. Identifying predictors of treatment response will also be essential to clarify optimal treatment sequencing and integration, thereby enabling more personalised care, and providing clarity to refine existing clinical guidelines.[8, 100]

Prior literature suggests patients with IBS and untreated psychological comorbidities respond less favourably to brain-gut behaviour therapies. This underscores the importance of addressing broader psychiatric needs through general psychotherapy prior to, or alongside, brain-gut behaviour therapies.[101] It is, therefore, essential for gastrointestinal clinicians to conduct a careful assessment of psychosocial contributors within a biopsychosocial framework during gastroenterology consultations,[102] to determine whether gastrointestinal-specific mechanisms or psychiatric comorbidities should be prioritised when planning treatment. In parallel, it is critical to identify which patients are most likely to benefit from gut-brain neuromodulators versus those who may require broader psychiatric intervention. Our prior work in this field does not support the notion that brain-gut behaviour therapies or gut-brain neuromodulators are most effective when reserved exclusively for patients with refractory symptoms.[15, 17, 46] Therefore, rather than positioning these treatments as last-line options, a more thorough diagnostic evaluation and comprehensive assessment of psychosocial factors may identify patients who could benefit from these approaches earlier in the disease course. Accordingly, future RCTs should evaluate the impact of introducing

brain-gut behaviour therapies and/or gut-brain neuromodulators soon after a diagnosis of IBS to determine their efficacy at an earlier stage of the condition. Further investigation into optimal treatment combinations, appropriate dosages, and sequencing has the potential to not only reduce disease burden and streamline interdisciplinary care but also decrease healthcare utilisation and associated costs. Insights gained from IBS may also be translatable to other disorders of gut-brain interaction, as many brain-gut behaviour therapies, and their gut-brain neuromodulator counterparts, target centralised gut-brain pathways and are not condition-specific.[14]

In summary, we found several gut-brain neuromodulators and brain-gut behaviour therapies to be efficacious for IBS. Gut-brain neuromodulators in the form of SNRIs and TCAs ranked highest in most of our analyses, although there were no significant differences in efficacy between the two. Part of the higher ranking for types of gut-brain neuromodulator may relate to trials of brain-gut behaviour therapies recruiting patients with symptoms that were refractory to these drugs, although we feel this is unlikely. Overall, certainty in the level of evidence was low or very low for most comparisons, meaning that although multiple therapeutic approaches are effective, differences between active treatments remain uncertain. Hence, results should be interpreted without a strict reliance on treatment rankings, considering instead effect sizes and the methodological limitations of the underlying data. Consequently, more RCTs comparing the efficacy of gut-brain neuromodulators and brain-gut behaviour therapies directly in IBS are required. Trials comparing the efficacy of combining gut-brain neuromodulators and brain-gut behaviour therapies, versus using either treatment alone, would also be useful. This approach has been used in RCTs in other chronic painful conditions.[103] In the interim, despite the acknowledged limitations of the analyses, our results provide useful information that may guide current clinical practice and influence updates to management guidelines for IBS, as well as highlighting future research priorities.

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AUTHORSHIP STATEMENT

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

Guarantor: ACF is guarantor.

DISCLOSURES

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ETHICS COMMITTEE APPROVAL

Not required.

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 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. Network Plot for Failure to Achieve an Improvement in Either Global IBS Symptoms or Abdominal Pain with Gut-brain Neuromodulators or Brain-gut Behaviour Therapies According to Treatment Class.

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

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

Figure 3. Forest Plot for Failure to Achieve an Improvement in Either Global IBS Symptoms or Abdominal Pain with Gut-brain Neuromodulators or Brain-gut Behaviour Therapies According to Treatment Class.

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

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.