REVIEW

CME

Effect of Antidepressants and Psychological Therapies, Including Hypnotherapy, in Irritable Bowel Syndrome: Systematic Review and Meta-Analysis

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OBJECTIVES: **Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder. Evidence relating to the treatment of this condition with antidepressants and psychological therapies continues to accumulate.**

METHODS: **We performed an updated systematic review and meta-analysis of randomized controlled trials (RCTs). MEDLINE, EMBASE, and the Cochrane Controlled Trials Register were searched (up to December 2013). Trials recruiting adults with IBS, which compared antidepressants with placebo, or psychological therapies with 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 3,788 citations. Forty-eight RCTs were eligible for inclusion: thirty-one compared psychological therapies with control therapy or "usual management," sixteen compared antidepressants with placebo, and one compared both psychological therapy and antidepressants with placebo. Ten of the trials of psychological therapies, and four of the RCTs of antidepressants, had been published since our previous meta-analysis. The RR of IBS symptom not improving with antidepressants vs. placebo was 0.67 (95% CI = 0.58–0.77), with similar treatment effects for both tricyclic antidepressants and selective serotonin reuptake inhibitors. The RR of symptoms not improving with psychological therapies was 0.68 (95% CI = 0.61–0.76). Cognitive behavioral therapy, hypnotherapy, multicomponent psychological therapy, and dynamic psychotherapy were all beneficial.**

CONCLUSIONS: **Antidepressants and some psychological therapies are effective treatments for IBS. Despite the considerable number of studies published in the intervening 5 years since we last examined this issue, the overall summary estimates of treatment effect have remained remarkably stable.**

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INTRODUCTION

Irritable bowel syndrome (IBS) is one of the commonest functional gastrointestinal disorders worldwide, with a prevalence of between 5 and 20%, depending on the criteria used to define its presence (1). Although the condition is more common in women and in younger individuals, evidence for the effect of socioeconomic status on prevalence is conflicting (2). Patients with IBS take more sickness-related absences from work than those without bowel symptoms (3). A recent burden-of-illness study in the United States estimated that IBS cost almost $1 billion in direct costs and another $50 million in indirect costs (4). In addition, patients with IBS

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consume >50% more health-care resources than matched controls without IBS (5).

Effective treatment of IBS is therefore extremely important for the individual, health-care systems, and society as a whole. However, the cause of IBS remains obscure, meaning that there is no single unifying explanation for the symptoms toward which therapy can be targeted. Patients with IBS demonstrate visceral hypersensitivity to painful stimuli (6,7), abnormal central processing of pain (8), and higher levels of psychological comorbidity compared with healthy controls without IBS (9,10). As a result, antidepressants, which have pain-modifying properties (11,12), and psychological therapies have been proposed as potential treatments for IBS.

Despite the fact that the use of antidepressants in IBS is widespread (13), until recently the evidence for their efficacy was disputed, partly owing to the fact that previous systematic reviews and meta-analyses that had examined this issue had limitations (14). In addition, despite the fact that the use of psychological therapies is recommended for the management of IBS by previous guidelines (15,16), access to these interventions is limited in some countries, and there may also be a reluctance on the part of physicians to consider referral (17). In our previous systematic review and meta-analysis (18), conducted to inform the American College of Gastroenterology's monograph on the management of IBS (15), we summarized all available evidence for both antidepressants and psychological therapies up to 2009. However, in the intervening 5 years, there has been a considerable amount of evidence published. We have therefore re-examined this issue.

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

METHODS

Search strategy and study selection

We updated our previous systematic review and meta-analysis (18). A search of the medical literature was conducted using MEDLINE (1946 to December 2013), EMBASE, and EMBASE Classic (1947 to December 2013), and the Cochrane central register of controlled trials. Randomized controlled trials (RCT) 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**). The first period of crossover RCTs, before crossover to the second treatment, were also eligible for inclusion. In the case of antidepressant trials, the control arms were required to receive placebo, whereas 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 at least 7 days. The diagnosis of IBS could be based on either a physician's opinion or symptom-based diagnostic criteria, supplemented by the results of investigations to exclude organic disease, where the investigators deemed this necessary. Subjects were required to be followed up for at least 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 gastrointestinal 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 American College of Gastroenterology's monograph on the management of IBS. Specifically, studies on IBS were identified with the terms *irritable bowel syndrome* and *functional diseases, colon* (both as medical subject heading 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 following terms: *psychotropic drugs*, *antidepressive agents*, *antidepressive agents (tricyclic)*, *desipramine*, *imipramine*, *trimipramine*, *doxepin, dothiepin, nortriptyline*, *amitriptyline*, *selective serotonin reuptake inhibitors*, *paroxetine, sertraline, fluoxetine, citalopram, venlafaxine, cognitive therapy, psychotherapy, behavior therapy, relaxation techniques,* or *hypnosis* (both as medical subject heading terms and free text terms). The following free text terms were used: *behavioral therapy*, *relaxation therapy*, or *hypnotherapy*.

There were no language restrictions, and 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. Abstract books of conference proceedings between 2001 and 2013 were handsearched to identify potentially eligible studies published only in abstract form. The bibliographies of all identified relevant studies were used to perform a recursive search of the literature. Articles were independently assessed by two reviewers using predesigned eligibility forms, according to the prospectively defined eligibility criteria. Any disagreement between investigators was resolved by consensus.

REVIEW

Box 2. Data extraction methodology

Outcome of interest: Improvement in global IBS symptoms preferable; if this was not reported then improvement in abdominal pain.
Reporting of outcomes: Patient-reported was preferable; if this was not available then investigator-reported.
Time of assessment: Upon completion of therapy.
Denominator used: True intention-to-treat analysis; if this was not available then all evaluable patients.
Cutoff 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 was available then we used ≥1 s.d. 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).

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 after cessation of therapy. Secondary outcomes included assessing efficacy according to a specific type of antidepressant or psychological therapy, and adverse events occurring as a result of therapy.

Data extraction

All data were extracted independently by two reviewers on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA) 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. 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

This was performed independently by two investigators, with disagreements resolved by discussion. Risk of bias was assessed as described in the Cochrane handbook (19), by recording the method used to generate the randomization schedule and conceal allocation, whether blinding was implemented, 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 (20), to give a more conservative estimate of the effect of antidepressants and psychological therapies, allowing for any 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 (CIs). Adverse events data were also summarized with RRs. The number needed to treat (NNT) and the number needed to harm, with 95% CIs, were calculated from the reciprocal of the risk difference of the meta-analysis.

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 cutoff of ≥50%, and the χ^2 test with a P-value <0.10, used to define a significant degree of heterogeneity (21). Where the degree of statistical heterogeneity was greater than this between-trial results in this meta-analysis, possible explanations were investigated using subgroup analyses according to the type of antidepressant or psychological therapy used, trial setting, criteria used to define IBS, whether method of randomization or concealment of allocation were reported, level of blinding, risk of bias of included trials, and, for trials of psychological therapies, method of handling of the control arm. We compared individual RRs between these analyses using the Cochran Q statistic. These were exploratory analyses only, and they may explain some of the observed variability, but the results should be interpreted with caution.

Review Manager version 5.1.4 (RevMan for Windows 2008, the Nordic Cochrane Centre, Copenhagen, Denmark) and StatsDirect version 2.7.7 (StatsDirect, Cheshire, England) were used to generate Forest plots of pooled RRs and risk differences 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 (22), if there were sufficient (10 or more) eligible studies included in the meta-analysis, in line with recent recommendations (23).

RESULTS

The search strategy identified a total of 3,788 citations, of which 92 published articles appeared to be relevant and were retrieved for further assessment (**Figure 1**). Of these 92 articles, 46 were excluded for various reasons, leaving 46 eligible articles, 29 of which compared psychological therapies with control therapy in the form of symptom monitoring, physician's "usual management," or supportive therapy, 16 compared antidepressants with placebo, and one compared both psychological therapies and antidepressants with placebo. Agreement between reviewers for assessment of trial eligibility was excellent (kappa statistic = 0.93). Ten of the trials of psychological therapies, and four of the RCTs of antidepressants, had been published since our previous meta-analysis.

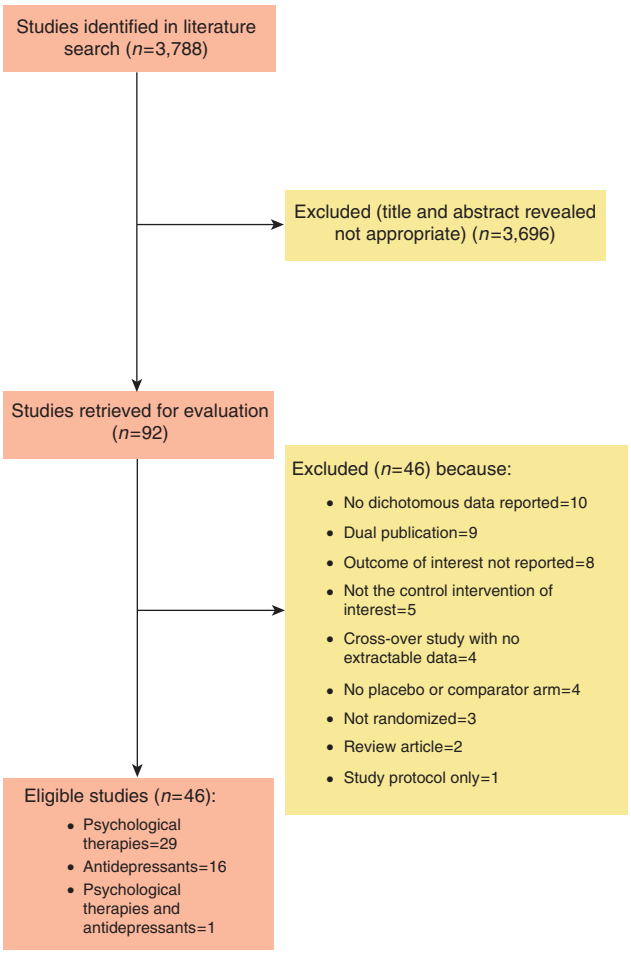

Figure 1. Flow diagram of assessment of studies identified in the updated systematic review and meta-analysis.

Efficacy of antidepressants in the treatment of IBS

In total, there were 17 RCTs comparing antidepressants with placebo in the treatment of IBS (24–40), which evaluated 1,084 patients, 592 of whom received active therapy and 492 received placebo. Ten trials used tricyclic antidepressants (TCAs) (24–26,28,29,34–38), six used selective serotonin reuptake inhibitor (SSRIs) (27,30,31,33,39,40), and one studied both (32). Only three of the RCTs were at a low risk of bias (36,38,39). 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 (27,30,31,33–35,39), one of which recruited only IBS-C patients (33) and another recruited only IBS-D patients (34). Detailed characteristics of individual RCTs are provided in **Table 1**.

Overall, 260 (43.9%) of 592 patients assigned to antidepressant therapy reported unimproved IBS symptoms following therapy, compared with 330 (65.0%) of 508 patients allocated to placebo. The RR of IBS symptoms not improving after treatment with antidepressant therapy vs. placebo was 0.67 (95% CI = 0.58–0.77), with marginally significant heterogeneity detected between studies ($I^2 = 37\%$, $P = 0.06$; **Figure 2**). There was statistically significant asymmetry in the funnel plot (Egger test, $P = 0.05$), suggesting publication bias or other small study effects; however, this was driven by the TCA arm of one small study (32) and disappeared with its exclusion from the analysis (Egger test, $P = 0.13$). The NNT with antidepressants was 4 (95% CI = 3–6).

Subgroup analyses were conducted (**Table 2**). Treatment effect appeared to be increased in secondary care-based studies, studies that did not state the method of generation of the randomization schedule or method of concealment of allocation, and studies at a high or unclear risk of bias. A statistically significant difference in treatment effect was detected for study setting and level of blinding only.

The effect of antidepressant therapy on abdominal pain was reported by seven RCTs (26,27,30,33–35,38), 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, and the RR of abdominal pain not improving was 0.62 (95% CI = 0.43–0.88), with considerable heterogeneity between studies ($I^2 = 72.4\%$, $P = 0.001$).

Efficacy of TCAs in the treatment of IBS. Eleven RCTs compared TCAs with placebo, including a total of 744 patients (24–26,28,29,32,34–38). Of 416 patients receiving active therapy, 180 (43.3%) had no improvement in symptoms after treatment, compared with 209 (63.7%) of 328 receiving placebo. The RR of IBS symptoms not improving with TCAs compared with placebo was 0.66 (95% CI = 0.56–0.79), with no statistically significant heterogeneity detected between studies ($I^2 = 35\%$, $P = 0.12$; **Figure 2**), and evidence of funnel plot asymmetry (Egger test, $P = 0.02$). Again, this was driven by one study (32), and when this was removed from the analysis there was no longer statistically significant publication bias (Egger test, $P = 0.06$). The NNT with TCAs was 4 (95% CI = 3–6).

Efficacy of SSRIs in the treatment of IBS. Seven trials compared SSRIs with placebo in a total of 356 patients (27,30–33,39,40). In all, 80 (45.5%) of 176 patients allocated to SSRIs had 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 = 0.51–0.91), but with statistically significant heterogeneity between studies ($I^2 = 49\%$, $P = 0.07$; **Figure 2**). The NNT with SSRIs was 4 (95% CI = 2.5–20).

Adverse events with antidepressant therapy

Only seven trials reported on overall adverse events with antidepressants vs. placebo (25–28,31,35,37). In total, 65 (31.3%) of 208 patients assigned to antidepressants experienced adverse events, compared with 33 (16.5%) of 200 patients 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 = 1.63; 95% CI = 1.18–2.25). The number needed to harm was 9 (95% CI = 5–111). There were no serious adverse events. Drowsiness and dry mouth were more

Table 1. Characteristics of randomized controlled trials of antidepressants vs. placebo in IBS

Study	Country	Setting	Diagnostic criteria used for IBS	Criteria used to define symptom improvement following therapy	Sample size (% female)	Antidepressant used	Duration of therapy	Methodology
Heefner (26)	USA	Tertiary care	Clinical diagnosis and investigations	Patient-reported improvement in abdominal pain	44 (Not reported)	Desipramine 150 mg o.d.	2 Months	Method of randomization and concealment of allocation not stated. Double-blind. Unclear if other IBS medications allowed
Myren (28)	Norway	Secondary care	Clinical diagnosis and investigations	Patient-reported improvement in global symptoms	61 (55)	Trimipramine 50 mg o.d.	4 Weeks	Method of randomization and concealment of allocation not stated. Double-blind. No other IBS medications allowed
Nigam (29)	India	Secondary care	Clinical diagnosis and investigations	Patient-reported improvement in global symptoms	42 (Not reported)	Amitriptyline 12.5 mg o.d.	12 Weeks	Method of randomization and concealment of allocation not stated. Double-blind. Unclear if other IBS medications allowed
Boerner (25)	Germany	Secondary care	Clinical diagnosis and investigations	Patient-reported improvement in global symptoms	83 (Not reported)	Doxepin 50 mg o.d.	8 Weeks	Method of randomization and concealment of allocation not stated. Double-blind. Unclear if other IBS medications allowed
Bergmann (24)	Germany	Secondary care	Clinical diagnosis and investigations	Patient-reported improvement in global symptoms	35 (87)	Trimipramine 50 mg o.d.	3 Months	Method of randomization and concealment of allocation not stated. Blinding not stated. No other IBS medications allowed
Vij (35)	India	Secondary care	Clinical diagnosis and investigations	Patient-reported improvement in global symptoms	50 (Not reported)	Doxepin 75 mg o.d.	6 Weeks	Method of randomization stated. Method of concealment of allocation not stated. Double-blind. Unclear if other IBS medications allowed
Drossman (36)	USA and Canada	Tertiary care	Rome I	≥Score of 28 on treatment satisfaction questionnaire	172 (100)	Desipramine 50 mg o.d. for 1 week, then 100 mg o.d. for 1 week, then 150 mg o.d. thereafter	12 Weeks	Method of randomization and concealment of allocation stated. Double-blind. Unclear if other IBS medications allowed
Kuiken (27)	Holland	Tertiary care	Rome I and investigations	Patient-reported improvement in global symptoms	40 (55)	Fluoxetine 20 mg o.d.	6 Weeks	Method of randomization and concealment of allocation stated. Double-blind. Unclear if other IBS medications allowed
Tabas (30)	USA	Tertiary care	Rome I	Patient-reported improvement in well-being	90 (74)	Paroxetine 10 mg, increasing to 20 mg then 40 mg if no improvement	12 Weeks	Method of randomization and concealment of allocation stated Double-blind. High fiber diet. Unclear if other IBS medications allowed
Vahedi (33)	Iran	Secondary care	Rome II and investigations	Patient-reported improvement in abdominal pain	44 (61)	Fluoxetine 20 mg o.d.	12 Weeks	Method of randomization stated. Method of concealment of allocation not stated. Double-blind. Unclear if other IBS medications allowed
Tack (31)	Belgium	Tertiary care	Rome II and investigations	Patient-reported 50% decrease in days with symptoms	23 (78)	Citalopram 20 mg o.d. for 3 weeks increasing to 40 mg o.d. for next 3 weeks	6 Weeks	Method of randomization and concealment of allocation stated. Double-blind. No other IBS medications allowed
Talley (32)	Australia	Tertiary care	Rome II and investigations	Patient-reported adequate relief of symptoms	51 (61)	Imipramine 50 mg o.d. or citalopram 40 mg o.d.	12 Weeks	Method of randomization and concealment of allocation stated. Double-blind. No other IBS medications allowed

Table 1 continued on following page

Table 1. Continued

Study	Country	Setting	Diagnostic criteria used for IBS	Criteria used to define symptom improvement following therapy	Sample size (% female)	Antidepressant used	Duration of therapy	Methodology
Vahedi (34)	Iran	Secondary care	Rome II and investigations	Patient-reported improvement in global symptoms	54 (44)	Amitriptyline 10 mg 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 (37)	Lebanon	Primary, secondary, and tertiary care	Rome II	Patient-reported relief of global symptoms	107 (42)	Impiramine 25 mg 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 (40)	USA	Tertiary care	Rome II and investigations	Patient-reported improvement in global symptoms	72 (88)	Paroxetine 12.5 mg o.d. increased to 50 mg o.d.	12 Weeks	Method of randomization and concealment of allocation not stated. Double-blind. No other IBS medications allowed
Ladabaum (39)	USA	Primary, secondary, and tertiary care	Rome II and investigations	Patient-reported adequate relief of global symptoms	54 (82)	Citalopram 20 mg o.d. for 4 weeks then 40 mg o.d. for 4 weeks	8 Weeks	Method of randomization and concealment of allocation stated. Double-blind. Fiber and loperamide allowed
Ghadir (38)	Iran	Secondary care	Rome III	Patient-reported improvement in abdominal pain	62 (Not reported)	Doxepin or nortiptyline 10 mg o.d.	2 Months	Method of randomization and concealment of allocation stated. Double-blind. Unclear if other IBS medications allowed

b.i.d., twice-daily; o.d., once-daily; IBS, irritable bowel syndrome.

common in patients randomized to TCAs than those receiving placebo.

Efficacy of psychological therapies in the treatment of IBS

There were a total of 30 articles, reporting on 32 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 2,189 patients (36,41–69). Six RCTs used cognitive behavioral therapy (CBT) (36,46,50,53,57,59); five trials used relaxation training or therapy (42,49,51,58,69); five RCTs, reported in four separate articles, used hypnotherapy (45,56,65,67); four trials, reported in three separate articles, used multicomponent psychological therapy (41,48,52); two RCTs used self-administered or minimal-contact CBT (54,68); two trials used Internet-delivered CBT (62,66); two RCTs used dynamic psychotherapy (44,47); one trial used mindfulness meditation training (61); one RCT used stress management (55); one trial used stress management or CBT (60); one RCT used CBT or self-administered CBT (64); one trial used multicomponent psychological therapy delivered in-person or mainly via the telephone (63); and one RCT used CBT or relaxation therapy (43).

The control arm received symptom monitoring in 16 RCTs, reported in 15 articles (41,42,45,46,49,51–54,57,59,60,62,64,66); usual care in 13 trials, reported in 12 articles (43,44,47,48,50,55,58,63,65,67–69); supportive therapy in 2 RCTs (56,61); and placebo in 1 trial (36). None of the trials were at a low risk of bias, owing 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 3**. Adverse events data were poorly reported by included RCTs, precluding any meaningful analysis.

Overall, IBS symptoms did not improve in 639 (51.9%) of 1,232 patients receiving psychological therapies, compared with 839 (76.1%) of 1,102 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 0.68 (95% CI = 0.61–0.76; **Figure 3**), with considerable heterogeneity detected between studies ($I^2 = 71\%$, $P < 0.001$), 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 (**Figure 4**). The NNT with psychological therapies was 4 (95% CI = 3–5).

Subgroup analyses were conducted (**Table 4**). Treatment effect appeared to be increased in tertiary care-based studies, RCTs that used clinical criteria to define IBS, studies that did not state the method of generation of the randomization schedule or method of concealment of allocation, unblinded studies, and studies that used waiting list control as the comparison. A statistically significant difference in treatment effect was detected for concealment of allocation and level of blinding only.

Efficacy of CBT in IBS. Nine trials compared CBT with control therapy in 610 patients (36,43,46,50,53,57,59,60,64). Symptoms

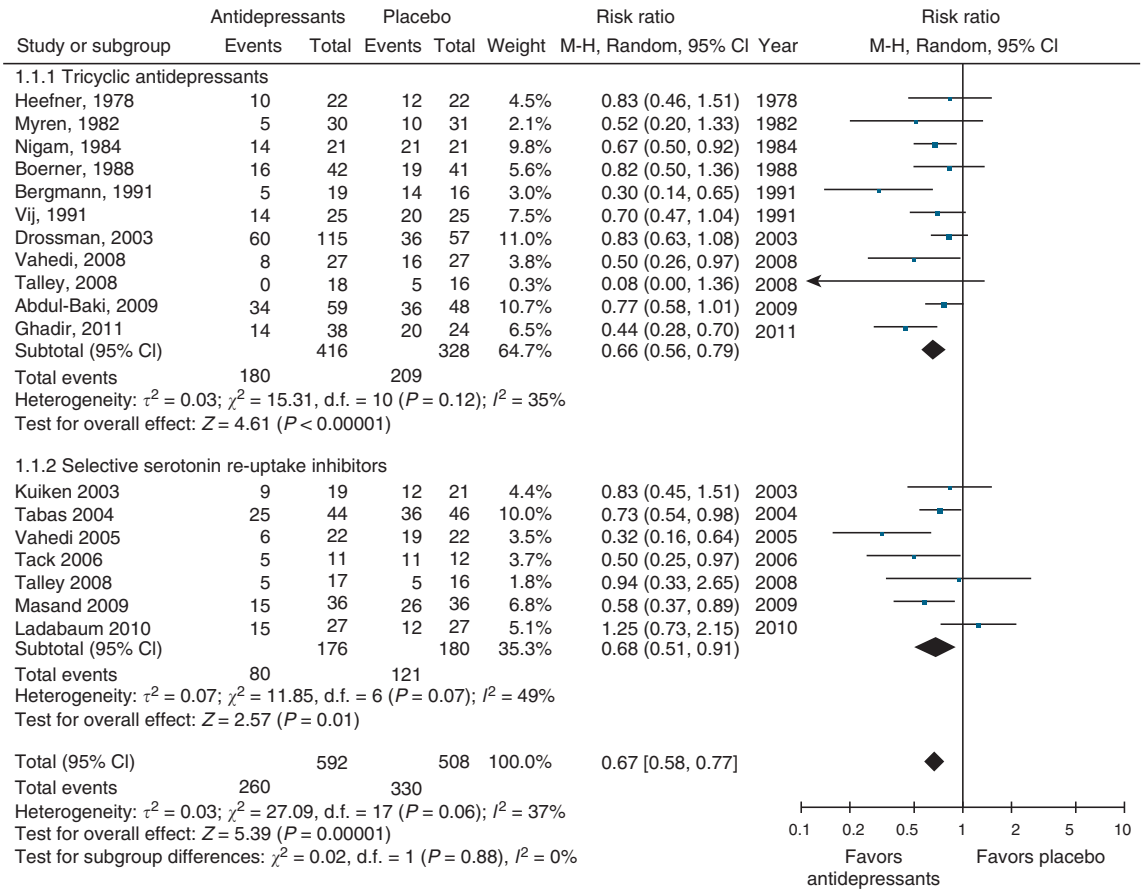

Figure 2. Forest plot of randomized controlled trials of antidepressants vs. placebo in irritable bowel syndrome.

of IBS did not improve in 145 (41.5%) of 349 patients assigned to CBT, compared with 166 (63.6%) of 261 patients allocated to control, with an RR of 0.60 (95% CI = 0.44–0.83; **Figure 3**), and statistically significant heterogeneity between studies ($I^2 = 70\%$, $P < 0.001$). The NNT with CBT was 3 (95% CI = 2–6).

Efficacy of relaxation training or therapy in IBS. Six RCTs compared relaxation training or therapy with control therapy in 255 patients (42,43,49,51,58,69). IBS symptoms did not improve in 96 (72.2%) of 133 patients randomized to relaxation training or therapy, compared with 107 (87.7%) of 122 patients receiving control therapy. Overall, no benefit of relaxation training or therapy in IBS was detected (RR of symptoms not improving = 0.77; 95% CI = 0.57–1.04; **Figure 3**), and there was statistically significant heterogeneity between studies ($I^2 = 71\%$, $P = 0.004$).

Efficacy of hypnotherapy in IBS. Five separate trials, reported in four articles (45,56,65,67), 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, and the RR of symptoms not improving was 0.74 (95% CI = 0.63–0.87; **Figure 3**), with no significant heterogeneity detected between studies ($I^2 = 0\%$, $P = 0.43$). The NNT with hypnotherapy was 4 (95% CI = 3–8).

Efficacy of multicomponent psychological therapy in IBS. Five separate RCTs, again reported in four articles (41,48,52,63), compared multicomponent psychological therapy with control therapy in 335 patients. Symptoms of IBS were not improved in 96 (57.1%) of 168 patients randomized to multicomponent psychological therapy, compared with 135 (80.8%) of 167 receiving control. The RR of IBS symptoms not improving was 0.72 (95% CI = 0.62–0.83; **Figure 3**), with no significant heterogeneity detected between studies ($I^2 = 0\%$, $P = 0.64$). The NNT with multicomponent psychological therapy was 4 (95% CI = 3–7).

Efficacy of self-administered or minimal-contact CBT in IBS. Three trials, involving 144 patients, used self-administered or minimal-contact CBT (54,64,68). 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 = 0.17–1.66), with significant heterogeneity detected between individual study results ($I^2 = 96\%$, $P < 0.001$).

Table 2. Subgroup analyses of randomized controlled trials of antidepressants vs. placebo in IBS

	Number of trials	Number of patients	Relative risk of IBS symptoms not improving (95% confidence interval)	*P* value for the difference	I^2 (*P* value)
Setting					
Secondary care	8	431	0.55 (0.43–0.70)	0.04	39% (0.12)
Tertiary care	8	508	0.74 (0.63–0.86)		0% (0.51)
Criteria used to define IBS					
Rome	12	785	0.66 (0.55–0.81)	0.92	48% (0.03)
Clinical diagnosis	6	315	0.67 (0.54–0.83)		12% (0.34)
Method of randomization					
Stated	11	740	0.69 (0.57–0.85)	0.53	48% (0.04)
Not stated	7	360	0.63 (0.51–0.77)		8% (0.37)
Concealment of allocation					
Stated	6	518	0.76 (0.61–0.94)	0.13	47% (0.09)
Not stated	12	582	0.61 (0.50–0.73)		23% (0.21)
Blinding					
Double	17	1,065	0.69 (0.60–0.79)	0.04	28% (0.38)
Not stated	1	35	0.30 (0.14–0.65)		NA
Risk of bias					
Low	3	288	0.76 (0.46–1.27)	0.60	78% (0.01)
Unclear or high	15	812	0.66 (0.57–0.76)		18% (0.26)

IBS, irritable bowel syndrome; NA, not applicable.

Efficacy of CBT delivered via the Internet in IBS. There were two trials that delivered CBT via the Internet, containing 140 patients (62,66). 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 = 0.48–1.17), with significant heterogeneity between the two RCTs ($I^2 = 90\%$, $P = 0.002$).

Efficacy of dynamic psychotherapy in IBS. Two RCTs compared dynamic psychotherapy with control therapy in 273 patients (44,47). No improvement in IBS symptoms was reported by 61 (44.2%) of 138 patients randomized to dynamic psychotherapy, compared with 95 (70.4%) of 135 patients receiving control; the RR of symptoms not improving was 0.60 (95% CI = 0.39–0.93; **Figure 3**), and the NNT was 3.5 (95% CI = 2–25). Again there was significant heterogeneity between studies ($I^2 = 72\%$, $P = 0.06$).

Efficacy of stress management in IBS. There were two trials using this therapy (55,60), involving 98 patients. Overall, 24 (40.7%) of 59 patients assigned to stress management reported no improvement in IBS symptoms, compared with 23 (59.0%) of 39 allocated to control. There was no beneficial effect detected for stress management in IBS (RR = 0.63; 95% CI = 0.19–2.08), and there was significant heterogeneity between studies ($I^2 = 83\%$, $P = 0.02$).

Efficacy of multicomponent psychological therapy mainly via the telephone or mindfulness meditation training in IBS. There was only one study that used each of these treatment modalities (61,63). Multicomponent psychological therapy mainly via the telephone appeared to be beneficial in IBS (RR of symptoms not improving = 0.78; 95% CI = 0.64–0.93) (63), but there was no benefit with mindfulness meditation training (RR = 0.57; 95% CI = 0.32–1.01) (61).

DISCUSSION

This updated systematic review and meta-analysis has demonstrated that antidepressants and psychological therapies are effective treatments for IBS. The NNT for both TCAs and SSRIs was 4, although in the latter instance there was significant heterogeneity between studies and widening of the 95% CI of effect. Adverse events were significantly higher among those taking antidepressants, with a number needed to harm of 9. When all psychological therapies, including hypnotherapy, were considered the NNT was again 4. Cognitive behavioral therapy, hypnotherapy,

Table 3. Characteristics of randomized controlled trials of psychological therapies vs. control in IBS

Study	Country	Setting	Diagnostic criteria used for IBS	Criteria used to define symptom improvement following therapy	Sample size	Psychological therapy used	Methodology
Neff (52)	USA	Tertiary care	Clinical diagnosis	≥50% Reduction in baseline symptom score	19 (79)	Multicomponent psychological therapy consisting of two 1-h 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 (51)	Canada	Tertiary care	Clinical diagnosis	≥50% Reduction in diary rating of symptoms	21 (67)	One 2-h 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 (47)	England	Tertiary care	Clinical diagnosis and investigations	Patient-reported improvement in global symptoms	102 (75)	One 2-h 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 (55)	Wales	Tertiary care	Clinical diagnosis and investigations	Patient-reported overall benefit from treatment	35 (57)	One 40-min 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 (41)	USA	Tertiary care	Clinical diagnosis and investigations	≥50% Reduction in baseline symptom score	20 (85) and 77 (66)[a]	Multicomponent psychological therapy consisting of two 1-h 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 (42)	USA	Tertiary care	Clinical diagnosis and investigations	≥ 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 min per day)	Method of randomization and concealment of allocation not stated. Unblinded. Other IBS medications "discouraged"
Greene (46)	USA	Tertiary care	Clinical diagnosis and investigations	≥50% Reduction in baseline symptom score	20 (75)	Two 1-h 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 (53)	USA	Tertiary care	Rome I and investigations	≥50% Reduction in baseline symptom score	22 (82)	Two 1-h 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
Galovski (45)	USA	Tertiary care	Clinical diagnosis	≥50% Reduction in baseline symptom score	12 (83)	One 30-min to 1-h 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 (59)	USA	Tertiary care	Rome I and investigations	≥50% Reduction in baseline symptom score	34 (76)	One 1-h session of individual CBT per week for 10 weeks, or one 90-min 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

Table 3 continued on following page

Table 3. Continued

Study	Country	Setting	Diagnostic criteria used for IBS	Criteria used to define symptom improvement following therapy	Sample size	Psychological therapy used	Methodology
Keefer (49)	USA	Tertiary care	Clinical diagnosis	≥50% Reduction in baseline symptom score	15 (Not reported)	One 30-min 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 (43)	Australia	Tertiary care	Rome I and investigations	≥1 Standard deviation decrease in baseline symptom score	105 (81)	One 1-h CBT session per week for 8 weeks, or one 30-min relaxation therapy session per week for 8 weeks	Method of randomization and concealment of allocation stated. Investigator blinded. No other IBS medications allowed
Creed (44)	England	Tertiary care	Rome I	Patient-reported improvement in global symptoms	171 (79)	One 2-h and seven 45-min psychodynamic interpersonal therapy sessions over 3 months	Method of randomization and concealment of allocation stated. Investigator blinded. Unclear if other IBS medications allowed
Drossman (36)	USA and Canada	Tertiary care	Rome I	≥Score of 28 on treatment satisfaction questionnaire	169 (100)	One 1-h CBT session per week for 12 weeks	Method of randomization and concealment of allocation stated. Investigator blinded. Unclear if other IBS medications allowed
Tkachuk (57)	Canada	Tertiary care	Rome I and investigations	Patient-reported improvement in global symptoms	28 (96)	Two 90-min 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 (48)	USA	Tertiary care	Rome I	≥50% Reduction in symptom score	95 (100)	One 1-h weekly multicomponent psychological therapy session per week for 8 weeks	Method of randomization and concealment of allocation not stated. Unblinded. Other IBS medications allowed
Simren (56)	Sweden	Tertiary care	Rome II and investigations	Patient-reported improvement in global symptoms	28 (68)	One 1-h 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 (50)	England	Primary care	Clinical diagnosis	Improvement in symptom severity banding by one band (graded severe to none on a four-point Likert-scale)	149 (not reported)	One 50-min 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 (54)	USA	Tertiary care	Rome II and investigations	≥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 (58)	Holland	Tertiary care	Rome II	Reliable change index ≥1.96 (pre-therapy score minus post-therapy score divided by standard error of the difference)	105 (Not reported)	One 90-min 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

Table 3 continued on following page

Table 3. Continued

Study	Country	Setting	Diagnostic criteria used for IBS	Criteria used to define symptom improvement following therapy	Sample size	Psychological therapy used	Methodology
Lackner (64)	USA	Primary, secondary, and tertiary care	Rome II	Patient-reported adequate relief of global symptoms	75 (87)	One 1-h CBT session per week for 10 weeks, or one 1-h 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 (62)	USA	Not reported	Clinical diagnosis	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 (63)	USA	Not reported	Rome II	≥50% Reduction in baseline symptom score	188 (86)	One 1-h multicomponent psychological therapy session per week delivered in-person for 9 weeks, or one 1-h 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 (66)	Sweden	Not reported	Rome III	≥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 (68)	New Zealand	Primary care	Rome I or Rome II	Patient-reported adequate relief of global symptoms	64 (72)	A self-administered CBT program divided into seven chapters and completed over 7–8 weeks	Method of randomization and concealment of allocation stated. Unblinded. Unclear if other IBS medications allowed
Shinozaki (69)	Japan	Tertiary care	Rome II and investigations	Patient-reported adequate relief of global symptoms	21 (52)	One 30- to 40-min 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 (60)	USA	Primary and tertiary care	Rome II	≥50% Reduction in baseline symptom score	110 (Not reported)	One 50-min CBT or stress management session per week for 10 weeks	Method of randomization and concealment of allocation stated. Unblinded. Other IBS medications allowed
Gaylord (61)	USA	Not reported	Rome II	≥50 Point reduction in the IBS symptom severity score	75 (100)	One 2-h 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 (65)	Sweden	Secondary or tertiary care	Rome II and investigations	≥25% Reduction of total score on the GI symptom questionnaire	48 (81) and 90 (79)[a]	One 1-h 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 (67)	Austria	Primary and tertiary care	Rome III	Patient-reported adequate relief of global symptoms	90 (79)	Ten 45-min 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

CBT, cognitive behavioral therapy; IBS, irritable bowel syndrome.
[a]Two separate studies reported in one paper.

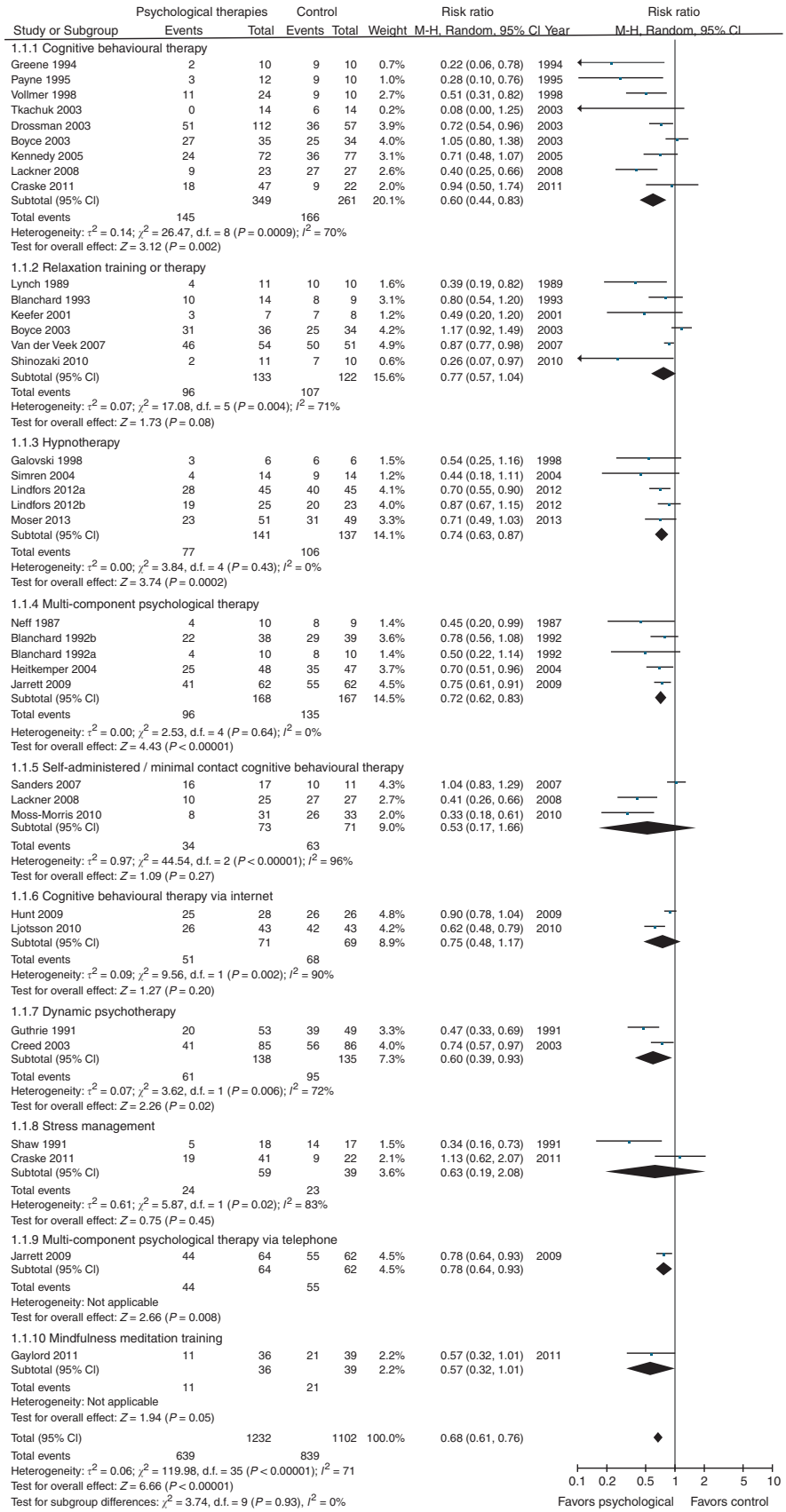

Figure 3. Forest plot of randomized controlled trials of psychological therapies vs. control in irritable bowel syndrome.

multicomponent psychological therapy, either in person or mainly via the telephone, and dynamic psychotherapy were all more effective than control therapy, with NNTs of between 3 and 4, and there was a trend toward a benefit of mindfulness meditation training. Although relaxation training, stress management, self-administered or minimal-contact CBT, and CBT delivered via the Internet were of no benefit, 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. Adverse events data were poorly reported among trials of psychological therapies. The assumption that the administration of psychological therapies is without the potential for adverse events is probably unrealistic. In the future, RCTs should report these data more completely.

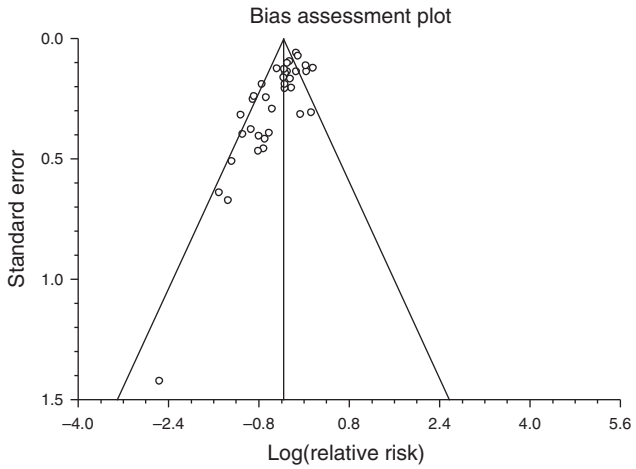

Figure 4. Funnel plot of randomized controlled trials of psychological therapies vs. control in irritable bowel syndrome.

A strength of this systematic review and meta-analysis is our use of rigorous methodology. We reported our search strategy, which included searching the "gray" literature, and assessment of eligibility and data extraction was performed independently by two reviewers. We also 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 gastrointestinal disorders from the analysis. This inclusive approach has provided us with access to data for >1,000 IBS patients treated with antidepressants vs. placebo, and >2,100 patients randomized to psychological therapies vs. control. We also performed subgroup analyses to explore the reasons for heterogeneity between studies, and to assess treatment effect according to individual therapy used, study setting, criteria used to define IBS, and

Table 4. Subgroup analyses of randomized controlled trials of psychological therapies vs. control in IBS

	Number of trials	Number of patients	Relative risk of IBS symptoms not improving (95% confidence interval)	*P* value for the difference	I^2 (*P* value)
Setting					
Tertiary care	22	1,103	0.65 (0.55–0.78)	0.53	75% (<0.001)
Other	14	1,231	0.70 (0.60–0.81)		65% (<0.001)
Criteria used to define IBS					
Rome	24	1,787	0.72 (0.63–0.81)	0.16	72% (<0.001)
Clinical diagnosis	12	547	0.58 (0.44–0.76)		73% (<0.001)
Method of randomization					
Stated	18	1,411	0.75 (0.65–0.87)	0.06	74% (<0.001)
Not stated	18	923	0.60 (0.50–0.71)		67% (<0.001)
Concealment of allocation					
Stated	12	1,104	0.80 (0.70–0.93)	0.007	67% (<0.001)
Not stated	24	1,230	0.59 (0.50 to 0.70)		73% (<0.001)
Blinding					
Investigator	6	654	0.83 (0.67–1.04)	0.05	68% (0.008)
Unblinded	30	1,680	0.64 (0.56–0.73)		73% (<0.001)
Handling of control arm					
Waiting list control	18	693	0.61 (0.49–0.76)	0.17	76% (<0.001)
Usual management/supportive	17	1,472	0.73 (0.63–0.83)		71% (<0.001)

IBS, irritable bowel syndrome.

study methodology and design. Finally, we extracted and pooled adverse events data, where reported.

There are limitations to this systematic review and meta-analysis, which arise from the nature of the studies available for synthesis. There were very few trials at a low risk of bias, and there was evidence of heterogeneity between RCTs in many of our analyses, although not for TCAs, hypnotherapy, or multicomponent psychological therapy. In addition, the difference in favor of antidepressants was no longer statistically significant when trials at high or unclear risk of bias were excluded from the analysis, although there were only three studies at a low risk of bias, containing 288 patients. There was 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. Subgroup analyses demonstrated that treatment effect was generally lower in studies that reported the method of generation of the randomization schedule and concealment of allocation, which is in line with reports from the systematic review literature in general (70). These issues may mean that the true treatment effect of both antidepressants and psychological therapies has been overestimated.

Our previous meta-analysis examining this issue demonstrated similar findings, in terms of the efficacy of both antidepressants and psychological therapies (18). Despite the addition of 4 trials of antidepressants (37–40), and 10 studies of psychological therapies (60–69), since its publication, the overall estimates of the efficacy of these treatments remain almost identical. However, more trials of antidepressants now report adverse events than previously, and these were significantly more common with active therapy than with placebo, which was not the case previously. In addition, there was a significant effect of antidepressant therapy on abdominal pain, an outcome that was reported by more RCTs in this updated meta-analysis (26,27,30,33–35,38).

It remains unclear whether antidepressants or psychological therapies are effective for the treatment of IBS in primary care, with only two of the RCTs we identified conducted entirely within this setting (50,68). The efficacy of these therapies according to predominant stool pattern reported by the patient has also not been well studied. TCAs have been shown to prolong orocecal and whole gut transit times, whereas SSRIs decreases orocecal transit time (71). 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 this has only been assessed in two studies to date (33,34).

In addition, whether the benefit of antidepressants arises from the treatment of coexistent depression is controversial (72). Three studies reported that there was no significant relationship between depression scores and improvement in IBS symptoms (30,31,35), and one RCT showed that treatment effect with desipramine was greater in those without evidence of coexistent depression (36). Overall, in our meta-analysis, there appeared to be a benefit of antidepressants in IBS, but there was significant heterogeneity between studies of SSRIs. However, in one RCT of citalopram, the authors screened for and excluded depressed individuals from the study, and in this trial there was no benefit of active therapy over placebo (39), leading to the conclusion that there was only weak evidence that citalopram was superior to placebo in achieving response in nondepressed patients with IBS. For SSRIs, this theory is plausible, as the doses used in treatment trials for IBS are very similar to those used to treat depression; however, this would seem less likely for TCAs, where the doses used are considerably lower than the therapeutic range considered as effective for the treatment of mood disorders.

There remains, therefore, a clear need for larger trials of both antidepressants and psychological therapies, perhaps in combination, that use rigorous methodology, are conducted among IBS patients in primary care, recruit patients based on predominant stool pattern, either exclude depressed or anxious individuals, or stratify for co-existent depression, anxiety, and other co-morbidities, and which use outcome measures in accordance with recommendations for the design of treatment trials for the functional gastrointestinal disorders from the Rome committee (73), or Food and Drug Administration-approved end points. It would also be insightful to understand more about the exact mechanisms by which these therapies have their beneficial effects in IBS. Functional magnetic resonance imaging studies have demonstrated that hypnotherapy appears to lead to normalization of abnormal central pain processing (74), and that amitriptyline reduces brain activation during painful rectal distension (75), but there are a few other studies that advance our understanding of how antidepressants and other psychological therapies may improve the symptoms of IBS patients.

In summary, this updated systematic review and meta-analysis has demonstrated that TCAs, SSRIs, CBT, hypnotherapy, multicomponent psychological therapy, either in person or mainly via the telephone, and dynamic psychotherapy are all effective treatments for IBS. Despite the considerable number of studies published in the intervening 5 years since we last examined this issue, the overall summary estimates of treatment effect have remained almost identical. The finding that antidepressants, as well as many of the psychological therapies we studied, are beneficial in IBS has implications for the management of a condition that clinicians often find challenging, and should encourage increased use of antidepressants by gastroenterologists and promote efforts to improve access for both patients and physicians to psychological therapies.

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CONFLICTS OF INTEREST

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Specific author contributions: A.C.F., E.M.M.Q., B.E.L., A.J.L., Y.A.S., L.R.S., E.E.S., B.M.R.S., and P.M. conceived the study. A.C.F. and P.M. collected all data, analyzed and interpreted the data. A.C.F. 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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REVIEW

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