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TITLE PAGE

Title: Effect of Antidepressants and Psychological Therapies in Irritable Bowel Syndrome: An Updated Systematic Review and Meta-analysis.

Short running head: Antidepressants and Psychological Therapies in IBS.

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Abbreviations:

ACG	American College of Gastroenterology
CBT	cognitive behavioral therapy

CI	confidence interval
CNS	central nervous system
GI	gastrointestinal
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with constipation
IBS-D	irritable bowel syndrome with diarrhea
IBS-M	mixed stool pattern irritable bowel syndrome
MeSH	medical subject headings
NNH	number needed to harm
NNT	number needed to treat
RCT	randomized controlled trial
RR	relative risk
SNRI	serotonin and norepinephrine re-uptake inhibitors
SSRI	selective serotonin re-uptake inhibitor
TCA	tricyclic antidepressant

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ABSTRACT

Objectives: Irritable bowel syndrome (IBS) is a chronic functional bowel disorder that is thought to be due to a disorder of brain-gut function. Drugs acting centrally, such as antidepressants, and psychological therapies may, therefore, be effective.

Methods: We updated a previous systematic review and meta-analysis of randomized controlled trials (RCTs). MEDLINE, EMBASE, PsychINFO, and the Cochrane Controlled Trials Register were searched (up to July 2017). Trials recruiting adults with IBS, which compared antidepressants versus placebo, or psychological therapies versus control therapy or "usual management" were eligible. Dichotomous symptom data were pooled to obtain a relative risk (RR) of remaining symptomatic after therapy, with a 95% confidence interval (CI).

Results: The search strategy identified 5316 citations. Fifty-three RCTs, reported in 51 separate articles, were eligible for inclusion: 17 compared antidepressants with placebo, 35 compared psychological therapies with control therapy or "usual management", and one compared both psychological therapy and antidepressants with placebo. Four of the trials of psychological therapies, and one of the RCTs of antidepressants, were identified since our previous meta-analysis. The RR of IBS symptoms not improving with antidepressants versus placebo was 0.66 (95% CI 0.57 to 0.76), with similar treatment effects for both tricyclic antidepressants and selective serotonin re-uptake inhibitors, although with heterogeneity between RCTs of the latter (I^2 = 49%, P = 0.07). The RR of symptoms not improving with psychological therapies was 0.69 (95% CI 0.62 to 0.76). Cognitive behavioral therapy, relaxation therapy, multi-component psychological therapy, hypnotherapy, and dynamic psychotherapy were all beneficial when data from two or more RCTs were pooled. There was significant heterogeneity between studies (I^2 = 69%, P < 0.001) and significant funnel plot asymmetry. There were also issues regarding trial design, including lack of blinding.

Conclusions: Antidepressants are efficacious in reducing symptoms in IBS patients. Psychological therapies also appear to be effective treatments for IBS, although there are limitations in the quality of the evidence, and treatment effects may be overestimated as a result.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder, defined as abdominal pain in association with disordered defecation. (1) The prevalence in the community is between 5% and 20%, (2) depending on the criteria used to define its presence, and it is more common in women and younger individuals. (2, 3) Although the pathophysiology is unknown, there have been recent attempts to redefine functional gastrointestinal (GI) conditions as disorders of gut-brain interaction, (4) characterized by one or more pathophysiological processes including, but not limited to, disturbed motility, visceral hypersensitivity, altered mucosal immune function, perturbations in the intestinal microbiota, and altered central nervous system (CNS) processing.

Psychiatric conditions including depression, anxiety, and somatization often coexist in IBS. (5, 6) However, antidepressants and psychological therapies may be beneficial in functional GI disorders, (7) such as IBS, not only because they have effects within the CNS, but also because they have peripheral effects on pain perception, visceral hypersensitivity, and GI motility. (8-14) These peripheral and central effects may make them ideal candidates to treat the heterogeneous etiologies that likely cause the symptoms of IBS. Although the use of antidepressants in IBS is widespread in some healthcare settings, (15) access to psychological therapies may be limited. (16) There may also be a reluctance on the part of physicians to consider recommending either, perhaps due to doubts about their efficacy, (17, 18) or because their use is perceived to be stigmatizing. (19)

Previous meta-analyses by our group, (20, 21) conducted to inform the American College of Gastroenterology's (ACG) monograph on the management of IBS, (22, 23) have suggested that both antidepressants and psychological therapies are effective treatments for IBS. Prior to these meta-analyses, evidence for their efficacy was disputed, (24) partly due to the fact that previous systematic reviews and meta-analyses that had examined this issue had

important limitations. (25) In the intervening 4 years since our last meta-analysis, further studies have been published. We have therefore re-examined this issue once again to update the latest iteration of the ACG monograph.

METHODS

Search Strategy and Study Selection

This was an update of our previous systematic review and meta-analysis. (20) The medical literature was searched using MEDLINE (1946 to July 2017), EMBASE and EMBASE Classic (1947 to July 2017), PsychINFO (1806 to July 2017), and the Cochrane central register of controlled trials. Randomized controlled trials (RCTs) examining the effect of antidepressants and psychological therapies in adult patients (over the age of 16 years) with IBS were eligible for inclusion (Box 1), including the first period of cross-over RCTs, prior to cross-over to the second treatment. In the case of antidepressant trials the control arms were required to receive placebo, whilst for studies of psychological therapies the control arm could receive placebo, symptom monitoring (including waiting list control), or a physician's "usual management".

Duration of therapy had to be ≥7 days. 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. Subjects were required to be followed up for ≥1 week, and 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 or via questionnaire data. Where studies included patients with IBS among patients with other functional disorders, or did not report these types of dichotomous data, but were otherwise eligible for inclusion in the systematic review, we attempted to contact the original investigators in order to obtain further information.

The literature search was performed as part of a broader exercise to inform an update of the ACG monograph on the management of IBS. (26) Specifically, studies on IBS were identified with the terms irritable bowel syndrome and functional diseases, colon (both as medical subject heading (MeSH) and free text terms), and IBS, spastic colon, irritable colon, or functional adj5 bowel (as free text terms). These were combined using the set operator AND with studies identified with the terms: psychotropic drugs, antidepressive agents, antidepressive agents (tricyclic), desipramine, imipramine, trimipramine, doxepin, dothiepin, nortriptyline, amitriptyline, selective serotonin re-uptake inhibitors, paroxetine, sertraline, fluoxetine, fluvoxamine, citalopram, serotonin uptake inhibitors, venlafaxine, duloxetine, mianserin, trazodone, sulpiride, quetiapine, aripiprazole, cognitive therapy, psychotherapy, behaviour therapy, relaxation techniques, or hypnosis (both as MeSH terms and free text terms), and the following free text terms: escitalopram, serotonin norepinephrine reuptake inhibitors, milnacipran, tetracyclic antidepressants, mirtazapine, atypical antipsychotics, levosulpiride, olanzapine, behavioral therapy, relaxation therapy, or hypnotherapy.

There were no language restrictions. Abstracts of the papers identified by the initial search were evaluated by the lead reviewer for appropriateness to the study question, and all potentially relevant papers were obtained and evaluated in detail. Foreign language papers were translated where necessary. In order to identify potentially eligible studies published only in abstract form, conference proceedings (Digestive Diseases Week, American College of Gastroenterology, and United European Gastroenterology Week) between 2001 and 2017 were also hand-searched. A recursive search of the literature was performed using the bibliographies of all relevant studies. Two reviewers assessed all articles independently using pre-designed eligibility forms, according to the eligibility criteria, which were defined prospectively. Disagreements between investigators were resolved by consensus.

Outcome Assessment

The primary outcomes assessed were the effects of antidepressants compared with placebo, and the effects of psychological therapies compared with control therapy or a physician's "usual management", on global IBS symptoms or abdominal pain at study end. Secondary outcomes included assessing efficacy according to specific type of antidepressant or psychological therapy, and adverse events occurring as a result of antidepressant therapy.

Data Extraction

All data were extracted independently by two reviewers on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (global IBS symptoms unimproved, or abdominal pain unimproved) (Box 2). In addition, the following clinical data were extracted for each trial: setting (primary, secondary, or tertiary care-based), number of centers, country of origin, dose of antidepressant or number of sessions of psychological therapy administered, duration of therapy, total number of adverse events reported, 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), diarrhea (IBS-D), or mixed stool pattern (IBS-M)). We also recorded the handling of the control arm for trials of psychological therapies. Data were extracted as intention-to-treat analyses, with all drop-outs assumed to be treatment failures, wherever trial reporting allowed this.

Assessment of Risk of Bias

Two investigators performed this independently. Disagreements were resolved by consensus. The Cochrane handbook was used to assess risk of bias, (27) by recording the

method used to generate the randomization schedule and conceal treatment allocation, whether blinding was implemented for participants, personnel, and outcomes assessment, what proportion of patients completed follow-up, whether an intention-to-treat analysis was extractable, and whether there was evidence of selective reporting of outcomes.

Data Synthesis and Statistical Analysis

Data were pooled using a random effects model, (28) to provide a more conservative estimate of the range of effects of antidepressants and psychological therapies, if there was heterogeneity between studies. The impacts of different interventions were expressed as a relative risk (RR) of global IBS symptoms or abdominal pain not improving with intervention compared with control with 95% confidence intervals (CI). RRs were also used to summarize adverse events data. The number needed to treat (NNT) and the number needed to harm (NNH), with 95% CIs, were calculated using the formula NNT or NNH = 1 / (control event rate x (1 – RR)).

Heterogeneity, which is variation between individual study results arising as a result of either differences in study participants or methodology, was assessed using both the I^2 statistic with a cut off of ≥ 50%, and the chi-squared test with a P value < 0.10, used to define a significant degree of heterogeneity. (29) Review Manager version 5.3.5 (RevMan for Windows 2014, the Nordic Cochrane Centre, Copenhagen, Denmark) and StatsDirect version 2.7.7 (StatsDirect Ltd, Sale, Cheshire, England) were used to generate Forest plots of pooled RRs for primary and secondary outcomes with 95% CIs, as well as funnel plots. The latter were assessed 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)

RESULTS

The search strategy identified a total of 5316 citations, of which 114 published articles appeared to be relevant, and were retrieved for further assessment (Figure 1). Of these 114, 63 were excluded for various reasons leaving 53 RCTs, reported in 51 eligible articles, 35 of which compared psychological therapies with control therapy in the form of symptom monitoring, physician's "usual management", or supportive therapy, and were reported in 33 separate articles, (10, 32-63) 17 RCTs, reported in 17 articles, compared antidepressants with placebo, (64-80) and one RCT, reported in one article, compared both psychological therapies and antidepressants with placebo. (81) Agreement between reviewers for assessment of trial eligibility was good (kappa statistic = 0.77). Two of the RCTs were conducted amongst mixed populations of patients with functional disorders. (80, 81) In both instances, we contacted the original investigators to obtain the data for only the patients with IBS. Four of the trials of psychological therapies, (47, 48, 61, 62) and one of the RCTs of antidepressants, (80) were identified since our previous meta-analysis. One of these had been missed by literature searches that informed prior versions of this meta-analysis, (62) but was identified in the bibliography of one of the other newly identified articles.

Efficacy of Antidepressants in the Treatment of IBS

In total, there were 18 RCTs comparing antidepressants with placebo in the treatment of IBS, (64-81) which evaluated 1127 patients, 612 of whom received active therapy and 515 placebo. Eleven trials used tricyclic antidepressants (TCAs), (71-81) six selective serotonin re-uptake inhibitors (SSRIs), (65-70) and one studied both. (64) Only four of the RCTs were at low risk of bias. (66, 79-81) The proportion of female patients recruited by trials ranged from 42% to 100%. The majority of trials did not differentiate between the type of IBS patients recruited, with only seven studies providing data on this, (65-68, 70, 75, 77) one of

which recruited only IBS-C patients, (70) and another only IBS-D patients. (77) Detailed characteristics of individual RCTs are provided in Table 1.

Overall, 266 (43.5%) of 612 patients assigned to antidepressant therapy reported unimproved IBS symptoms following therapy, compared with 340 (66.0%) of 515 allocated to placebo. The RR of IBS symptoms not improving after treatment with antidepressant therapy versus placebo was 0.66 (95% CI 0.57 to 0.76), with significant heterogeneity detected between studies (I^2 = 37%, P = 0.06) (Figure 2). There was statistically significant asymmetry in the funnel plot (Egger test, P = 0.03), suggesting publication bias or other small study effects, but this was driven by the TCA arm of one small study, (64) and disappeared with its exclusion from the analysis (Egger test, P = 0.13), with no impact on the overall efficacy estimate. The NNT with antidepressants was 4.5 (95% CI 3.5 to 6).

The effect of antidepressant therapy on abdominal pain was reported by seven RCTs, (67, 68, 70, 71, 75, 77, 79) with 87 (47.8%) of 182 patients receiving antidepressants having no improvement in abdominal pain following treatment, compared with 123 (72.8%) of 169 subjects allocated to placebo, giving a RR of abdominal pain not improving of 0.62 (95% CI 0.43 to 0.88), but with considerable heterogeneity between studies (I^2 = 72%, P = 0.001) (Figure 3). This beneficial effect on abdominal pain appeared to be limited to TCAs (RR = 0.59; 95% CI 0.42 to 0.83, I^2 = 35%), with no statistically significant effect of SSRIs (RR = 0.64; 95% CI 0.32 to 1.27, I^2 = 86%), although the point estimate of effect was similar for both drug classes, and there was no statistically significant difference between them (subgroup differences, I^2 = 0%, P = 0.85).

Efficacy of TCAs in the Treatment of IBS

Twelve RCTs compared TCAs with placebo, including a total of 787 patients. (64, 71-81) Of 436 patients receiving active therapy, 186 (42.7%) had no improvement in

symptoms after treatment, compared with 224 (63.8%) of 351 receiving placebo. The RR of IBS symptoms not improving with TCAs compared with placebo was 0.65 (95% CI 0.55 to 0.77), with no statistically significant heterogeneity detected between studies (I^2 = 34%, P = 0.12) (Figure 2), and evidence of funnel plot asymmetry (Egger test, P = 0.01). The NNT with TCAs was 4.5 (95% CI 3.5 to 7).

Efficacy of SSRIs in the Treatment of IBS

There were seven trials comparing SSRIs with placebo, recruiting a total of 356 patients. (64-70) In total, 80 (45.5%) of 176 patients allocated to SSRIs reported no improvement in symptoms following therapy, compared with 121 (67.2%) of 180 placebo patients. The RR of IBS symptoms not improving with SSRIs compared with placebo was 0.68 (95% CI 0.51 to 0.91), but with statistically significant heterogeneity between studies (I^2 = 49%, P = 0.07) (Figure 2). The NNT with SSRIs was 5 (95% CI 3 to 16.5).

Adverse Events with Antidepressant Therapy

Eight trials reported on overall adverse events with antidepressants versus placebo. (65, 68, 71, 72, 74, 75, 78, 80) In total, 83 (36.4%) of 228 patients assigned to antidepressants experienced adverse events, compared with 47 (21.1%) of 223 allocated to placebo. When data were pooled the incidence of adverse events was significantly higher among those taking antidepressants (RR of experiencing any adverse event = 1.56; 95% CI 1.23 to 1.98) (Figure 4). The NNH was 8.5 (95% CI 5 to 21). There were no serious adverse events. Six of the RCTs used TCAs (71, 72, 74, 75, 78, 80) and, in these trials, there was a significantly higher rate of adverse events (RR = 1.59; 95% CI 1.23 to 2.06). Drowsiness and dry mouth were more common in patients randomized to TCAs than those receiving placebo.

Efficacy of Psychological Therapies in the Treatment of IBS

There were a total of 34 articles, reporting on 36 separate RCTs, comparing various psychological therapies with control therapy in the form of symptom monitoring, physician's "usual management", supportive therapy, or placebo for the treatment of IBS in a total of 2487 patients. (10, 32-63, 81) Six RCTs used cognitive behavioral therapy (CBT), (35, 39, 41, 42, 53, 81) six trials used relaxation training or therapy, (33, 36, 37, 55, 60, 61) five RCTs, reported in four separate articles, used hypnotherapy, (10, 34, 57, 58) four trials, reported in three separate articles, used multi-component psychological therapy, (32, 38, 52) two RCTs used self-administered or minimal contact CBT, (40, 59) two trials used internet-delivered CBT, (44, 46) two RCTs used dynamic psychotherapy, (50, 51) two trials used mindfulness meditation training, (47, 63) one RCT used stress management, (54) one trial used stress management or CBT, (43) one RCT used stress management or contingency management, (62) one RCT used CBT or self-administered CBT, (45) one trial used multi-component psychological therapy delivered in-person or mainly via the telephone, (56) one RCT used CBT or relaxation therapy, (49) and one RCT used emotional awareness and expression training or relaxation therapy (48).

The control arm received symptom monitoring in 18 RCTs, reported in 17 articles, (32-48) usual care in 15 trials, reported in 14 articles, (49-62) supportive therapy in two RCTs, (10, 63) and placebo in one trial. (81) None of the trials were at low risk of bias, due to the inability to blind participants to the nature of the intervention received. The proportion of female patients recruited by trials ranged from 52% to 100%. Detailed characteristics of individual trials are provided in Table 2. Adverse events data were poorly reported by included RCTs, precluding any meaningful analysis.

Overall, IBS symptoms did not improve in 735 (52.2%) of 1407 patients receiving psychological therapies, compared with 820 (75.9%) of 1080 receiving control in the form of

symptom monitoring, physician's "usual management", supportive therapy, or placebo. The RR of IBS symptoms not improving with psychological therapies was 0.69 (95% CI 0.62 to 0.76) (Figure 5), with considerable heterogeneity detected between studies (I^2 = 69%, P < 0.001), and evidence of funnel plot asymmetry, or other small study effects (Egger test, P <0.001), with a lack of small studies showing no effect of psychological therapies on the symptoms of IBS. The NNT with psychological therapies was 4 (95% CI 3.5 to 5.5).

Efficacy of CBT in IBS

Nine trials compared CBT with control therapy in 610 patients. (35, 39, 41-43, 45, 49, 53, 81) Symptoms of IBS did not improve in 145 (41.5%) of 349 assigned to CBT, compared with 166 (63.6%) of 261 allocated to control, with a RR of 0.60 (95% CI 0.44 to 0.83) (Figure 5), and statistically significant heterogeneity between studies (I^2 = 70%, P < 0.001). The NNT with CBT was 4 (95% CI 3 to 9).

Efficacy of Relaxation Training or Therapy in IBS

Eight RCTs compared relaxation training or therapy with control therapy in 360 patients. (33, 36, 37, 48, 49, 55, 60, 61) IBS symptoms did not improve in 126 (68.1%) of 185 patients randomized to relaxation training or therapy, compared with 147 (84.0%) of 175 receiving control therapy. Overall, there was a benefit of relaxation training or therapy in IBS (RR of symptoms not improving = 0.80; 95% CI 0.65 to 0.98) (Figure 5), but with statistically significant heterogeneity between studies (I^2 = 61%, P = 0.01). The NNT was 6 (95% CI 3 to 60).

Efficacy of Multi-component Psychological Therapy in IBS

Five separate RCTs, reported in four articles, (32, 38, 52, 56) compared multi-component psychological therapy with control therapy in 335 patients. Symptoms of IBS were not improved in 96 (57.1%) of 168 patients randomized to multi-component psychological therapy, compared with 135 (80.8%) of 167 receiving control. The RR of IBS symptoms not improving was 0.72 (95% CI 0.62 to 0.83) (Figure 5), with no significant heterogeneity detected between studies (I^2 = 0%, P = 0.64). The NNT with multi-component psychological therapy was 4 (95% CI 3 to 7).

Efficacy of Hypnotherapy in IBS

Five separate trials, again reported in four articles, (10, 34, 57, 58) compared hypnotherapy with control therapy in 278 patients. IBS symptoms did not improve in 77 (54.6%) of 141 patients assigned to hypnotherapy, compared with 106 (77.4%) of 137 allocated to control therapy. Overall, hypnotherapy was of benefit in IBS, with a RR of symptoms not improving of 0.74 (95% CI 0.63 to 0.87) (Figure 5), with no significant heterogeneity detected between studies (I^2 = 0%, P = 0.43). The NNT with hypnotherapy was 5 (95% CI 3.5 to 10).

Efficacy of Self-administered or Minimal Contact CBT in IBS

Three trials, involving 144 patients, used self-administered or minimal contact CBT. (40, 45, 59) Overall, 34 (46.6%) of 73 patients allocated to receive self-administered or minimal contact CBT reported no improvement in symptoms, compared with 63 (88.7%) of 71 assigned to control. The RR of IBS symptoms not improving with self-administered or minimal contact CBT was 0.53 (95% CI 0.17 to 1.66) (Figure 5), with significant heterogeneity detected between individual study results (I^2 = 96%, P < 0.001).

Efficacy of Stress Management in IBS

There were three trials using this therapy, (43, 54, 62) involving 142 patients. Overall, 37 (46.3%) of 80 patients assigned to stress management reported no improvement in IBS symptoms, compared with 43 (69.4%) of 62 allocated to control. There was no beneficial effect detected for stress management in IBS (RR = 0.68; 95% CI 0.39 to 1.20) (Figure 5), and there was significant heterogeneity between studies (I^2 = 66%, P = 0.05).

Efficacy of Dynamic Psychotherapy in IBS

Two RCTs compared dynamic psychotherapy with control therapy in 273 patients. (50, 51) No improvement in IBS symptoms was reported by 61 (44.2%) of 138 randomized to dynamic psychotherapy, compared with 95 (70.4%) of 135 receiving control, with a RR of symptoms not improving of 0.60 (95% CI 0.39 to 0.93) (Figure 5), and a NNT of 4 (95% CI 2 to 20). Again there was significant heterogeneity between studies (I^2 = 72%, P = 0.06).

Efficacy of Mindfulness Meditation Training in IBS

There were two studies, recruiting 165 patients. (47, 63) Overall, 44 (55.7%) of 79 patients assigned to mindfulness meditation symptoms were not improved, compared with 58 (67.4%) of 86 allocated to control, with no beneficial effect detected (RR = 0.78; 95% CI 0.44 to 1.41) (Figure 5), and with significant heterogeneity between studies (I^2 = 74%, P = 0.05).

Efficacy of CBT Delivered Via the Internet in IBS

There were two trials that delivered CBT via the internet, containing 140 patients. (44, 46) Among 71 patients randomized to CBT via the internet, 51 (71.8%) reported no improvement in symptoms. This compared with 68 (98.6%) of 69 allocated to control

therapy. The RR of IBS symptoms not improving with CBT via the internet was 0.75 (95% CI 0.48 to 1.17) (Figure 5), with significant heterogeneity between the two RCTs (I^2 = 90%, P = 0.002).

Efficacy of Multi-component Psychological Therapy Mainly Via the Telephone, Contingency Management in IBS, or Emotional Awareness and Expression Training

There was only one study using each of these treatment modalities. (48, 56, 62) Multi-component psychological therapy mainly via the telephone (RR of symptoms not improving = 0.78; 95% CI 0.64 to 0.93), (56) contingency management (RR = 0.45; 95% CI 0.26 to 0.77), (62) and emotional awareness and expression training (RR = 0.49; 95% CI 0.28 to 0.87) (48) all appeared to be beneficial in IBS (Figure 5).

DISCUSSION

This updated systematic review and meta-analysis has once again demonstrated that antidepressants and psychological therapies appear to be effective treatments for IBS. The NNT for TCAs and SSRIs was 4.5 and 5 respectively, although in the latter instance there was significant heterogeneity between studies, several negative RCTs, and a widening of the 95% CI of effect. Adverse events were significantly higher among those taking antidepressants, particularly among those allocated to TCAs, with a NNH of 8.5. When all psychological therapies, including hypnotherapy, were considered the NNT was 4. Cognitive behavioral therapy, relaxation therapy, multi-component psychological therapy, hypnotherapy, and dynamic psychotherapy were all more effective than control therapy, when data from two or more RCTs were pooled, with NNTs of between 4 and 6. Self-administered or minimal contact CBT, stress management, mindfulness meditation training, and CBT delivered via the internet were of no benefit, although it should be noted that, in most cases, the proportions with an improvement in symptoms were higher with active therapy, and the number of included individuals in the eligible trials was small. Multi-component psychological therapy delivered mainly via the telephone, contingency management, and emotional awareness and expression training also appeared beneficial, although there was only one RCT for each of these treatment modalities. Finally, adverse events data were poorly reported among trials of psychological therapies.

We used an exhaustive search strategy, which involved searching the "gray" literature. Assessment of eligibility and data extraction was performed independently by two reviewers. We used an intention-to-treat analysis and pooled data with a random effects model, to minimize the likelihood that treatment effect would be overestimated. We included non-English RCTs in the analysis, and contacted investigators of potentially eligible studies to either obtain dichotomous data or to exclude patients with other functional disorders from

the analysis. This inclusive approach has provided us with access to data for >1000 IBS patients treated with antidepressants versus placebo, and almost 2500 patients randomized to psychological therapies versus control. We also performed subgroup analyses to assess treatment effect according to individual therapy used. Finally, we extracted and pooled adverse events data, where reported.

Limitations of this systematic review and meta-analysis arise from the studies available for synthesis. There were very few trials at low risk of bias, and there was evidence of heterogeneity between RCTs of SSRIs and psychological therapies as a whole, although not for TCAs, hypnotherapy, or multi-component psychological therapy. There was also evidence of publication bias, or other small study effects, for both antidepressants and psychological therapies. For antidepressants, this disappeared when one small outlying RCT was excluded from the analysis. As we have highlighted in previous versions of this meta-analysis, this may have led to overestimation of the treatment effect for both antidepressants and psychological therapies, but this is likely to be more pronounced for psychological therapies.

It is interesting that there was no evidence for any benefit of psychological therapies that minimize personal contact with patients, such as internet-delivered therapies or minimal contact CBT. This suggests that more intensive personal contact is needed for psychological therapies to be effective. There is, however, a paucity of data on which patients and what type of IBS symptoms respond best to therapy, and in which setting. Only two of the RCTs we identified were conducted entirely within primary care, (53, 59) and definitive trials in this setting are needed. The efficacy of these therapies according to predominant stool pattern reported by the patient has also not been well studied. TCAs prolong orocecal and whole gut transit times, (12, 82) whereas SSRIs decrease orocecal transit time. (12, 14) It would, therefore, seem biologically plausible that TCAs would be more effective in diarrhea-

predominant IBS, and SSRIs of greater benefit in constipation-predominant IBS, but only two published RCTs have assessed this approach. (70, 77) Antidepressants may have their beneficial effects in IBS in other ways. Although evidence for any effect of antidepressants on visceral hypersensitivity in the GI tract is limited, (68, 83) there are data demonstrating the efficacy of TCAs in other painful functional disorders, such as fibromyalgia, (84) and chronic headache, (85) but high quality data for SSRIs in these conditions are lacking. (86, 87) Interestingly, some of the strongest evidence for the pain-modifying effects of antidepressants in chronic painful disorders comes from high quality RCTs of the serotonin and norepinephrine re-uptake inhibitors (SNRIs) duloxetine and milnacipran, (88-92) neither of which have been tested in IBS trials to date.

Whether the benefit of antidepressants arises from the treatment of co-existent depression is controversial. Data from the RCTs included in this meta-analysis are conflicting, with three studies reporting no significant relationship between depression scores and improvement in IBS symptoms, (65, 67, 75) one trial demonstrating that treatment effect with desipramine was actually greater in those without evidence of co-existent depression, (81) and a fifth RCT of citalopram, where depressed individuals were excluded, showing no benefit of the drug in IBS. (66) In treatment trials of SSRIs in IBS, the doses used were almost identical to those used to treat depression, but any effect on mood would seem less likely for TCA trials, where the doses used were considerably lower than those used for mood disorders. Interestingly, in a recent study, presence of depression seemed to modify the central response to pain in patients with IBS, (93) suggesting that if antidepressants are indeed improving mood in patients with IBS this may have other beneficial effects.

In terms of future research, there remains a clear need for larger, high quality trials of both antidepressants and psychological therapies that are conducted in primary care, and which stratify patients according to both predominant stool pattern and presence or absence

of mood disorder. Psychological therapies, such as CBT, work differently to pharmacological therapies in IBS, by acting on frontal "executive" areas of the brain in order to modify cognitive, behavioral, and emotional responses to symptoms. This may lead to a reduction in the anxiety that results from such symptoms, which can itself drive exacerbations of IBS via the enteric nervous system, and also improved social functioning. Trials that also test the hypothesis that there is an augmentative effect of combining psychological therapies with antidepressants, as appears to be the case in the treatment of chronic headache, (94) are therefore also warranted. Perhaps surprisingly, to date, there have been no trials of SNRIs in IBS, and this should also be addressed, given their known efficacy in other painful functional disorders.

In summary, this updated systematic review and meta-analysis has demonstrated that TCAs, SSRIs, CBT, relaxation therapy, hypnotherapy, multi-component psychological therapy, and dynamic psychotherapy are probably effective treatments for IBS. Adverse effects are more common with antidepressants, particularly TCAs. Despite another five studies identified in the years since we last examined this issue, the overall summary estimates of treatment effect have remained very similar. Better knowledge of the point in the natural history at which to consider these therapies, as well as those subgroups of patients who are more likely to respond, could lead to improved treatment outcomes for patients with this difficult to treat chronic disorder.

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CONFLICTS OF INTEREST/STUDY SUPPORT

Guarantor of the article: ACF is guarantor.

Specific author contributions: ACF, BEL, LAH, EMMQ, and PM conceived the study. ACF and PM collected all data. ACF and PM analyzed 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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Box 1. Eligibility criteria.

Randomized controlled trials

Adults (participants aged > 16 years)

Diagnosis of IBS based on either a clinician's opinion, or meeting specific diagnostic criteria*, supplemented by negative investigations where trials deemed this necessary.

Compared antidepressants with placebo, or psychological therapies with a control therapy, including a physician's "usual management", symptom monitoring, supportive therapy, or placebo.

Minimum duration of therapy 7 days.

Minimum duration of follow-up 7 days.

Dichotomous assessment of response to therapy in terms of effect on global IBS symptoms or abdominal pain following therapy.†

*Manning, Kruis score, Rome I, II, III or IV.

†Preferably patient-reported, but if this was not available then as assessed by a physician or questionnaire data.

Box 2. Data extraction methodology.

Outcome of interest: improvement in global IBS symptoms preferable, if not reported then improvement in abdominal pain.

Reporting of outcomes: patient-reported preferable, if not available then investigator-reported.

Time of assessment: upon completion of therapy.

Denominator used: true intention-to-treat analysis, if not available then all evaluable patients.

Cut off used for dichotomization: any improvement in global IBS symptoms or abdominal pain for Likert-type scales, investigator-defined improvement for continuous scales, if no investigator definition available then we used ≥ 1 standard deviation decrease in symptom score from baseline to completion of therapy (we assessed if the use of any decrease in symptom score from baseline to completion of therapy altered our analysis).

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FIGURE LEGENDS

Figure 1. Flow Diagram of Assessment of Studies Identified in the Updated Systematic Review and Meta-analysis.

Figure 2. Forest Plot of Randomized Controlled Trials of Antidepressants Versus Placebo in Irritable Bowel Syndrome.

Figure 3. Forest Plot of Randomized Controlled Trials of Antidepressants Versus Placebo in Terms of Effect on Abdominal Pain in Irritable Bowel Syndrome.

Figure 4. Forest Plot of Adverse Events in Randomized Controlled Trials of Antidepressants Versus Placebo in Irritable Bowel Syndrome.

Figure 5. Forest Plot of Randomized Controlled Trials of Psychological Therapies Versus Control in Irritable Bowel Syndrome.

Table 1. Characteristics of Randomized Controlled Trials of Antidepressants Versus Placebo in Irritable Bowel Syndrome.

Study	Country	Setting	Diagnostic criteria used for IBS and subtype	Criteria used to define symptom improvement following therapy	Sample size (% female)	Antidepressant used	Duration of therapy	Methodology
Heefner 1978 (71)	USA	Tertiary care	Clinical diagnosis and investigations, subtype not stated	Patient-reported improvement in abdominal pain	44 (not reported)	Desipramine 150mg o.d.*	2 months	Method of randomization and concealment of allocation not stated. Double-blind. Unclear if other IBS medications allowed.
Myren 1982 (72)	Norway	Secondary care	Clinical diagnosis and investigations. subtype not stated	Patient-reported improvement in global symptoms	61 (55)	Trimipramine 50mg o.d.	4 weeks	Method of randomization and concealment of allocation not stated. Double-blind. No other IBS medications allowed.

Nigam 1984 (73)	India	Secondary care	Clinical diagnosis and investigations, subtype not stated	Patient-reported improvement in global symptoms	42 (not reported)	Amitriptyline 12.5mg o.d.	12 weeks	Method of randomization and concealment of allocation not stated. Double-blind. Unclear if other IBS medications allowed.
Boerner 1988 (74)	Germany	Secondary care	Clinical diagnosis and investigations, subtype not stated	Patient-reported improvement in global symptoms	83 (not reported)	Doxepin 50mg o.d.	8 weeks	Method of randomization and concealment of allocation not stated. Double-blind. Unclear if other IBS medications allowed.

Bergmann 1991 (76)	Germany	Secondary care	Clinical diagnosis and investigations, subtype not stated	Patient-reported improvement in global symptoms	35 (87)	Trimipramine 50mg o.d.	3 months	Method of randomization and concealment of allocation not stated. Blinding not stated. No other IBS medications allowed.
Vij 1991 (75)	India	Secondary care	Clinical diagnosis and investigations, 20% IBS-C, 68% IBS-D, 12% IBS-M	Patient-reported improvement in global symptoms	50 (not reported)	Doxepin 75mg o.d.	6 weeks	Method of randomization stated. Method of concealment of allocation not stated. Double-blind. Unclear if other IBS medications allowed.
Drossman 2003 (81)	USA and Canada	Tertiary care	Rome I, subtype not stated	Score of ≥28 on treatment satisfaction questionnaire	172 (100)	Desipramine 50mg o.d. for 1 week, then 100mg o.d. for 1 week, then 150mg o.d. thereafter	12 weeks	Method of randomization and concealment of allocation stated. Double-blind. Unclear if other IBS medications allowed.

Kuiken 2003 (68)	Holland	Tertiary care	Rome I and investigations, 28% IBS-C, 40% IBS-D, 32% IBS-M	Patient-reported improvement in global symptoms	40 (55)	Fluoxetine 20mg o.d.	6 weeks	Method of randomization and concealment of allocation stated. Double-blind. Unclear if other IBS medications allowed.
Tabas 2004 (67)	USA	Tertiary care	Rome I, 19% IBS-C, 58% IBS-D, 23% IBS-M	Patient-reported improvement in well-being	90 (74)	Paroxetine 10mg, increasing to 20mg then 40mg if no improvement	12 weeks	Method of randomization and concealment of allocation stated. Double-blind. High fibre diet. Unclear if other IBS medications allowed.
Vahedi 2005 (70)	Iran	Secondary care	Rome II and investigations, 100% IBS-C	Patient-reported improvement in abdominal pain	44 (61)	Fluoxetine 20mg o.d.	12 weeks	Method of randomization stated. Method of concealment of allocation not stated. Double-blind. Unclear if other IBS medications allowed.

Tack 2006 (65)	Belgium	Tertiary care	Rome II and investigations, 17% IBS-C, 22% IBS-D, 61% IBS-M	Patient-reported 50% decrease in days with symptoms	23 (78)	Citalopram 20mg o.d. for 3 weeks increasing to 40mg o.d. for next 3 weeks	6 weeks	Method of randomization and concealment of allocation stated. Double-blind. No other IBS medications allowed.
Talley 2008 (64)	Australia	Tertiary care	Rome II and investigations, subtype not stated	Patient-reported adequate relief of symptoms	51 (61)	Imipramine 50mg o.d. or citalopram 40mg o.d.	12 weeks	Method of randomization and concealment of allocation stated. Double-blind. No other IBS medications allowed.
Vahedi 2008 (77)	Iran	Secondary care	Rome II and investigations, 100% IBS-D	Patient-reported improvement in global symptoms	54 (44)	Amitriptyline 10mg o.d.	2 months	Method of randomization stated. Method of concealment of allocation not stated. Double-blind. Unclear if other IBS medications allowed.

Abdul-Baki 2009 (78)	Lebanon	Primary, secondary, and tertiary care	Rome II, subtype not stated	Patient-reported relief of global symptoms	107 (42)	Impiramine 25mg o.d. titrated up to b.i.d.†	12 weeks	Method of randomization and concealment of allocation stated. Double-blind. No other IBS medications allowed.
Masand 2009 (69)	USA	Tertiary care	Rome II and investigations, subtype not stated	Patient-reported improvement in global symptoms	72 (88)	Paroxetine 12.5mg o.d. increased to 50mg o.d.	12 weeks	Method of randomization and concealment of allocation not stated. Double-blind. No other IBS medications allowed.
Ladabaum 2010 (66)	USA	Primary, secondary, and tertiary care	Rome II and investigations, 39% IBS-C, 43% IBS-D, 18% IBS-M	Patient-reported adequate relief of global symptoms	54 (82)	Citalopram 20mg o.d. for 4 weeks then 40mg o.d. for 4 weeks	8 weeks	Method of randomization and concealment of allocation stated. Double-blind. Fibre and loperamide allowed.

Ghadir 2011 (79)	Iran	Secondary care	Rome III, subtype not stated	Patient-reported improvement in abdominal pain	62 (not reported)	Doxepin or nortiptyline 10mg o.d.	2 months	Method of randomization and concealment of allocation stated. Double-blind. Unclear if other IBS medications allowed.
Agger 2017 (80)	Denmark	Tertiary care	Rome I, subtype not stated	Patient-reported improvement in global symptoms	43 (not reported)	Imipramine titrated to a maximum of 75mg o.d.	10 weeks	Method of randomization and concealment of allocation stated. Double-blind. Unclear if other IBS medications allowed.

*o.d.; once-daily

†b.i.d.; twice-daily

Table 2. Characteristics of Randomized Controlled Trials of Psychological Therapies Versus Control in Irritable Bowel Syndrome.

Study	Country	Setting	Diagnostic criteria used for IBS	Criteria used to define symptom improvement following therapy	Sample size (% female)	Psychological therapy used	Methodology
Neff 1987 (38)	USA	Tertiary care	Clinical diagnosis, 42% IBS-C, 37% IBS-D, 21% IBS-M	≥50% reduction in baseline symptom score	19 (79)	Multi-component psychological therapy consisting of two 1-hour sessions per week for 4 weeks of a combination of relaxation therapy, thermal biofeedback, education and training in stress coping strategies then one session per week for a further 4 weeks	Method of randomization and concealment of allocation not stated. Unblinded. Unclear if other IBS medications allowed.

Lynch 1989 (37)	Canada	Tertiary care	Clinical diagnosis, 29% IBS-C, 38% IBS-D, 33% IBS-M	≥50% reduction in diary rating of symptoms	21 (67)	One 2-hour relaxation therapy session per week for 8 weeks, with audiotapes to practice relaxation techniques twice daily	Method of randomization and concealment of allocation not stated. Unblinded. Unclear if other IBS medications allowed.
Guthrie 1991 (51)	England	Tertiary care	Clinical diagnosis and investigations, subtype not stated	Patient-reported improvement in global symptoms	102 (75)	One 2-hour dynamic psychotherapy session followed by six further sessions over 3 months, and a relaxation audiotape provided for use at home	Method of randomization and concealment of allocation not stated. Unblinded. No new IBS medications allowed but could continue on current therapy.

Shaw 1991 (54)	Wales	Tertiary care	Clinical diagnosis and investigations, subtype not stated	Patient-reported overall benefit from treatment	35 (57)	One 40-minute stress management technique session per week for at least 4 weeks (total number of sessions was flexible)	Method of randomization and concealment of allocation not stated. Unblinded. Unclear if other IBS medications allowed.
Blanchard 1992 (32)	USA	Tertiary care	Clinical diagnosis and investigations, subtype not stated in the first RCT, 24% IBS-C, 29% IBS-D, 47% IBS-M in the second	≥50% reduction in baseline symptom score	20 (85) and 77 (66)*	Multi-component psychological therapy consisting of two 1-hour sessions per week for 4 weeks of a combination of relaxation therapy, thermal biofeedback, education and training in stress coping strategies then one session per week for a further 4 weeks	Method of randomization and concealment of allocation not stated. Unblinded. Unclear if other IBS medications allowed.

Blanchard 1993 (33)	USA	Tertiary care	Clinical diagnosis and investigations, 22% IBS-C, 26% IBS-D, 52% IBS-M	≥50% reduction in baseline symptom score	23 (78)	Two progressive muscle relaxation sessions per week for 2 weeks then one session per week for a further 6 weeks, with regular home practice emphasized (at least 25 minutes per day)	Method of randomization and concealment of allocation not stated. Unblinded. Other IBS medications "discouraged".
Greene 1994 (35)	USA	Tertiary care	Clinical diagnosis and investigations, subtype not stated	≥50% reduction in baseline symptom score	20 (75)	Two 1-hour CBT sessions per week for 2 weeks then one session per week for a further 6 weeks	Method of randomization and concealment of allocation not stated. Unblinded. Unclear if other IBS medications allowed.

Payne 1995 (39)	USA	Tertiary care	Rome I and investigations, 27% IBS-C, 32% IBS-D, 41% IBS-M	≥50% reduction in baseline symptom score	22 (82)	Two 1-hour CBT sessions per week for 2 weeks then one session per week for a further 6 weeks	Method of randomization and concealment of allocation not stated. Unblinded. Unclear if other IBS medications allowed.
Fernandez 1998 (62)	Spain	Secondary care	Manning criteria, subtype not stated	Asymptomatic or symptoms improved, as assessed by investigator	44 (68)	One 1-hour education session per week for 2 weeks then one 1-hour session per week of either stress management/progressive muscle relaxation or contingency management for a further 10 weeks	Method of randomization and concealment of allocation not stated. Investigator-blinded. Unclear if other IBS medications allowed.

Galovski 1998 (34)	USA	Tertiary care	Clinical diagnosis, subtype not stated	≥50% reduction in baseline symptom score	12 (83)	One 30-minute to 1-hour gut-directed hypnotherapy session per week for 6 weeks	Method of randomization and concealment of allocation not stated. Unblinded. Unclear if other IBS medications allowed.
Vollmer 1998 (42)	USA	Tertiary care	Rome I and investigations, 14% IBS-C, 43% IBS-D, 43% IBS-M	≥50% reduction in baseline symptom score	34 (76)	One 1-hour session of individual CBT per week for 10 weeks, or one 90-minute session of group CBT per week for 10 weeks	Method of randomization and concealment of allocation not stated. Unblinded. Unclear if other IBS medications allowed.

Keefer 2001 (36)	USA	Tertiary care	Clinical diagnosis, subtype not stated	≥50% reduction in baseline symptom score	15 (not reported)	One 30-minute relaxation response meditation session per week for 6 weeks	Method of randomization and concealment of allocation not stated. Unblinded. Unclear if other IBS medications allowed.
Boyce 2003 (49)	Australia	Tertiary care	Rome I and investigations, subtype not stated	≥1 standard deviation decrease in baseline symptom score	105 (81)	One 1-hour CBT session per week for 8 weeks, or one 30-minute relaxation therapy session per week for 8 weeks	Method of randomization and concealment of allocation stated. Investigator-blinded. No other IBS medications allowed.

Creed 2003 (50)	England	Tertiary care	Rome I, 23% IBS-C, 31% IBS-D	Patient-reported improvement in global symptoms	171 (79)	One 2-hour and seven 45-minute psychodynamic interpersonal therapy sessions over 3 months	Method of randomization and concealment of allocation stated. Investigator-blinded. Unclear if other IBS medications allowed.
Drossman 2003 (81)	USA and Canada	Tertiary care	Rome I, subtype not stated	Score of ≥28 on treatment satisfaction questionnaire	169 (100)	One 1-hour CBT session per week for 12 weeks	Method of randomization and concealment of allocation stated. Double-blind. Unclear if other IBS medications allowed.

Tkachuk 2003 (41)	Canada	Tertiary care	Rome I and investigations, subtype not stated	Patient-reported improvement in global symptoms	28 (96)	Two 90-minute group CBT sessions per week for 1 week then one session per week for 8 weeks	Method of randomization and concealment of allocation not stated. Unblinded. Unclear if other IBS medications allowed.
Heitkemper 2004 (52)	USA	Tertiary care	Rome I, 15.5% IBS-C, 8% IBS-D, 56% IBS-M	≥50% reduction in symptom score	95 (100)	One 1-hour weekly multi-component psychological therapy session per week for 8 weeks	Method of randomization and concealment of allocation not stated. Unblinded. Other IBS medications allowed.

Simren 2004 (10)	Sweden	Tertiary care	Rome II and investigations, 18% IBS-C, 28.5% IBS-D, 53.5% IBS-M	Patient-reported improvement in global symptoms	28 (68)	One 1-hour gut-directed hypnotherapy session per week for 12 weeks	Method of randomization stated. Method of concealment of allocation not stated. Unblinded. No other IBS medications allowed.
Kennedy 2005 (53)	England	Primary care	Clinical diagnosis, subtype not stated	Improvement in symptom severity banding by one band (graded severe to none on a four-point Likert-scale)	149 (not reported)	One 50-minute CBT session per week for 6 weeks	Method of randomization stated. Method of concealment of allocation not stated. Unblinded. No new IBS medications allowed.

Sanders 2007 (40)	USA	Tertiary care	Rome II and investigations, 46% IBS-C, 18% IBS-D, 36% IBS-M	≥50% reduction in baseline symptom score	28 (79)	Self-administered CBT mailed as five modules over 10 weeks.	Method of randomization stated. Method of concealment of allocation not stated. Unblinded. Unclear if other IBS medications allowed.
van der Veek 2007 (55)	Holland	Tertiary care	Rome II, subtype not stated	Reliable change index ≥1.96 (pre-therapy score minus post-therapy score divided by standard error of the difference)	105 (not reported)	One 90-minute relaxation training session per week for 4 weeks with one booster session after 3 months	Method of randomization not stated. Method of concealment of allocation stated. Unblinded. Other IBS medications allowed.

Lackner 2008 (45)	USA	Primary, secondary, and tertiary care	Rome II, 25% IBS-C, 53% IBS-D, 21% IBS-M	Patient-reported adequate relief of global symptoms	75 (87)	One 1-hour CBT session per week for 10 weeks, or one 1-hour CBT session on four occasions over 10 weeks	Method of randomization stated. Method of concealment of allocation not stated. Unblinded. Other IBS medications allowed.
Hunt 2009 (44)	USA	Not reported	Clinical diagnosis, subtype not stated	Patient reported they had "recovered" according to the gastrointestinal symptom rating scale.	54 (82)	One module of CBT delivered via the internet per week for 5 weeks, with homework assignments	Method of randomization and concealment of allocation not stated. Unblinded. Unclear if other IBS medications not allowed.

Jarrett 2009 (56)	USA	Not reported	Rome II, 22% IBS-C, 53% IBS-D, 20% IBS-M	≥50% reduction in baseline symptom score	188 (86)	One 1-hour multi-component psychological therapy session per week delivered in-person for 9 weeks, or one 1-hour session per week delivered in-person for 2 weeks, then six sessions delivered via the telephone with the final session delivered in-person	Method of randomization and concealment of allocation not stated. Unblinded. No other IBS medications allowed.
Ljottson 2010 (46)	Sweden	Not reported	Rome III, subtype not stated	≥50% reduction in baseline symptom score	86 (not reported)	A CBT protocol consisting of five steps and delivered via the internet over 10 weeks	Method of randomization and concealment of allocation stated. Unblinded. Unclear if other IBS medications allowed.

Moss-Morris 2010 (59)	New Zealand	Primary care	Rome I or Rome II, subtype not stated	Patient-reported adequate relief of global symptoms	64 (72)	A self-administered CBT program divided into seven chapters and completed over 7 to 8 weeks	Method of randomization and concealment of allocation stated. Unblinded. Unclear if other IBS medications allowed.
Shinozaki 2010 (60)	Japan	Tertiary care	Rome II and investigations, 19% IBS-C, 33% IBS-D, 48% IBS-M	Patient-reported adequate relief of global symptoms	21 (52)	One 30 to 40-minute relaxation training session per week for 8 weeks	Method of randomization and concealment of allocation not stated. Unblinded. Unclear if other IBS medications allowed.

Craske 2011 (43)	USA	Primary and tertiary care	Rome II, subtype not stated	≥50% reduction in baseline symptom score	110 (not reported)	One 50-minute CBT or stress management session per week for 10 weeks	Method of randomization and concealment of allocation stated. Unblinded. Other IBS medications allowed.
Gaylord 2011 (63)	USA	Not reported	Rome II, subtype not stated	≥50 point reduction in the IBS symptom severity score	75 (100)	One 2-hour mindfulness meditation training session per week for 8 weeks plus one half--day retreatment session	Method of randomization stated. Method of concealment of allocation not stated. Investigator-blinded. Other IBS medications allowed.

Lindfors 2012 (57)	Sweden	Secondary or tertiary care	Rome II and investigations, 16% IBS-C, 33% IBS-D, 51% IBS-M in the first RCT, 23% IBS-C, 47% IBS-D, 44% IBS-M in the second	≥25% reduction of total score on the GI symptom questionnaire	48 (81) and 90 (79)*	One 1-hour gut-directed hypnotherapy session per week for 12 weeks, with encouragement to practice at home on a regular basis and audiotapes provided in one study	Method of randomization and concealment of allocation stated. Unblinded. Other IBS medications allowed.
Moser 2013 (58)	Austria	Primary and tertiary care	Rome III, 24% IBS-C, 51% IBS-D, 24% IBS-M	Patient-reported adequate relief of global symptoms	90 (79)	Ten 45-minute gut-directed hypnotherapy sessions over 12 weeks, with encouragement to practice at home on a regular basis and compact disc provided	Method of randomization and concealment of allocation stated. Investigator-blinded. Other IBS medications allowed.

Zernicke 2013 (47)	Canada	Secondary and tertiary care	Rome III, subtype not stated	Decrease of ≥50 points in the IBS-symptom severity score	90 (90)	One 90-minute session of mindfulness-based stress reduction per week for 8 weeks, plus a 3-hour morning workshop retreat between weeks 6 and 7	Method of randomization stated. Method of concealment of allocation not stated. Unblinded. Other IBS medications allowed.
Boltin 2015 (61)	Israel	Tertiary care	Rome III, 29.5% IBS-C, 47% IBS-D, 23.5% IBS-M	≥50% reduction in symptom score	34 (77)	One 3-hour session of psychotherapy with guided affective imagery per week for 8 weeks	Method of randomization and concealment of allocation stated. Investigator-blinded. Other IBS medications allowed.

Thakur 2017 (48)	USA	Primary, secondary, and tertiary care	Rome III, subtype not stated	≥50 point reduction in the IBS symptom severity score	106 (80)	Three 50-minute sessions of emotional awareness and expression training or relaxation therapy over 2 weeks.	Method of randomization and concealment of allocation stated. Unblinded. Other IBS medications allowed.

* Two separate studies reported in one paper