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TITLE PAGE

Title: Efficacy of Gut-brain Neuromodulators in Irritable Bowel Syndrome: An Updated Systematic Review and Meta-analysis.

Short title: Gut-brain Neuromodulators in IBS.

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Abbreviations:

CI	confidence interval
DGBI	disorder of gut-brain interaction
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with constipation
IBS-D	irritable bowel syndrome with diarrhoea
IBS-M	mixed stool pattern irritable bowel syndrome

MeSH	medical subject headings
RCT	randomised controlled trial
RR	relative risk
SD	standard deviation
SNRI	serotonin and norepinephrine reuptake inhibitors
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant

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SUMMARY

Background: Gut-brain neuromodulators may be efficacious for irritable bowel syndrome (IBS), but there has been no synthesis of the evidence from randomised controlled trials (RCTs) of some drug classes and whether they have pain modifying properties is unclear. We updated a previous systematic review and meta-analysis of RCTs examining this.

Methods: We searched MEDLINE, EMBASE and EMBASE Classic, and the Cochrane Controlled Trials Register (up to 1st January 2025). Trials recruiting adults with IBS, which compared gut-brain neuromodulators versus placebo were eligible. Dichotomous symptom data were pooled to obtain a relative risk (RR) of remaining symptomatic after therapy, with a 95% confidence interval (CI).

Findings: The search strategy identified 3625 citations. 28 RCTs were eligible containing 2475 patients. Ten were identified since our previous meta-analysis, containing 1348 patients. The RR of global IBS symptoms not improving with gut-brain neuromodulators versus placebo in 22 RCTs (2222 patients) was 0.78 (95% CI 0.70-0.87). The best evidence in terms of persistence of global IBS symptoms was for tricyclic antidepressants (TCAs) in 11 trials (1144 patients) (RR = 0.71; 95% CI 0.62-0.82). The RR of abdominal pain not improving with gut-brain neuromodulators versus placebo in 19 RCTs (1792 patients) was 0.72 (95% CI 0.62-0.83). Again, the best evidence was for TCAs in seven trials (708 patients) (RR = 0.69; 95% CI 0.54-0.88), but there was also a benefit of selective serotonin reuptake inhibitors in seven RCTs (324 patients) (RR = 0.74; 95% CI 0.56-0.99), and serotonin and norepinephrine reuptake inhibitors in two trials (94 patients) (RR = 0.22; 95% CI 0.08-0.59). Adverse events were no more common with gut-brain neuromodulators, although rates of withdrawal due to adverse events were significantly higher.

Interpretation: Some gut-brain neuromodulators are efficacious in reducing global symptoms and abdominal pain in IBS. The certainty in the evidence for TCAs for global IBS

symptoms was moderate, but it was low to very low for all other endpoints and drug classes studied.

Funding: None.

RESEARCH IN CONTEXT

Evidence before this study

The mainstay of management of irritable bowel syndrome (IBS) is symptom-directed therapy. First-line treatments include lifestyle advice, dietary changes, laxatives, antispasmodics, and anti-diarrhoeals. For those whose symptoms do not respond to such measures, the use of gut-brain neuromodulators is recommended by management guidelines. These include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tetracyclic antidepressants, azapirones, or alpha-2-delta ligand agents. They may be beneficial in IBS because they have effects on visceral hypersensitivity, gastrointestinal motility, and central pain processing. At the time of our last meta-analysis 6 years ago, there were no randomised controlled trials (RCTs) of some classes of drug. In addition, although gut-brain neuromodulators are recommended for abdominal pain, trials reporting this as an endpoint were limited. A comprehensive search of the medical literature using MEDLINE, EMBASE, EMBASE Classic, and the Cochrane central register of controlled trials from 1946 to 1st January 2025, and including foreign language articles, identified multiple new RCTs of gut-brain neuromodulators in IBS published since the conduct of the prior meta-analysis, providing the rationale for this update. We aimed to re-assess the evidence for their efficacy, not only for global IBS symptoms, but also for abdominal pain, and their safety in terms of treatment-emergent adverse events.

Added value of this study

We did a contemporaneous systematic review and meta-analysis of placebo-controlled trials of gut-brain neuromodulators in adults with IBS, identifying 28 eligible trials, recruiting 2475

patients. In terms of global symptoms, in 22 RCTs recruiting 2222 patients, the relative risk (RR) of symptoms not improving after treatment with gut-brain neuromodulators versus placebo was 0.78 (95% CI 0.70 to 0.87). Eleven RCTs compared TCAs with placebo in 1144 patients. There was moderate certainty in the evidence by GRADE criteria for a benefit of TCAs for global IBS symptoms (RR = 0.71; 95% CI 0.62 to 0.82). There was no evidence of efficacy for SSRIs, alpha-2-delta ligand agents or SNRIs, but tandospirone, an azapirone, was superior to placebo in one RCT (RR = 0.76; 95% CI 0.59 to 0.98), and mirtazapine in one RCT (RR = 0.55; 95% CI 0.34 to 0.89). For abdominal pain, in 19 RCTs, containing 1792 patients, the RR of abdominal pain not improving with gut-brain neuromodulators was 0.72 (95% CI 0.62 to 0.83). There was low certainty in the evidence for a benefit of TCAs in seven RCTs, containing 708 patients (RR = 0.69; 95% CI 0.54 to 0.88) and very low certainty in the evidence for a benefit of SSRIs in seven trials containing 324 patients (RR = 0.74; 95% CI 0.56 to 0.99) and SNRIs in two RCTs containing 94 patients (RR = 0.22; 95% CI 0.08 to 0.59). There was no benefit of alpha-2-delta ligand agents for abdominal pain in two trials recruiting 415 patients. Tandospirone (RR = 0.80; 95% 0.65 to 0.99) and mirtazapine were each assessed in one RCT (RR = 0.49; 95% CI 0.29 to 0.80) and appeared beneficial. Treatment-emergent adverse events were no more likely with gut-brain neuromodulators (RR = 1.36; 95% CI 0.97 to 1.91) but withdrawals due to adverse events were significantly higher, particularly with TCAs (RR = 1.67; 95% CI 1.08 to 2.57) and alpha-2-delta ligand agents (RR = 4.15; 95% CI 1.48 to 11.67).

Implications of all the available evidence

This systematic review and meta-analysis identified 10 new RCTs of gut-brain neuromodulators in IBS, including some, such as SNRIs and tetracyclic antidepressants, that had not been studied at the time of the last meta-analysis. As a result of these new trials, our

certainty in the evidence for the efficacy of TCAs for global symptoms in IBS has increased, and we have been able to demonstrate beneficial effects of TCAs, SSRIs, and SNRIs for abdominal pain, albeit with lower certainty. Therefore, some gut-brain neuromodulators, particularly TCAs, are beneficial for global symptoms and abdominal pain in IBS. The findings support national management guidelines for IBS, which recommend use of TCAs for ongoing global symptoms or abdominal pain, but also highlight a potential for SSRIs to be modestly effective for abdominal pain. More data for SNRIs are required, despite guidelines suggesting these may be beneficial in IBS. Definitive trials of SNRIs, azapirones, and tetracyclic antidepressants in IBS are, therefore, warranted, given the promising results seen in RCTs reported to date.

INTRODUCTION

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction (DGBI),[5] affecting approximately 1 in 20 people globally.[6,7] It is characterised by abdominal pain that is related to defaecation and occurs in association with either a change in stool form or frequency.[8] Because the pathophysiology is incompletely understood,[9] there is no cure for IBS and it is a chronic condition.[10] This means that the disorder represents a substantial burden to patients, in terms of impaired quality of life and social functioning,[11,12] and society due to its economic impact on employment and health services.[12,13]

The mainstay of management is symptom-directed therapy. First-line treatments generally include lifestyle advice, dietary changes, laxatives, antispasmodics, and anti-diarrhoeals.[1-4] For those whose symptoms do not respond to such measures, treatment with a drug targeted against predominant bowel habit may be considered,[1,2,14,15] or the use of gut-brain neuromodulators,[16] given that abdominal pain is a cardinal feature of the disorder and there is a considerable overlap of IBS with psychological symptoms.[17,18] Gut-brain neuromodulators encompass tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tetracyclic antidepressants, such as mirtazapine, azapirones, including buspirone or tandospirone, or alpha-2-delta ligand agents, such as pregabalin or gabapentin. These drugs may be beneficial in IBS because they have effects on visceral hypersensitivity, gastrointestinal motility, and central pain processing.[19,20]

We have conducted prior meta-analyses of the efficacy of gut-brain neuromodulators in IBS,[21-23] but it is 6 years since we last examined this issue. At the time of our last meta-analysis, there were no randomised controlled trials (RCTs) of SNRIs, tetracyclic antidepressants, or alpha-2-delta ligand agents. In addition, although there were 12 trials of TCAs that suggested a benefit of this class of drug, most RCTs were small and used historical

definitions of IBS and endpoints that are less stringent than those used currently. Finally, although gut-brain neuromodulators are recommended for the treatment of abdominal pain,[1-4] there were only seven trials that reported on this as a dichotomous endpoint. We, therefore, updated our previous meta-analysis of all gut-brain neuromodulators in IBS,[22] to re-assess the evidence for their efficacy, not only for global IBS symptoms, but also for abdominal pain. We also assessed their safety in terms of adverse event rates.

METHODS

Search Strategy and Study Selection

We searched the medical literature using MEDLINE (1st January 1946 to 1st January 2025), EMBASE and EMBASE Classic (1st January 1947 to 1st January 2025), and the Cochrane central register of controlled trials. We searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2019 and 2024 to identify potentially eligible studies published only in abstract form. Finally, we used bibliographies of all obtained articles to perform a recursive search. As this was an update of a previous meta-analysis the protocol was not registered.

RCTs examining the effect of gut-brain neuromodulators versus placebo in adult patients (aged ≥16 years) with IBS were eligible for inclusion (see appendix page 2). Duration of therapy had to be ≥4 weeks and the diagnosis of IBS could be based on either a physician's opinion or accepted symptom-based diagnostic criteria, supplemented by the results of investigations to exclude organic disease, where investigators deemed this necessary. Studies had to report either a global assessment of IBS symptom cure or improvement, or abdominal pain cure or improvement, after completion of therapy, preferably as reported by the patient, but if this was not recorded then as documented by the investigator. We contacted original investigators to obtain further information if studies included patients with IBS among patients with other DGBI, or did not report these types of dichotomous data, but otherwise appeared eligible for inclusion,

Two investigators (MK and ACF) conducted the literature search, independently from each other. We identified studies on IBS with the terms: *irritable bowel syndrome* and *functional diseases, colon* (both as medical subject heading (MeSH) and free text terms), and

IBS, *spastic colon*, *irritable colon*, or *functional* adj5 *bowel* (as free text terms). We combined these using the set operator AND with studies identified with the terms: *amitriptyline*, *antidepressive agents*, *antidepressive agents (tricyclic)*, *antipsychotic agents*, *aripiprazole*, *citalopram*, *desipramine*, *dothiepin, doxepin, duloxetine*, *escitalopram*, *fluoxetine*, *fluvoxamine*, *gabapentin*, *imipramine*, *mianserin*, *milnacipran*, *mirtazapine*, *nortriptyline*, *olanzapine*, *paroxetine*, *pregabalin*, *psychotropic drugs*, *quetiapine*, *serotonin and noradrenaline reuptake inhibitors*, *serotonin uptake inhibitors*, *sertraline*, *sulpiride*, *trazodone*, *trimipramine*, or *venlafaxine* (both as MeSH terms and free text terms), and the following free text terms: *antidepressants*, *antipsychotics*, *atypical antipsychotics*, *desimipramine*, *levosulpiride*, *serotonin norepinephrine reuptake inhibitors*, *serotonin norepinephrine re-uptake inhibitors*, *selective serotonin re-uptake inhibitors*, *serotonin re-uptake inhibitors*, *selective serotonin reuptake inhibitors*, *serotonin reuptake inhibitors*, *tetracyclic antidepressants*, or *tandospirone*.

There were no language restrictions. We evaluated abstracts of the papers identified by the initial search for appropriateness to the study question, and all potentially relevant papers were obtained and evaluated in detail. We translated foreign language papers where necessary. Two reviewers (MK and ACF) assessed all new articles independently using pre-designed eligibility forms, according to the eligibility criteria, which were defined prospectively. We resolved disagreements between investigators by consensus.

Outcome Assessment

We assessed the efficacy of gut-brain neuromodulators in IBS, compared with placebo, in terms of the proportion of patients failing to achieve an improvement in global IBS symptoms as the primary outcome, and the proportion of patients failing to achieve an improvement in abdominal pain as a secondary outcome. Other secondary outcomes assessed

included total number of people experiencing treatment-emergent adverse events or any treatment-emergent adverse event leading to withdrawal.

Data Extraction

All data from new eligible RCTs were extracted independently by two reviewers (MK and ACF) on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (global IBS symptoms improved or not improved, abdominal pain improved or not improved). Otherwise, if mean IBS symptom scores or abdominal pain scores at baseline and after completion of treatment were available, along with a standard deviation (SD), we imputed dichotomous responder and non-responder data, according to the methodology described by Furukawa *et al*.[24] For example, a 30% improvement in abdominal pain score is determined from the formula: number of participants in each treatment arm at final follow-up multiplied by normal SD. The latter corresponds to (70% of the baseline mean abdominal pain score – follow-up mean abdominal pain score) / follow-up SD.

In addition, we extracted the following clinical data for each trial: setting (primary, secondary, or tertiary care-based), number of centres, country of origin, dose of gut-brain neuromodulator, duration of therapy, criteria used to define IBS, primary outcome measure used to define symptom improvement or cure following therapy, duration of follow-up, proportion of female patients, and proportion of patients according to predominant stool pattern (IBS with constipation (IBS-C), IBS with diarrhoea (IBS-D), or IBS with mixed bowel habits (IBS-M)). We extracted all data as intention-to-treat analyses, with dropouts assumed to be treatment failures, wherever trial reporting allowed this. If this was not clear from the original article, we performed an analysis on all patients with reported evaluable

data.

Risk of Bias and Quality of Evidence Assessment

Two investigators (MK and ACF) performed this independently for all new trials. We used the Cochrane risk of bias tool to assess risk of bias at the study level.[25] 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. We resolved disagreements by consensus and summarised the quality of the evidence, where individual classes of gut-brain neuromodulators appeared efficacious in IBS, using GRADE criteria.[26] We downgraded certainty if any of high or uncertain risk of bias in individual trials, inconsistency between trial results, evidence of publication bias, or imprecision were present.

Data Synthesis and Statistical Analysis

We pooled data using a random effects model,[27] to provide a more conservative estimate of the range of effects of gut-brain neuromodulators in IBS, if there was heterogeneity between studies. We expressed the impact of gut-brain neuromodulators as a relative risk (RR) of global IBS symptoms or abdominal pain not improving with active drug compared with placebo with 95% confidence intervals (CIs), where if the RR was less than 1 and the 95% CI did not cross 1, there was a significant benefit of gut-brain neuromodulators over placebo. 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.[28] We also used RRs to summarise adverse events data.

We assessed heterogeneity, which is variation between individual study results arising due to either differences in study participants or methodology, using both the χ^2 test, with a P value <0.10 used to define a significant degree of heterogeneity, and the I^2 statistic. The I^2 ranges between 0% and 100%, with values of 25% to 49% considered low, 50% to 74% moderate, and ≥75% high heterogeneity.[29]

We used Review Manager version 5.4.1 (The Cochrane Collaboration 2020) to generate Forest plots of pooled RRs for primary and secondary outcomes with 95% CIs, as well as funnel plots. We assessed the latter for evidence of asymmetry and, therefore, possible publication bias or other small study effects using the Egger test,[30] if there were sufficient (≥10) eligible studies included in the meta-analysis, in line with recommendations.[31]

Role of the funding source

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

RESULTS

We identified a total of 3625 citations, of which 47 published articles appeared to be relevant, and were retrieved for further assessment (Figure 1). Of these 47, 19 were excluded for various reasons, leaving 28 RCTs comparing gut-brain neuromodulators with placebo, which contained 2475 patients, 1344 of whom received active therapy and 1131 placebo.[32-59] Agreement between reviewers for assessment of trial eligibility was good (kappa statistic = 0.78). Two RCTs were conducted amongst mixed populations of patients with DGBI.[39,44] In both instances, we contacted original investigators to obtain data only for patients with IBS. Ten trials, containing 1348 patients, were identified since our previous meta-analysis.[38,45,52-59] There were 13 trials of TCAs,[32-40,42-45] seven trials of SSRIs,[46-52] three trials of SNRIs,[53-55] two trials of alpha-2-delta ligand agents,[56,57] one trial of either a TCA or an SSRI,[41] one trial of tandospirone,[58] and one trial of mirtazapine.[59] Detailed characteristics of individual RCTs are provided in the appendix pages 3 to 5 and risk of bias items for individual trials in the appendix page 6. The proportion of female patients recruited by trials ranged from 28% to 100%. Fourteen RCTs reported data on IBS subtype among recruited patients,[37,40,45-49,51,52,54,56-59] four of which recruited only IBS-D patients,[40,54,58,59] and one only IBS-C patients.[48] Ten trials were at low risk of bias across all domains.[39,41,42,44-46,49,51,56,59]

Efficacy of Gut-brain Neuromodulators for Global Symptoms in IBS

Twenty trials reported effect on global IBS symptoms as a dichotomous endpoint,[33-37,39-42,44-47,50,51,54,56-59] and we imputed data for another two trials.[49,55] Overall, 644 (53.2%) of 1210 patients assigned to gut-brain neuromodulators reported unimproved global IBS symptoms following therapy, compared with 661 (65.3%) of 1012 allocated to placebo. The RR of global IBS symptoms not improving after treatment with gut-brain neuromodulators versus placebo was 0.78 (95% CI 0.70 to 0.87), with moderate heterogeneity detected

between studies (I^2 = 54%, P = 0.0014) (Figure 2). There was statistically significant asymmetry in the funnel plot (Egger test, P = 0.0022), suggesting publication bias or other small study effects (see appendix page 11).

Eleven RCTs compared TCAs with placebo, including a total of 1144 patients.[33-37,39-42,44,45] Of 608 patients receiving active therapy, 281 (46.2%) had no improvement in global IBS symptoms after treatment, compared with 339 (63.2%) of 536 receiving placebo. There was moderate certainty in the evidence by GRADE criteria for a benefit of TCAs in terms of persistence of global IBS symptoms (RR = 0.71; 95% CI 0.62 to 0.82), with low heterogeneity between studies (I^2 = 28%, P = 0.18) (Figure 2 and appendix page 7), but evidence of funnel plot asymmetry (Egger test, P = 0.0011) (see appendix page 12). When the analysis was restricted to the four largest trials of TCAs,[35,39,42,45] containing 825 patients, which are likely to give the most precise estimates of the efficacy of TCAs in IBS, this was more modest (RR = 0.80; 95% CI 0.71 to 0.90) with no heterogeneity between studies (I^2 = 0%, P = 0.98) (see appendix page 13).

There were six trials comparing SSRIs with placebo, recruiting a total of 312 patients.[41,46,47,49-51] In total, 80 (51.9%) of 154 patients allocated to SSRIs reported no improvement in global IBS symptoms following therapy, compared with 103 (65.2%) of 158 placebo patients. The RR of global IBS symptoms not improving with SSRIs compared with placebo was 0.85 (95% CI 0.65 to 1.10), with moderate heterogeneity between studies (I^2 = 60%, P = 0.028) (Figure 2).

There was no evidence of efficacy of alpha-2-delta ligand agents for global IBS symptoms, in two trials containing 415 patients,[56,57] or SNRIs in two trials recruiting 100 patients,[54,55] respectively (Figure 2). Tandospirone was superior to placebo in one RCT containing 200 patients (RR = 0.76; 95% CI 0.59 to 0.98),[58] and mirtazapine in one RCT containing 67 patients (RR = 0.55; 95% CI 0.34 to 0.89) (Figure 2).[59]

Efficacy of Gut-brain Neuromodulators for Abdominal Pain in IBS

The effect of gut-brain neuromodulators on abdominal pain was reported by 19 RCTs,[32,37,38,40,41,43,45-50,52-54,56-59] containing 1792 patients. Twelve of these trials reported effect on abdominal pain as a dichotomous endpoint,[32,37,40,43,45-48,50,56-58] and for the remaining seven RCTs we imputed data.[38,41,49,52-54,59] In total, 531 (54.8%) of 969 patients receiving gut-brain neuromodulators had no improvement in abdominal pain following treatment, compared with 567 (68.9%) of 823 subjects allocated to placebo, giving a RR of abdominal pain not improving of 0.72 (95% CI 0.62 to 0.83), with moderate heterogeneity between studies (I^2 = 64%, P < 0.0001) (Figure 3) and evidence of funnel plot asymmetry (Egger test, P = 0.0009) (see appendix page 14).

There was low certainty in the evidence by GRADE criteria for a benefit of TCAs in terms of persistence of abdominal pain in seven RCTs,[32,37,38,40,41,43,45] containing 708 patients (RR = 0.69; 95% CI 0.54 to 0.88, I^2 = 57%, P = 0.030) (Figure 3 and appendix page 8). There was very low certainty in the evidence by GRADE criteria for a benefit of SSRIs in terms of persistence of abdominal pain in seven trials containing 324 patients (RR = 0.74; 95% CI 0.56 to 0.99, I^2 = 69%, P = 0.0031) (Figure 3 and appendix page 9),[41,46-50,52] and for a benefit of SNRIs in two RCTs containing 94 patients (RR = 0.22; 95% CI 0.08 to 0.59) (Figure 3 and appendix page 10).[53,54] There was no statistically significant effect of alpha-2-delta ligand agents on abdominal pain in two trials recruiting 415 patients (Figure 3).[56,57] Tandospirone was assessed in one trial (RR = 0.80; 95% 0.65 to 0.99),[58] and mirtazapine in one RCT (RR = 0.49; 95% CI 0.29 to 0.80) (Figure 3).[59]

Treatment-emergent Adverse Events with Gut-brain Neuromodulators in IBS

Twelve trials reported total number of treatment-emergent adverse events with gut-brain neuromodulators versus placebo.[32,33,35,37,42,44-46,49,54,56,57] In total, 440 (64.4%) of 683

patients assigned to gut-brain neuromodulators experienced treatment-emergent adverse events, compared with 296 (53.5%) of 553 allocated to placebo. When data were pooled the incidence of treatment-emergent adverse events was not significantly higher among those taking gut-brain neuromodulators (RR of experiencing any treatment-emergent adverse event = 1.36; 95% CI 0.97 to 1.91) (Figure 4), but with high heterogeneity between studies (I^2 = 90%, P < 0.0001). Seven of the RCTs, containing 706 patients, used TCAs.[32,33,35,37,42,44,45] In these trials, again there was no significantly higher rate of treatment-emergent adverse events (RR = 1.76; 95% CI 0.73 to 4.23) (Figure 4). However, drowsiness and dry mouth were generally more common in patients randomised to TCAs than those receiving placebo.

There were 23 RCTs that reported withdrawals due to adverse events.[32-37,40,42,45-59] Overall, 108 (9.7%) of 1111 patients assigned to gut-brain neuromodulators experienced adverse events leading to withdrawal, compared with 48 (4.9%) of 988 allocated to placebo. The RR of withdrawal due to adverse events was significantly higher with gut-brain neuromodulators (1.79; 95% CI 1.28 to 2.51) (Figure 5), with no heterogeneity between trials (I^2 = 0%, P = 0.93). TCAs were associated with a higher likelihood of experiencing adverse events leading to withdrawal, in nine trials containing 939 patients (RR = 1.67; 95% CI 1.08 to 2.57, I^2 = 0%, P = 0.94),[32-37,40,42,45] and alpha-2-delta ligand agents in two RCTs containing 407 patients (RR = 4.15; 95% CI 1.48 to 11.67) (Figure 5).[56,57]

DISCUSSION

This updated systematic review and meta-analysis has pooled data from 28 placebo-controlled trials of gut-brain neuromodulators in IBS, containing over 2400 patients. Overall, gut-brain neuromodulators were superior to placebo for both global IBS symptoms and abdominal pain. However, there was only evidence of efficacy for certain classes of these drugs. By GRADE criteria there was moderate certainty that TCAs are efficacious for global symptoms in IBS, low certainty that they are efficacious for abdominal pain, and very low certainty that SSRIs or SNRIs are efficacious for abdominal pain. SSRIs and SNRIs were no more efficacious than placebo for global symptoms, and there was no evidence that alpha-2-delta ligand agents were beneficial for either global symptoms or abdominal pain. Although tandospirone and mirtazapine appeared beneficial for both global symptoms and abdominal pain, they were studied in only one RCT and so these findings require confirmation in other trials. Treatment-emergent adverse events were not significantly higher among those taking gut-brain neuromodulators, but treatment-emergent adverse events leading to withdrawal were significantly higher, particularly with TCAs and alpha-2-delta ligand agents. Reasons for withdrawal due to adverse events were not detailed in many trials, but in the largest RCT of a TCA conducted, to date, drowsiness and deterioration of mood were the commonest reasons for stopping treatment.[45]

We performed independent assessment of eligibility and data extraction. We used an intention-to-treat analysis and pooled data with a random effects model, to minimise the likelihood that treatment effect of gut-brain neuromodulators would be overestimated, although this can lead to attrition bias, as it cannot be assumed those who continue in the trial are the same as those who drop out.[60] We translated three non-English RCTs and contacted investigators of potentially eligible studies to either obtain dichotomous data or to exclude patients with other DGBI from the analysis, and imputed dichotomous responder data from

means and SDs, to maximise the number of eligible RCTs. Individual RCTs were conducted in a diverse range of countries, including North America, Australasia, Europe, the Middle East, and Asia, meaning that the results of the meta-analysis are likely to be broadly generalisable to patients with IBS in most geographical regions.

Despite this, there are limitations of this meta-analysis. Trials used a variety of doses and titration regimens, with some RCTs using doses of gut-brain neuromodulators that would be considered in the range of those used for the treatment of depression. Endpoints were inconsistent between individual trials and, in some cases, we had to impute dichotomous responder data. Only 10 of the included trials were at low risk of bias. There was evidence of funnel plot asymmetry, or other small study effects, when all RCTs were pooled for global symptoms and abdominal pain, and when only trials of TCAs were pooled for global symptoms. There was also significant heterogeneity in some of our analyses. These limitations may have led to overestimation of the efficacy of gut-brain neuromodulators in IBS. The effect of gut-brain neuromodulators on other symptoms of IBS, including stool form or frequency, or IBS-specific quality of life could not be assessed due to a lack of data. Several trials were small, recruiting less than 50 patients. This can lead to small sample bias.[61] There were a low number of event rates for some of the outcomes of interest. Heterogeneity between studies may, therefore, have been underestimated.[62] Zero events in one or both treatment arms, where events are rare, can also cause issues in meta-analysis. The Review Manager software corrects for this,[25] but this fixed correction can bias study estimates towards no difference and over-estimate variances of study estimates.[63] Where events are rare, meta-analyses are also vulnerable to sparse data bias, which can inflate summary estimates.[64] Finally, there were few RCTs of some of the drugs of interest, including SNRIs, alpha-2-delta ligand agents, azapirones, and tetracyclic antidepressants, meaning that no firm conclusions can be drawn about their efficacy.

The mechanism by which gut-brain neuromodulators are having their beneficial effects in IBS remains a subject of controversy. Proposed mechanisms include central effects on mood,[65] peripheral effects on gastrointestinal motility,[19,66] or their pain-modifying properties,[20,46] which may arise from a combination of central and peripheral effects. Previous trials have demonstrated conflicting results as to whether the efficacy of gut-brain neuromodulators is affected by coexistent depression.[39,47,51] Among eligible RCTs, the doses of SSRIs used were in the range of those used to treat depression, but TCAs are often used at lower doses in IBS, where any effect on mood would seem less likely. In support of this, in the largest RCT of a TCA, to date, which used 10mg to 30mg of amitriptyline per day and measured anxiety and depression scores at baseline and after treatment, there was no significant difference in the improvement in anxiety or depression scores seen with low-dose amitriptyline versus placebo at 6 months, despite the fact that amitriptyline was superior to placebo for both global IBS symptoms and abdominal pain.[45] When predictors of response to amitriptyline were examined in this trial, there was no consistent effect of either anxiety or depression scores at baseline on likelihood of response.[67] Given that some of these drugs have different effects on motility, with TCAs prolonging orocaecal transit time,[19,66] and SSRIs decreasing it,[19] it would seem biologically plausible that TCAs would be more efficacious in IBS-D, and SSRIs of greater benefit in IBS-C, but only two published RCTs have assessed this approach, specifically.[40,48] Again, in the largest RCT of a gut-brain neuromodulator, to date, which recruited 463 patients with IBS irrespective of subtype, amitriptyline was superior to placebo for IBS-C, IBS-D, and IBS-M, although the greatest therapeutic gain over placebo was seen in those with IBS-D.[45] Evidence for the ability of gut-brain neuromodulators to attenuate visceral hypersensitivity in the gastrointestinal tract is limited,[20,46] but there are meta-analyses and RCTs demonstrating the efficacy of TCAs and SNRIs in other painful disorders, such as fibromyalgia, low back pain, and chronic

headache.[68-74] The SNRI duloxetine was consistently the highest-ranked drug with moderate- to high-certainty evidence for a range of chronic painful conditions in a network meta-analysis.[75]

In terms of future research, there is a need for definitive RCTs of SNRIs, azapirones, and tetracyclic antidepressants. Given the recent publication of a large RCT of an alpha-2-delta ligand, which demonstrated no benefit in IBS, it is debatable whether this drug class should be studied further.[57] Investigators should give consideration as to whether these should be placebo-controlled, given that there is now moderate certainty evidence that TCAs are efficacious for global symptoms. Head-to-head trials of gut-brain neuromodulators would facilitate the conduct of network meta-analyses to assess which of the various gut-brain neuromodulators is likely to be the most efficacious for both global symptoms and abdominal pain in IBS. To date, we are aware of one RCT of the SNRI duloxetine versus the SSRI fluoxetine in IBS,[76] and another of duloxetine versus the TCA imipramine.[77] The first demonstrated that duloxetine was superior to fluoxetine for both abdominal pain and stool frequency, and the second that duloxetine and imipramine performed similarly for both symptoms, but that adverse events were more frequent with duloxetine. However, both trials were relatively small, recruiting only 122 patients and 48 patients, respectively. Any future RCTs, whether placebo-controlled or head-to-head, should be powered adequately, assess the effect of gut-brain neuromodulators on the individual symptoms of IBS, as well as quality of life and mood, and assess their efficacy according to IBS subtype.

In summary, this updated systematic review and meta-analysis has identified 10 new RCTs, including trials of SNRIs, alpha-2-delta ligand agents, azapirones, and mirtazapine, none of which had been studied in our previous meta-analysis. Compared with the previous meta-analysis it has demonstrated that there is now moderate certainty evidence that TCAs are efficacious for global symptoms in IBS. There was also evidence that TCAs are

efficacious for abdominal pain, although certainty was low, and evidence that SSRIs or SNRIs are also efficacious for abdominal pain, although here certainty was very low. The findings, therefore, support national management guidelines for IBS, which recommend use of TCAs for ongoing global symptoms or abdominal pain,[1-4] but also highlight a potential for SSRIs to be modestly effective for abdominal pain. More data for SNRIs are required, despite guidelines suggesting these may be beneficial in IBS. Adverse effects were no more common with gut-brain neuromodulators when considered either together or separately. However, withdrawals due to adverse events were more common, particularly with TCAs and alpha-2-delta ligand agents, suggesting that patients need to be counselled carefully about potential side effects from these drugs. Evidence from the ATLANTIS trial demonstrates that it is unlikely these drugs are having their effects through an improvement in coexistent depression and that, if patients are given a clear rationale for the use of gut-brain neuromodulators in IBS, based on their gastrointestinal and pain-modifying effects,[78] many are willing to consider taking them.

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CONFLICTS OF INTEREST/STUDY SUPPORT

Guarantor of the article: ACF is guarantor.

Specific author contributions: MK, MM, PM, CJB, and ACF conceived the study. ACF and MK collected all data. ACF analysed and interpreted the data. ACF drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript.

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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 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 of Randomised Controlled Trials of Gut-brain Neuromodulators Versus Placebo for Global Symptoms in Irritable Bowel Syndrome.

Figure 3. Forest Plot of Randomised Controlled Trials of Gut-brain Neuromodulators Versus Placebo for Abdominal Pain in Irritable Bowel Syndrome.

Figure 4. Forest Plot of Treatment-emergent Adverse Events in Randomised Controlled Trials of Gut-brain Neuromodulators Versus Placebo in Irritable Bowel Syndrome.

Figure 5. Forest Plot of Treatment-emergent Adverse Events Leading to Withdrawal in Randomised Controlled Trials of Gut-brain Neuromodulators Versus Placebo in Irritable Bowel Syndrome.

Commented [AF1]: Please change risk ratio to relative risk on figures 2 to 4 as per Dr. Brierley's instructions