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Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome (Review)

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[Intervention Review]

Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome

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ABSTRACT

Background

Irritable bowel syndrome (IBS) is a common chronic gastrointestinal disorder. The role of pharmacotherapy for IBS is limited and focused mainly on symptom control.

Objectives

The objective of this systematic review was to evaluate the efficacy of bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome.

Search methods

Computer assisted structured searches of MEDLINE, EMBASE, The Cochrane library, CINAHL and PsychInfo were conducted for the years 1966-2009. An updated search in April 2011 identified 10 studies which will be considered for inclusion in a future update of this review.

Selection criteria

Randomized controlled trials comparing bulking agents, antispasmodics or antidepressants with a placebo treatment in patients with irritable bowel syndrome aged over 12 years were considered for inclusion. Only studies published as full papers were included. Studies were not excluded on the basis of language. The primary outcome had to include improvement of abdominal pain, global assessment or symptom score.

Data collection and analysis

Two authors independently extracted data from the selected studies. Risk Ratios (RR) and Standardized Mean Differences (SMD) with 95% confidence intervals (CI) were calculated. A proof of practice analysis was conducted including sub-group analyses for different types of bulking agents, spasmolytic agents or antidepressant medication. This was followed by a proof of principle analysis where only the studies with adequate allocation concealment were included.

Main results

A total of 56 studies (3725 patients) were included in this review. These included 12 studies of bulking agents (621 patients), 29 of antispasmodics (2333 patients), and 15 of antidepressants (922 patients). The risk of bias was low for most items. However, selection bias

is unclear for many of the included studies because the methods used for randomization and allocation concealment were not described. No beneficial effect for bulking agents over placebo was found for improvement of abdominal pain (4 studies; 186 patients; SMD 0.03; 95% CI -0.34 to 0.40; P = 0.87), global assessment (11 studies; 565 patients; RR 1.10; 95% CI 0.91 to 1.33; P = 0.32) or symptom score (3 studies; 126 patients SMD -0.00; 95% CI -0.43 to 0.43; P = 1.00). Subgroup analyses for insoluble and soluble fibres also showed no statistically significant benefit. Separate analysis of the studies with adequate concealment of allocation did not change these results. There was a beneficial effect for antispasmodics over placebo for improvement of abdominal pain (58% of antispasmodic patients improved compared to 46% of placebo; 13 studies; 1392 patients; RR 1.32; 95% CI 1.12 to 1.55; P < 0.001; NNT = 7), global assessment (57% of antispasmodic patients improved compared to 39% of placebo; 22 studies; 1983 patients; RR 1.49; 95% CI 1.25 to 1.77; P < 0.0001; NNT = 5) and symptom score (37% of antispasmodic patients improved compared to 22% of placebo; 4 studies; 586 patients; RR 1.86; 95% CI 1.26 to 2.76; P < 0.01; NNT = 3). Subgroup analyses for different types of antispasmodics found statistically significant benefits for cimteropium/ dicyclomine, peppermint oil, pinaverium and trimebutine. Separate analysis of the studies with adequate allocation concealment found a significant benefit for improvement of abdominal pain. There was a beneficial effect for antidepressants over placebo for improvement of abdominal pain (54% of antidepressants patients improved compared to 37% of placebo; 8 studies; 517 patients; RR 1.49; 95% CI 1.05 to 2.12; P = 0.03; NNT = 5), global assessment (59% of antidepressants patients improved compared to 39% of placebo; 11 studies; 750 patients; RR 1.57; 95% CI 1.23 to 2.00; P < 0.001; NNT = 4) and symptom score (53% of antidepressants patients improved compared to 26% of placebo; 3 studies; 159 patients; RR 1.99; 95% CI 1.32 to 2.99; P = 0.001; NNT = 4). Subgroup analyses showed a statistically significant benefit for selective serotonin releasing inhibitors (SSRIs) for improvement of global assessment and for tricyclic antidepressants (TCAs) for improvement of abdominal pain and symptom score. Separate analysis of studies with adequate allocation concealment found a significant benefit for improvement of symptom score and global assessment. Adverse events were not assessed as an outcome in this review.

Authors' conclusions

There is no evidence that bulking agents are effective for treating IBS. There is evidence that antispasmodics are effective for the treatment of IBS. The individual subgroups which are effective include: cimetropium/dicyclomine, peppermint oil, pinaverium and trimebutine. There is good evidence that antidepressants are effective for the treatment of IBS. The subgroup analyses for SSRIs and TCAs are unequivocal and their effectiveness may depend on the individual patient. Future research should use rigorous methodology and valid outcome measures.

PLAIN LANGUAGE SUMMARY

Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome

This review evaluates the effectiveness of medical therapies for patients with irritable bowel syndrome (IBS). We considered studies involving bulking agents (a fibre supplement), antispasmodics (smooth muscle relaxants) or antidepressants (drugs used to treat depression that can also change pain perceptions) that used outcome measures including improvement of abdominal pain, global assessment (overall relief of IBS symptoms) or symptom score. We found that bulking agents are not effective for treating IBS. There is evidence that antispasmodics including cimetropium/dicyclomine peppermint oil, pinaverium and trimebutine are effective for the treatment of IBS. Antidepressants are effective for the treatment of IBS. The side effects of these medications were not evaluated in this review. Physicians should be aware of the limitations of drug therapies and discuss these limitations with their patients before prescribing medication for IBS.

BACKGROUND

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder characterized by fluctuating complains of abdominal pain or discomfort and an altered bowel habit resulting in diarrhoea or constipation. The prevalence of IBS ranges from 5-18 % depending on the clinical setting and the diagnostic criteria that are used. IBS is slightly more common in females (Hungin 2003; Hillila 2004). IBS is associated with depressive and anxiety disorders as well with somatic co-morbidities including fibromyalgia, chronic fatigue syndrome and chronic pelvic pain (Riedl 2008).

Research shows that IBS can result in impaired health-related quality of life and that IBS symptoms have a large impact on work productivity (Pare 2006; Creed 2001). IBS is also associated with increased health care utilization and costs (Longstreth 2003).

In the absence of a gold-standard for diagnosing IBS, classification models have been developed including the Kruis scoring system, Manning criteria and Rome I, II, and III criteria (Manning 1978; Drossman 2006). Only the Rome I classification is validated (Ford 2010). These criteria are not widely used in clinical practice and the diagnosis of IBS is often made by a typical history, normal physical examination and the absence of alarm-symptoms such as gastrointestinal bleeding, weight loss, or an abdominal mass (Jones 2000a).

The pathophysiology of IBS is still unclear. There are several putative mechanisms including visceral hypersensitivity, altered colonic motility, abnormal brain activation, serotine dysregulation, inflammation, abnormal colonic flora, stress, psychological factors and genetic factors (Talley 2006).

In the absence of a clear pathophysiology, explanation and reassurance are essential elements in the management of IBS (Jones 2000b). Pharmacotherapeutic interventions are limited and focus mostly on symptom control. High fibres diets and bulking agents are traditionally advised for their effect on stools and transit time (Burkitt 1972). Antispasmodics are given for their supposed effect on gastrointestinal motility. The more recent therapeutic options include the use of antidepressants, which are also given for other diseases associated with chronic pain (Verdu 2008).

OBJECTIVES

The objective of this systematic review was to evaluate the efficacy of bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials comparing bulking agents, antispasmodics or antidepressants with a placebo were considered for inclusion. Cross-over studies were eligible if data from the first phase were reported separately. Only studies published as a full paper were included. Studies were not excluded on the basis of language.

Types of participants

Patients aged over 12 years with irritable bowel syndrome, diagnosed either using predefined diagnostic criteria (e.g. Manning or Rome) or on clinical grounds were considered for inclusion. Studies including patients with functional bowel disorders without separate data for IBS patients were also included if the proportion of IBS patients was more than 75% of the total included patients.

Types of interventions

Interventions including bulking agents, antispasmodics or antidepressants compared with a placebo treatment were considered for inclusion.

Types of outcome measures

Outcome measures for clinical trials of interventions in IBS have been discussed in several studies (Irvine 2006; Schoenfeld 2006). Primary outcome measures included:

- Improvement of symptoms of abdominal pain;
- Improvement of patients overall global assessment; and
- Improvement of IBS-symptom score.

Subgroup analyses included:

- Soluble and insoluble bulking agents;
- Individual antispasmodics; and
- Selective serotonin releasing inhibitors (SSRIs) and tricyclic antidepressants (TCAs).

A sensitivity analysis excluded studies with poor methodological quality.

Search methods for identification of studies

Electronic searches

Computer assisted structured searches of MEDLINE, EMBASE, The Cochrane Library, CINAHL and PsychInfo were conducted, searching entries from 1966 to March 2009. The following search strategies were used:

Title/abstract search: spastic colon, irritable colon, irritable bowel, functional bowel, colonic disease, colonic diseases, IBS, gastrointestinal syndrome, gastrointestinal syndromes

Combined with title/abstract search: bulking agent, bulking agents, fiber, fibers, fibre, fibres, psyllium, plantago ovata, husk, bran, ispaghula, wheat, oat, sterculia, karaya gum

Or combined with title/abstract search: antispasmodic, antispasmodics, parasympatholytic, parasympatholytics. spasmolytic , spasmolytics, mebeverine, rociverine, pinaverium bromide, otilonium bromide, cimetropium bromide, trimebutine, pirenzipine, alverine, scopolamine, butylscopolamine, hyoscine , muscarinic antagonist, peppermint oil, mint oil

Or combined with title/abstract search: antidepressant, antidepressants, antidepressive agent, antidepressive agents, tricyclic, TCA, TCAs, selective serotonin reuptake inhibitor, selective serotonin reuptake inhibitors, SSRI, SSRIs

No limits or filters were used.

An updated search in April 2011 identified 10 studies which will be considered for inclusion in a future update of this review (See Characteristics of studies awaiting classification).

Searching other resources

The reference lists of the retrieved articles and reviews were hand searched to identify additional studies.

Data collection and analysis

Selection of studies

One author (LR) screened the title and abstract of all studies identified by the literature searches for eligibility . The full text articles were retrieved for all potentially eligible studies. The full text articles were screened according to predefined criteria by the same reviewer. All the doubtful articles were screened by a second reviewer (AOQ) and consensus on inclusions/ exclusion was achieved by discussion.

The predefined exclusion criteria included:

1. Not a randomised controlled trial
2. No placebo group
3. Inappropriate patient group
4. Patients younger than 12, diagnosis of functional bowel disorders not specified as IBS
5. Intervention not involving bulking agent, antispasmodic or antidepressant or mixed preparations
6. An outcome measurement other than abdominal pain, global assessment or IBS-symptom score.
7. No extractable results or cross-over trial with no report of first phase data
8. Duplicate trials

Data extraction and management

All studies were blinded for the reviewers in respect of authors, date of publication and journal or database of publication. Data were extracted independently by two authors for each study. A standardized data extraction form was used. Where necessary data were extracted from figures. If essential data were absent, the author of the article was contacted and requested to provide additional information.

Assessment of risk of bias in included studies

The methodological quality of included trials was independently assessed by two authors (AOQ and LR or NdW or GR).

Quality assessment criteria included: method of randomisation, concealment of allocation, blinding of patients and outcome measurers and description of lost to follow-up.

Differences of opinion were resolved by discussion between two reviewers, and in case of disagreement by all the reviewers. A methodology expert (GvdH) was consulted for specific queries

In consultation with the Dutch Cochrane centre, concealment of allocation was used for additional analyses, since concealment of allocation is the only quality item that has proven to be associated with study outcome (Pidal 2007, Wood 2008).

Measures of treatment effect

The analyses were conducted using RevMan 5.0 software. For the dichotomous outcomes the risk ratio (RR) with 95% confidence intervals were calculated. For the continuous data standardized mean difference (SMD) with 95% confidence intervals were calculated.

A fixed- or random-effects model was used, based on the heterogeneity between study data. Statistical heterogeneity was explored with the Chi square test with significance set at P <0.10. When statistically significant heterogeneity occurred, a random-effects model was used for the analyses.

There were differences in the direction of the scales for the continuous data. To correct for this the data from scales increasing with disease severity were multiplied by -1.

First, a proof of practice analysis was conducted, including all available data. This was followed by a proof of principle analysis where only the studies with adequate allocation concealment were included.

RESULTS

Description of studies

Bulking agents

The search identified 1118 studies, of which, after screening title and abstract 72 were potentially eligible. After applying the exclusion criteria to the full-text publications of these 72 potentially eligible studies, 12 articles remained for review and meta-analysis.

Sixty articles were excluded (table of characteristics of excluded studies), of which twenty-six were not randomized controlled trials (exc1). Fourteen studies did not involve a placebo treatment (exc2). Four studies included patients with functional bowel disorders without providing extractable results for the patients with IBS (exc3 and exc4). Two studies involved an intervention with a mixed preparation (exc5). Two studies did not report the outcome of interest (exc6). Eleven studies were cross-over trials with no report of the first phase data or did not provide extractable results (exc7). One study was a duplicate publication (exc8).

Twelve papers remained for review and meta-analysis (Table of characteristics of included studies). Two studies had a cross-over design (Jalihal 1990; Lucey 1987). The studies were published between 1976 and 2005 (Soltoft 1976; Rees 2005). The research setting was a GI out patients' clinic in 11 studies, in the other three the setting was unclear (Arthurs 1983; Longstreth 1981; Soltoft 1976). Seven studies used a run-in period of 1 to 4 weeks before beginning the actual trial (Fowlie 1992; Longstreth 1981; Prior 1987; Rees 2005; Soltoft 1976). The studies included between 20 and 168 participants (Jalihal 1990; Nigam 1984). The mean age of the participants ranged from 28 years to 46 years (Arthurs 1983; Aller 2004). The percentage of female participants included ranged from 20% to 83% (Jalihal 1990; Longstreth 1981). Six studies used insoluble fibres as intervention (Aller 2004; Fowlie 1992; Kruis 1986; Lucey 1987; Rees 2005; Soltoft 1976) and six studies used soluble fibres as intervention (Arthurs 1983; Jalihal 1990; Longstreth 1981; Nigam 1984; Prior 1987; Ritchie 1979). The intervention period lasted from 4 weeks (Ritchie 1979) to 16 weeks (Kruis 1986).

Antispasmodics

The search identified 444 studies, of which, after screening title and abstract, 144 were potentially eligible. After applying the exclusion criteria to the full-text publications of these 144 potentially eligible studies, 29 articles remained for review and meta-analysis.

One hundred and fifteen articles were excluded (table of characteristics of excluded studies). Thirty-eight were not randomised controlled trials (exc1). Thirty four studies did not involve a placebo treatment (exc2). Six studies included patients with functional bowel disorders without providing extractable results for the patients with IBS (exc3 and exc4). Three studies involved an intervention with a mixed preparation (exc5). Twelve studies did not report the outcome of interest (exc6). Nineteen studies had no extractable results or were cross-over trials with no report of the first phase data (exc7). Three were duplicate publications (exc8) (Baldi 1992; Glende 2002; Koch 1998).

Twenty-nine papers remained review and meta-analysis (Table of characteristics of included studies; Awad 1995; Baldi 1991; Battaglia 1998; Capanni 2005; Cappello 2007; Centonze 1988; Chen 2004; Czalbert 1990; d'Arienzo 1980; Delmont 1981; Dobrilla 1990; Dubarry 1977; Fielding 1980; Ghidini 1986; Gilvarry 1989; Kruis 1986; Lech 1988; Levy 1977; Liu 1997; Mitchell 2002; Moshal 1979; Nigam 1984; Page 1981; Passaretti 1989a; Piai 1979; Pulpeiro 2000; Ritchie 1979; Schafer 1990; Virat 1987). Two studies had a cross-over design (Moshal 1979; Piai 1979). The studies were published between 1977 and 2007 (Levy 1977; Cappello 2007). The research setting was definitely defined as secondary care in 18 studies, none of the studies was definitely conducted in primary care. Fourteen studies used a run-in period of 1 to 4 weeks before beginning the actual trial. Five of these used a placebo during the run-in period and one used a high fibre diet (Gilvarry 1989). The studies included between 18 (Piai 1979) and 360 participants (Schafer 1990). The mean age of the participants ranged from 26 years (Fielding 1980) to 60.6 years (Baldi 1991). The percentage of female participants included ranged from 35% (Moshal 1979) to 100% (Awad 1995). The intervention period lasted from 1 week (Virat 1987) to 6 months (Centonze 1988). The antispasmodics are divided into ten pharmacological subgroups: Alverine (1 study), cimetropium/dicyclomine (4 studies), mebeverine (2 studies), Otilonium (6 studies), peppermint oil (5 studies), pinaverium (6 studies),pirenzepine (1 study), propinox (1 study), scopolamine derivates (4 studies), and trimebutine (3 studies).

Antidepressants

The search identified 419 studies, of which, after screening title and abstract 56 were potentially eligible. After applying the exclusion criteria on the full-text publications of these 56 potentially eligible studies, 15 articles remained for review and meta-analysis.

Forty articles were excluded (table of characteristics of excluded studies). Twenty were not randomized controlled trials (exc1). Six studies did not involve a placebo treatment (exc2). One study involved an intervention with a mixed preparation (exc5). Four studies did not report the outcome of interest (exc6). Three studies had no extractable results or were cross-over trials with no report of the first phase data (exc7). Six studies were duplicate publications (exc8) (Kalpert 2005, Han 2009; Marks 2008; Block 1983; Tripathi 1983; Greenbaum 1987).

Fifteen studies remained for review and meta-analysis (table of characteristics of included studies). One study had a cross-over design (Tack 2006a). The studies were published between 1978 and 2009 (Heefner 1978; Masand 2009). Two studies were partly conducted in primary care (Myren 1982; Boerner 1988), the remainder in secondary care. Three studies used a run-in period of 1 to 2 weeks before beginning the actual trial (Rajagopalan 1998; Tack 2006a; Talley 2008a). One study had a placebo run-in period of unspecified duration (Masand 2009). One study randomised patients who had completed a 7 week open-label high-fibre trial (Tabas 2004). The studies included between 23 and 201 participants (Tack 2006a; Drossman 2003). The mean age of the participants ranged from 32 years to 49 years (Masand 2009). The percentage of female participants included ranged from 13% (Heefner 1978) to 100% (Drossman 2003). Five studies used a SSRI as the intervention (Kuiken 2003; Masand 2009; Tabas 2004; Tack 2006a; Vahedi 2005). Nine studies used a TCA the as intervention (Bahar 2008; Myren 1982; Boerner 1988; Drossman 2003; Heefner 1978; Rajagopalan 1998; Vahedi 2008; Vij 1991). One study compared an SSRI and a TCA with placebo treatment (Talley 2008a). The intervention period lasted from 4 weeks (Myren 1982) to 12 weeks (Vahedi 2005).

Risk of bias in included studies

The results of the risk of bias assessment are shown in Figure 1.The risk of bias was low for most items. However, selection bias is unclear for many of the included studies because the methods used for randomization and allocation concealment were not described.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

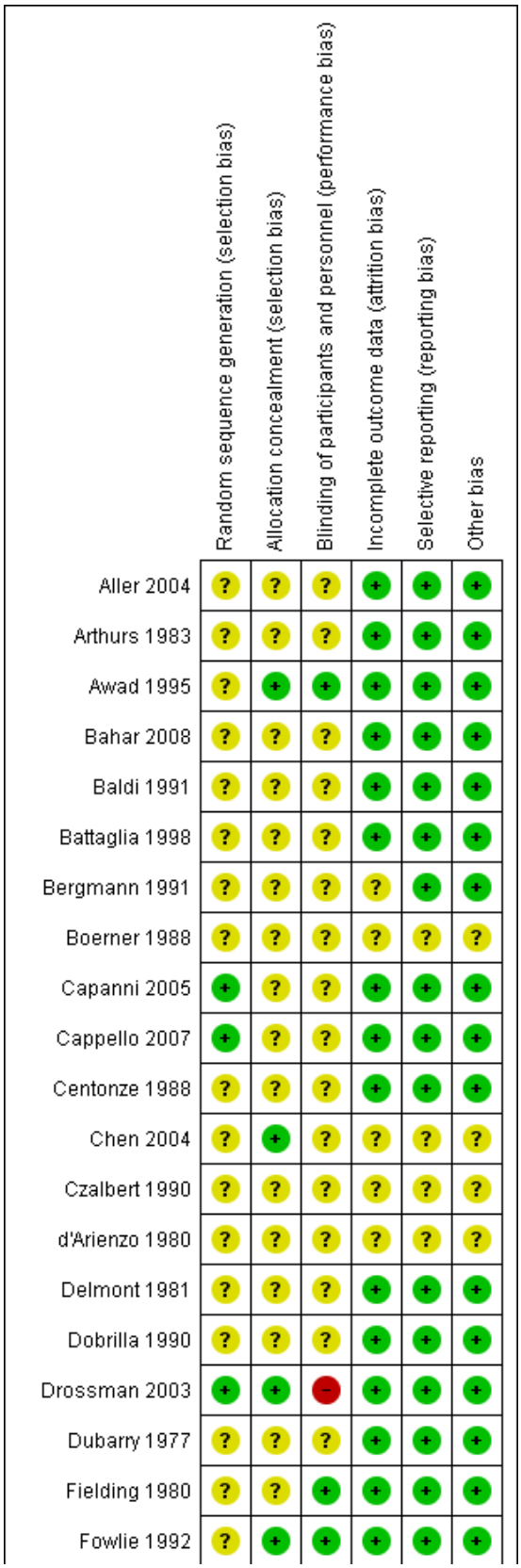


Figure 1. (Continued)

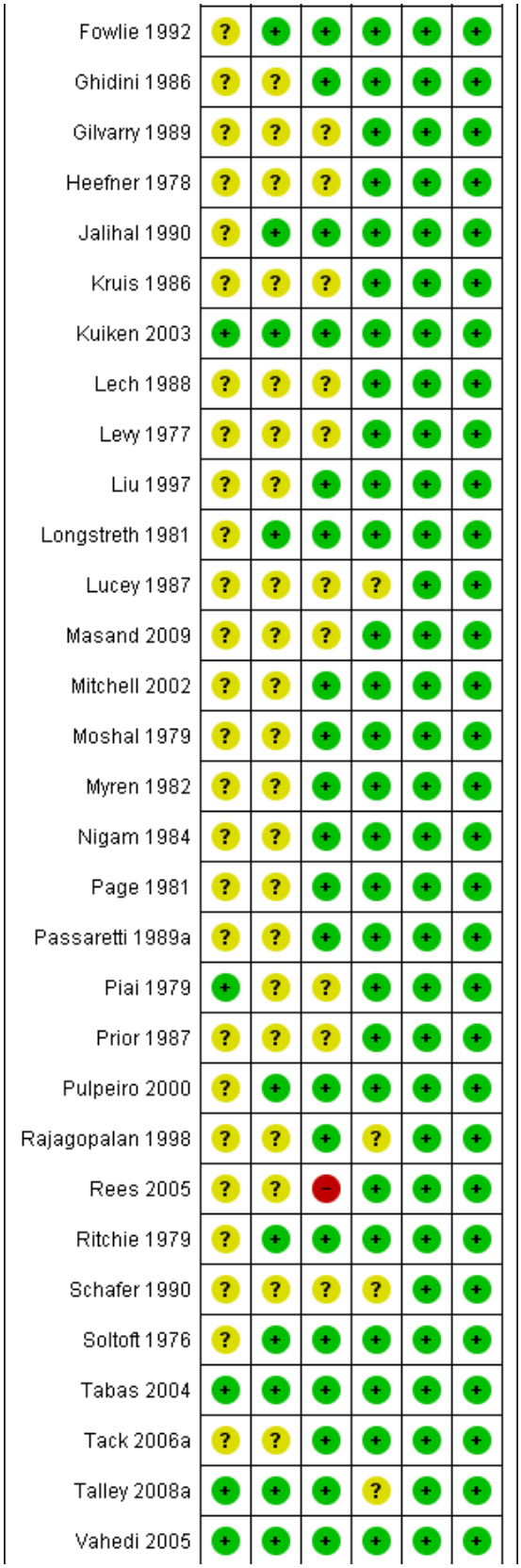
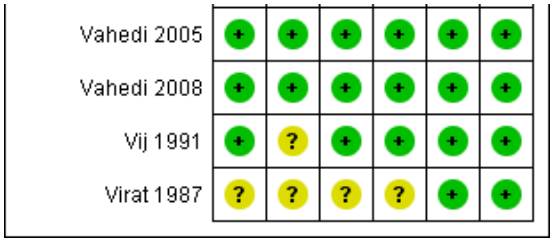


Figure 1. (Continued)



Allocation

Bulking agents

None of the twelve studies on bulking agents described the methods used for randomization and these studies were rated as unclear for this item. Five of the studies were rated as low risk for allocation concealment (Fowlie 1992; Jalihal 1990; Longstreth 1981; Ritchie 1979; Soltoft 1976). The other seven studies were rated as unclear for allocation concealment.

Antispasmodics

Three studies reported on the methods used for randomization (Capanni 2005; Cappello 2007; Piai 1979) and were rated as low risk for this item. The other twenty-six studies did not report on methods used for randomization and were rated as unclear. Four studies were rated as low risk for allocation concealment (Awad 1995; Chen 2004; Pulpeiro 2000; Ritchie 1979). The other studies were rated as unclear for this item.

Antidepressants

Seven studies were reported the methods used for randomization and were rated as low risk for this item (Drossman 2003; Kuiken 2003; Tabas 2004; Talley 2008a; Vahedi 2005; Vahedi 2008; Vij 1991). The other studies were rated as unclear. Six studies were rated as low risk for allocation concealment (Drossman 2003; Kuiken 2003; Tabas 2004; Talley 2008a; Vahedi 2005; Vahedi 2008). The other studies were rated as unclear for this item.

Blinding

Bulking agents

Six studies were rated as low risk for blinding (Fowlie 1992; Jalihal 1990; Longstreth 1981; Nigam 1984; Ritchie 1979; Soltoft 1976). Rees 2005 used a single blind design and was rated as a high risk of bias. The other studies did not describe methods used for blinding and were rated as unclear.

Antispasmodics

Eleven studies were rated as low risk for blinding (Awad 1995; Fielding 1980; Ghidini 1986; Liu 1997; Mitchell 2002; Moshal 1979; Nigam 1984; Page 1981; Passaretti 1989a; Pulpeiro 2000; Ritchie 1979). The other studies did not describe methods used for blinding and were rated as unclear.

Antidepressants

Nine studies were rated as low risk for blinding (Kuiken 2003; Myren 1982; Rajagopalan 1998; Tabas 2004; Tack 2006a; Talley 2008a; Vahedi 2005; Vahedi 2008; Vij 1991). Drossman 2003 used a single blind design and was rated as a high risk of bias. The other studies did not describe methods used for blinding and were rated as unclear.

Incomplete outcome data

Bulking agents

Eleven studies were rated as low risk for incomplete outcome date (Aller 2004; Arthurs 1983; Fowlie 1992; Jalihal 1990; Kruis 1986; Longstreth 1981; Nigam 1984; Prior 1987; Rees 2005; Ritchie 1979; Soltoft 1976). One study was rated as unclear for this item (Lucey 1987).

Antispasmodics

Twenty-four studies were rated as low risk for incomplete outcome data (Awad 1995; Baldi 1991; Battaglia 1998; Capanni 2005; Cappello 2007; Centonze 1988; Delmont 1981; Dobrilla 1990; Dubarry 1977; Fielding 1980; Ghidini 1986; Gilvarry 1989; Kruis 1986; Lech 1988; Levy 1977; Liu 1997; Mitchell 2002; Moshal 1979; Nigam 1984; Page 1981; Passaretti 1989a; Piai 1979; Pulpeiro 2000; Ritchie 1979). Five studies were rated as unclear for this item (Chen 2004; Czalbert 1990; d'Arienzo 1980; Schafer 1990; Virat 1987).

Antidepressants

Eleven studies were rated as low risk for incomplete outcome data (Bahar 2008; Drossman 2003; Heefner 1978; Kuiken 2003; Masand 2009; Myren 1982; Tabas 2004; Tack 2006a; Vahedi 2005; Vahedi 2008; Vij 1991). Four studies were rated as unclear for this item (Bergmann 1991; Boerner 1988; Rajagopalan 1998; Talley 2008a).

Selective reporting

Bulking agents

All twelve studies were rated as low risk for selective reporting (Aller 2004; Arthurs 1983; Fowlie 1992; Jalihal 1990; Kruis 1986; Longstreth 1981; Lucey 1987; Nigam 1984; Prior 1987; Rees 2005; Ritchie 1979; Soltoft 1976).

Antispasmodics

Twenty-six studies were rated as low risk for selective reporting (Awad 1995; Baldi 1991; Battaglia 1998; Capanni 2005; Cappello 2007; Centonze 1988; Delmont 1981; Dobrilla 1990; Dubarry 1977; Fielding 1980; Ghidini 1986; Gilvarry 1989; Kruis 1986; Lech 1988; Levy 1977; Liu 1997; Mitchell 2002; Moshal 1979; Nigam 1984; Page 1981; Passaretti 1989a; Piai 1979; Pulpeiro 2000; Ritchie 1979; Schafer 1990; Virat 1987). Three studies were rated as unclear for this item (Chen 2004; Czalbert 1990; d'Arienzo 1980).

Antidepressants

Fourteen studies were rated as low risk for selective reporting (Bahar 2008; Bergmann 1991; Drossman 2003; Heefner 1978; Kuiken 2003; Masand 2009; Myren 1982; Rajagopalan 1998; Tabas 2004; Tack 2006a; Talley 2008a; Vahedi 2005; Vahedi 2008; Vij 1991). One study was rated as unclear for this item (Boerner 1988).

Other potential sources of bias

Bulking agents

All twelve studies were rated as low risk for other potential sources of bias (Aller 2004; Arthurs 1983; Fowlie 1992; Jalihal 1990; Kruis 1986; Longstreth 1981; Lucey 1987; Nigam 1984; Prior 1987; Rees 2005; Ritchie 1979; Soltoft 1976).

Antispasmodics

Twenty-six studies were rated as low risk for other potential sources of bias Awad 1995; Baldi 1991; Battaglia 1998; Capanni 2005; Cappello 2007; Centonze 1988; Delmont 1981; Dobrilla 1990; Dubarry 1977; Fielding 1980; Ghidini 1986; Gilvarry 1989; Kruis 1986; Lech 1988; Levy 1977; Liu 1997; Mitchell 2002; Moshal 1979; Nigam 1984; Page 1981; Passaretti 1989a; Piai 1979; Pulpeiro 2000; Ritchie 1979; Schafer 1990; Virat 1987). Three studies were rated as unclear for this item (Chen 2004; Czalbert 1990; d'Arienzo 1980).

Antidepressants

Fourteen studies were rated as low risk for other potential sources of bias (Bahar 2008; Bergmann 1991; Drossman 2003; Heefner 1978; Kuiken 2003;Masand 2009; Myren 1982; Rajagopalan 1998; Tabas 2004; Tack 2006a; Talley 2008a; Vahedi 2005; Vahedi 2008; Vij 1991). One study was rated as unclear for this item (Boerner 1988).

Effects of interventions

Bulking agents

Improvement of abdominal pain (outcome 1)

One study with a total of 80 patients reported a dichotomous outcome for improvement of abdominal pain. The RR was 0.91 (95% CI 0.61 to 1.36) using a fixed-effect model. A planned subgroup analysis for insoluble compared to soluble bulking agents could not be performed because there was only one study with soluble (Prior 1987) bulking agents.

Four studies with a total of 186 patients reported a continuous outcome for improvement of abdominal pain. Two of these studies did not report sufficient data to calculate a SMD (Fowlie 1992; Rees 2005). One study of an insoluble bulking agent with a total of 56 patients remained (Aller 2004). There was one study of a soluble fibre (Longstreth 1981). The pooled SMD was 0.03 (95% CI -0.34 to 0.40) using a fixed-effect model.

Improvement of global assessment (outcome 2)

Eleven studies, with a total of 565 patients reported a dichotomous outcome for improvement of global assessment. The chi-square test for heterogeneity was not statistically significant (P = 0.12). The pooled relative risk was not statistically significant using a random-effects model (RR 1.10; 95% CI 0.91 to 1.33). A RR of 0.95 (95% CI 0.76 to 1.19) was calculated for the studies using an insoluble bulking agent (244 patients) (Fowlie 1992; Kruis 1986; Lucey 1987; Rees 2005; Soltoft 1976). In the six studies with a soluble bulking agent the RR was 1.28 (95% CI 0.91 to 1.78; 321 patients) (Arthurs 1983; Jalihal 1990; Longstreth 1981; Nigam 1984; Prior 1987; Ritchie 1979).

One study of an insoluble bulking agent, comprising 56 patients, reported a continuous outcome for improvement of global assessment (Aller 2004). The standardized mean difference was not statistically significant (SMD -0.22; 95% CI -0.74 to 0.31).

Improvement of IBS symptom score (outcome 3)

Three studies, with a total of 126 patients reported a continuous outcome for improvement of IBS symptom score. One study did not report sufficient data to calculate a SMD (Fowlie 1992). Two studies, both of insoluble fibre, with a total of 84 patients remained (Aller 2004; Fowlie 1992). The chi-square test for heterogeneity was not statistically significant (P = 0.16). The pooled SMD was not statistically significant (SMD 0.00; 95%CI -0.43 to 0.43).

The main results for the bulking agents studies are summarized in additional Table 1.

Antispasmodics

Improvement of abdominal pain (outcome 4)

Thirteen studies with a total of 1392 patients reported a dichotomous outcome for improvement of abdominal pain. The chi-square test for heterogeneity was statistically significant (P = 0.01). The pooled RR was 1.32 (95% CI 1.12 to 1.55) using a random-effects model. Subgroup analyses showed statistically significant benefit for pinaverium bromide (RR 1.57; 95% CI 1.08 to 2.26; 158 patients) (Delmont 1981; Dubarry 1977; Virat 1987) and trimebutine (RR 1.32; 95% CI 1.07 to 1.64; 140 patients) (Fielding 1980; Ghidini 1986; Moshal 1979). There was no statistically significant benefit for scopolamine derivatives (RR 1.00; 95% CI 0.84 to 1.19; 360 patients) (Page 1981; Schafer 1990). The other subgroups contained only one study each.

Eight studies comprising 455 patients reported a continuous outcome for improvement of abdominal pain. The chi-square test for heterogeneity was statistically significant (P < 0.00001) The pooled SMD was 1.14 (95% CI 0.47 to 1.81) using a random-effects model. Statistically significant benefit was present for the subgroup cimetropium/dicyclomine (SMD 1.08; 95% CI 0.73 to 1.43; 146 patients) (Centonze 1988; Dobrilla 1990; Passaretti 1989a). There was no statistically significant benefit for pinaverium (SMD 0.44; 95% CI -0.20 to 1.08; 114 patients) (Awad 1995; Virat 1987). The other subgroups contained none or only one study each.

Improvement of global assessment (outcome 5)

Twenty-two studies with a total of 1983 patients reported a dichotomous outcome for improvement of global assessment. The chi-square test for heterogeneity was statistically significant (P < 0.0001). The pooled relative risk was statistically significant (RR 1.49; 95% CI 1.25 to 1.77) using a random-effects model. Statistically significant benefit was present for the subgroups cimetropium/dicyclomine (RR 1.78; 95% CI 1.15 to 2.75; 255 patients) (Centonze 1988; Dobrilla 1990; Page 1981; Passaretti 1989a), otilonium (RR 1.79; 95% CI 1.31 to 2.44; 363 patients) (Battaglia 1998; d'Arienzo 1980; Piai 1979); peppermint-oil (RR 2.25; 95% CI 1.70 to 2.98; 225 patients) (Capanni 2005; Lech 1988) and pinaverium bromide (RR 1.66; 95% CI 1.25 to 2.19; 308 patients) (Chen 2004; Delmont 1981; Levy 1977; Virat 1987). There was no statistically significant benefit for alverine (RR 1.20; 95% CI 0.80 to 1.80; 107 patients) (Mitchell 2002); mebeverine (RR 0.42; 95% CI 0.16 to 1.07; 80 patients) (Kruis 1986), scolpamine derivates (RR 4.43; 95% CI 0.47 to 41.67; 426 patients) (Nigam 1984; Ritchie 1979; Schafer 1990) and trimebutine (RR 0.97; 95% CI 0.68 to 1.38; 120 patients) (Fielding 1980; Ghidini 1986).

Two studies comprising 331 patients reported a continuous outcome for improvement of global assessment. The pooled SMD could not be estimated because of lack of data provided by the studies (Battaglia 1998; Delmont 1981).

Improvement of IBS symptom score (outcome 6)
Four studies with a total of 586 patients reported a dichotomous outcome for improvement of IBS symptom score. The chi-square test for heterogeneity was statistically significant (P = 0.004). The pooled relative risk was statistically significant (RR 1.86; 95% CI 1.26 to 2.76) using a random-effects model. Statistically significant benefit was present for the subgroups peppermint-oil (RR 1.94; 95% CI 1.09 to 3.46; 269 patients) (Capanni 2005; Cappello 2007; Czalbert 1990) and otilonium (RR 1.64; 95% CI 1.15 to 2.34; 317 patients) (Battaglia 1998).

Four studies comprising 243 patients reported a continuous outcome for improvement of global assessment. The chi-square test for heterogeneity was statistically significant (P = 0.00001). The pooled SMD was statistically significant (SMD 2.39; 95% CI 0.50 to 4.29) using a random-effects model. A statistically significant benefit was found for the pinaverium subgroup (SMD 0.51; 95% CI 0.19 to 0.84; 158 patients) (Awad 1995; Chen 2004). The other subgroups contained none or only one study each.

The main results for antispasmodics are summarized in additional Table 2.

Individual spasmolytic agents:

Cimetropium/dicyclomine
No statistically significant effect for improvement of abdominal pain was found for *Cimetropium/dicyclomine* (SMD 1.08; 95% CI 0.73 to 1.43; 146 patients) (Centonze 1988; Dobrilla 1990; Passaretti 1989a). A statistically significant effect for improvement of global assessment was found for *Cimetropium/dicyclomine* (RR 1.88; 95% CI 1.04 to 3.42; 255 patients) (Centonze 1988; Dobrilla 1990; Page 1981; Passaretti 1989a).

Mebeverine
No statistically significant effect for improvement of global assessment was found for *Mebeverine* (RR 0.83; 95% CI 0.31 to 2.23; 149 patients) (Kruis 1986).

Peppermint oil
A statistically significant effect for improvement of global assessment was found for *peppermint oil* (RR 2.25; 95% CI 1.70 to 2.98; 225 patients) (Capanni 2005; Lech 1988). A statistically significant effect for improvement of IBS symptom score was found for *peppermint oil* (RR 1.94; 95% CI 1.09 to 3.46; 269 patients) (Capanni 2005; Cappello 2007; Czalbert 1990).

Pinaverium
Pinaverium provided a statistically significant benefit for improvement of abdominal pain, RR 1.57 (95% CI 1.08 to 2.26; 158 patients) (Delmont 1981; Dubarry 1977; Virat 1987) and SMD 0.44 (95% CI -0.20 to 1.08; 114 patients) (Awad 1995; Virat 1987). A statistically significant effect for improvement of global assessment, RR1.87 (95% CI1.41 to 2.48; 308 patients) (Chen 2004; Delmont 1981; Levy 1977; Virat 1987) and IBS-symptom score was also found, SMD 0.51 (95% CI 0.19 to 0.84; 158 patients) (Awad 1995; Chen 2004).

Scopolamine derivatives
No statistically significant effect for improvement of global assessment was found for *Scopolamine derivatives* (RR 1.42; 95% CI 0.94 to 2.14; 442 patients) (Nigam 1984; Ritchie 1979; Schafer 1990).

Trimebutine
A statistically significant effect for improvement of abdominal pain was found for *Trimebutine* (RR 1.32; 95% CI 1.07 to 1.64; 140 patients) (Fielding 1980; Ghidini 1986; Moshal 1979). No statistically significant effect for improvement of global assessment (RR 0.97; 95% CI 0.68 to 1.38; 120 patients) (Fielding 1980; Ghidini 1986).

Other subgroups
There was not enough data to calculate a pooled estimate effect.

Antidepressants

Improvement of abdominal pain (outcome 7)
Eight studies with a total of 517 patients reported a dichotomous outcome for improvement of abdominal pain. The chi-square test for heterogeneity was statistically significant (P = 0.01). The pooled relative risk was statistically significant (RR was 1.49; 95% CI 1.05 to 2.12) using a random-effects model. Subgroup analyses showed no benefit for SSRIs (RR 2.29; 95% CI 0.79 to 6.68; 197 patients) (Kuiken 2003; Tabas 2004; Tack 2006a; Vahedi 2005), and a statistically significant benefit for TCAs (RR 1.26; 95% CI 1.03 to 1.55; 320 patients) (Drossman 2003; Heefner 1978; Vahedi 2008; Vij 1991).

Three studies with a total of 124 patients reported a continuous outcome for improvement of abdominal pain. The chi-square test for heterogeneity was statistically significant (P < 0.00001). The pooled RR was 1.80 (95% CI -0.57 to 4.16). Subgroup analyses showed no significant benefit for TCA's (SMD was 0.53; 95% CI -1.23 to 2.29; 101 patients) (Boerner 1988; Drossman 2003; Rajagopalan 1998).

Improvement of global assessment (outcome 8)
Twelve studies, with a total of 750 patients reported a dichotomous outcome for improvement of global assessment. The chi-square test for heterogeneity was statistically significant (P = 0.01). The pooled relative risk was statistically significant (RR 1.57; 95% CI 1.23 to 2.00) using a random-effects model. Subgroup analyses suggest a benefit for SSRIs (RR 1.79; 95% CI 1.01 to 3.20; P = 0.05; 227 patients) (Kuiken 2003; Masand 2009; Tabas 2004; Talley 2008a) and showed a statistically significant benefit for TCAs (RR 1.45; 95% CI 1.13 to 1.86; 523 patients) (Bergmann 1991; Boerner 1988; Drossman 2003; Myren 1982; Nigam 1984; Talley 2008a; Vahedi 2008; Vij 1991).

One study assessing an SSRI (Tack 2006a), with a total of 22 patients reported a continuous outcome for improvement of global assessment. The pooled SMD was 3.32 (95% CI 1.95 to 4.68).

Improvement of IBS symptom score (outcome 9)

Three studies with a total of 159 patients reported a dichotomous outcome for improvement of symptom score. The chi-square test for heterogeneity was not statistically significant (P = 0.12). The pooled RR was 1.99 (95% CI 1.32 to 2.99) using a fixed-effect model. Subgroup analyses showed a statistically significant benefit for TCAs (RR 3.16; 95% CI 1.59 to 6.29; 87 patients) (Bahar 2008; Vahedi 2008).

Two studies, with a total of 122 patients reported a continuous outcome for improvement of IBS symptom score. The chi-square test for heterogeneity was statistically significant (P = 0.07). The pooled SMD was 0.38 (95% CI -0.30 to 1.06) using a random-effects model.

The main results for antidepressants are summarized in Table 3.

Additional comparison: adequate concealment of allocation

Bulking agents abdominal pain (outcome 10.2)
Two studies of bulking agents with adequate concealment of allocation reported a continuous outcome for improvement of abdominal pain (Longstreth 1981; Fowlie 1992). The chi-square test for heterogeneity was not statistically significant (P = 0.88). The pooled SMD using a fixed-effect model was -0.04 (95%CI -0.40 to 0.32; 119 patients).

Bulking agents: global assessment (outcome 11.1)
Five studies of bulking agents with adequate concealment of allocation reported a dichotomous outcome for improvement of abdominal pain (Fowlie 1992; Jalihal 1990; Longstreth 1981; Ritchie 1979; Soltoft 1976). Using a random-effects model, the pooled RR was 0.91 (95% CI 0.68 to 1.23; 193 patients).

Antispasmodics: abdominal pain (outcome 12.1)
Two studies of spasmolytic agents with adequate concealment of allocation reported a continuous outcome for improvement of abdominal pain (Awad 1995; Pulpeiro 2000). The chi-square test for heterogeneity was not statistically significant (P = 0.88). Using a fixed-effect model, the pooled SMD was 0.43 (95% CI 0.06 to 0.80; 115 patients).

Antispasmodics: global assessment (outcome 13.1)
Three studies of spasmolytic agents with adequate concealment of allocation reported a dichotomous outcome for improvement of global assessment (Chen 2004; Pulpeiro 2000; Ritchie 1979). The chi-square test for heterogeneity was not statistically significant (P= 0.25). Using a fixed-effect model, the pooled RR was 1.35 (95% CI 0.85 to 2.12; 219 patients).

Antidepressants: abdominal pain (outcome 14.1)
Five studies of antidepressant agents with adequate concealment of allocation reported a dichotomous outcome for improvement of abdominal pain. The chi-square test for heterogeneity was statistically significant (P = 0.06). Using a random-effects model, the pooled RR was 1.35 (95% CI 0.98 to 1.86; 364 patients) . Subgroup analyses showed no statistically significant benefit for SSRIs (RR 1.20; 95% CI 0.87 to 1.67) (Kuiken 2003; Tabas 2004; Vahedi 2005) or TCAs (RR 2.19; 95% CI 0.59 to 8.11) (Drossman 2003; Vahedi 2008).

Antidepressants: global assessment (outcome 15.1)
Four studies of antidepressant agents with adequate concealment of allocation reported a dichotomous outcome for global assessment. The chi-square test for heterogeneity was not statistically significant (P = 0.23). Using a fixed-effect model, the pooled RR was 1.42 (95% CI 1.12 to 1.80; 329 patients) (Drossman 2003; Kuiken 2003; Tabas 2004; Talley 2008a).

Antidepressants: IBS symptom score (outcome 16.1)
One study of antidepressants with adequate concealment of allocation reported a continuous outcome for improvement of IBS symptom score (Vahedi 2008). Using a fixed-effect model, the SMD was 0.75 (95% CI 0.17 to 1.32; 50 patients).

DISCUSSION

Bulking agents
The pooled data suggest that bulking agents do not provide any benefit for the treatment of IBS. No statistically significant differences between bulking agents and placebo were found for abdominal pain, global assessment or symptom score. Only 7 of the included studies had more than 30 patients and all studies had quality limitations (i.e. method of randomisation, double-blinding, concealment of treatment allocation, description of withdrawals). There were five studies with adequate allocation concealment (Fowlie 1992; Jalihal 1990; Longstreth 1981; Ritchie 1979; Soltoft 1976). A sensitivity analysis of those studies with adequate allocation concealment, did not change the results. Subgroup analyses for the different type of bulking agents, soluble versus insoluble fibre, also gave no statistically significant findings.

We are aware of five systematic reviews of bulking agents for IBS. Jailwala 2000, who used less strict exclusion criteria than the present review, also concluded from an analysis of 13 studies that the efficacy of bulking agents is not clearly established. When Jailwala 2000 separately analysed high and low quality trials, the conclusion remained the same (Jailwala 2000). Akehurst 2001 included 7 studies on bulking agents in a review of IBS therapies and concluded that there was little reason to believe that bulking agents were effective for IBS (Akehurst 2001). Lesbros-Pantoflickova 2004 included 13 studies in their meta-analyses, of which 5 studies reported a statistically significant benefit of fibre treatment for the relief of global symptoms (OR 1.9; 95% CI 1.5 to 2.4). However, after exclusion of the low-quality trials, this effect was not statistically significant. In conclusion, they found no evidence to recommend bulking agents for the treatment of IBS (Lesbros-Pantoflickova 2004). Ford 2008 included 12 studies comparing fibre with placebo, and used persistent symptoms after treatment as an outcome measure. Ford 2008 calculated a RR of 0.87 (95% CI 0.76 to 1.00). A subgroup analysis identified a statistically significant benefit for ispaghula a soluble fibre (RR 0.78; 95% CI 0.63 to 0.96). Ford 2008 had almost the same strict inclusion criteria as our review but included different outcome analyses. Ford 2008 did not use an ITT-analyses, only extracted dichotomous outcome and pooled all the outcomes (global assessment of symptoms and abdominal pain) as one.

Bijkerk 2004 examined the separate effects of soluble and insoluble fibres, on global assessment and constipation. Bijkerk 2004 found a beneficial overall effect for fibre in general (RR 1.33; 95% CI 1.19 to 1.50) and soluble fibres for global assessment of IBS (RR 1.55; 95% CI 1.35 to 1.78). We could not reproduce these findings (outcomes 1.1 to 3.2). A possible explanation for this is that Bijkerk 2004 included cross-over trials (7 of the 17 included studies), which were excluded in this review. Bijkerk 2004 also included two studies with no placebo comparison.

Antispasmodics

Spasmolytic agents compared to placebo provided a statistically significant benefit for abdominal pain, global assessment and IBS-symptom score. Spasmolytic agents are pharmacologically diverse and arbitrary choices were made regarding the pooling of results. We decided to treat peppermint-oil as an anti-spasmodic because of its known effect on smooth muscles. Trimebutine appears to be effective for abdominal pain, pinaverium for abdominal pain and global assessment, cimetropium/dicyclominand for global assessment and peppermint-oil for global assessment and symptom score. Only four studies had adequate allocation concealment (Awad 1995; Chen 2004; Pulpeiro 2000; Ritchie 1979). It is important to note that none of the studies involving peppermint-oil had adequate allocation concealment. When analysing the studies with adequate allocation concealment separately, the results get weaker and only improvement of abdominal pain has still a statistically significant benefit. Spasmolytics are extensively studied for their use in the treatment of IBS, however due to the diversity of types of spasmolytic agents, the number of studies for each compound are limited. Therefore most subgroups could not be pooled, and a type II error could have occurred.

Eight systematic reviews of antispasmodics for IBS have been published (Akehurst 2001; Brandt 2002; Ford 2008; Jailwala 2000; Lesbros-Pantoflickova 2004; Poynard 1994; Poynard 2001; Tack 2006b). Jailwala 2000 included 13 studies and found that all of the 7 high-quality trials demonstrated a benefit, mainly for abdominal pain, less so for constipation. Akehurst 2001 identified 12 studies and came to similar conclusions. Ford 2008 found consistent evidence of efficacy for otilonium (RR 0.55; 95% CI 0.31 to 0.97) and scopolamine (RR 0.63; 95% CI 0.51 to 0.78). Ford 2008 identified peppermint-oil as an individual group, included 4 studies and calculated a RR of 0.43 (95% CI 0.33 to 0.59). These results are almost identical to our own. However, Ford 2008 used a different method to assess methodological quality (Jadad scale), and rated three studies as high quality, resulting in a greater effect than seen in this review. In an update of a 1994 meta-analysis, Poynard 2001 included 23 trials comprising 6 types of drugs. Using a fixed-effect model, there was a statistically significant benefit for global assessment (Peto OR 2.13; 95%CI 1.77 to 2.58) and pain (Peto OR 1.65; 95%CI 1.30 to 2.10) (Poynard 2001).This review provides similar evidence of the efficacy of spasmolytic agents for IBS. The reviews from Lesbros-Pantoflickova 2004 and Tack 2006b concluded that there is some evidence that antispasmodic may improve symptoms of abdominal pain but are careful in recommending antispasmodics for the treatment of IBS due to the low methodological quality of the included RCTs.

Antidepressants

Antidepressants provide a statistically significant benefit over placebo for abdominal pain, global assessment and IBS-symptom score. Subgroup analyses for SSRIs and TCAs, showed a statistically significant improvement in global assessment for SSRIs and a statistically significant improvement in abdominal pain and symptom score for TCAs. A sensitivity analysis of the six studies with adequate allocation concealment showed a statistically significant benefit for improvement of symptom score and global assessment (Drossman 2003; Kuiken 2003; Tabas 2004; Talley 2008a; Vahedi 2005; Vahedi 2008).

Given the significantly positive effects of antidepressant medication, the clinical indication of antidepressant medication in IBS needs to be discussed. Careful examination of the domain descriptions in the individual studies, shows no differences in patient population between studies investigating antidepressants, antispasmodics or bulking agents. Two studies performed a direct comparison of antidepressants with bulking agents or antispasmodics (Nigam 1984; Ritchie 1979), but found no proof of the superiority of either compound.

We are aware of eight systematic reviews of antidepressants for IBS (Akehurst 2001; Brandt 2002; Ford 2009; Jailwala 2000; Jackson 2000; Lesbros-Pantoflickova 2004; Tack 2006b; Rahimi 2009). Most of these reviews are consistent with our results. Akehurst 2001 concluded from two studies that antidepressants were effective. Ford 2009 included 13 RCTs and found a RR of 0.66 (95% CI 0.57 to 0.78) for persistent symptoms after treatment, and no difference between SSRIs and TCAs. The Jailwala 2000 meta-analysis included 7 studies, all reporting beneficial effect, and concluded that it was not clear whether this was due to resolving abdominal symptoms, or to improved psychological health. The Jackson 2000 review included 11 studies on functional gastro-intestinal disorders, 8 of which were enrolled IBS patients exclusively. Jackson 2000 identified a statistically significant effect for overall assessment (7 studies; OR 4.2; 95% CI 2.3 to 7.9) and abdominal pain (9 studies; SMD 0.9; 95% CI 0.6 to 1.2). The Lesbros-Pantoflickova 2004 review included 12 studies and found an OR: 2.6 (95% CI 1.9 to 3.5). They recommend antidepressant medication for the treatment of patients with severe IBS symptoms, i.e. patients with daily or persistent pain. Rahimi 2009 only investigated TCAs and found clinically and statistically significant control of IBS symptoms. They advised that treatment with TCAs should be limited to patients with moderate to severe IBS.

Brandt 2002 and Tack 2006b (a extended version of Brandt 2002) reported no beneficial effect for antidepressant medication. This difference may be due to less strict inclusion criteria: both included cross-over studies with no report of the first phase data. They also failed to conduct a meta-analysis of the data.

AUTHORS' CONCLUSIONS

Implications for practice

The limitations of drug therapy should be discussed with the patient before deciding to prescribe medication for IBS. Agreement should be reached on treatment objectives, usually this will be relief of the most troublesome symptom. Our findings support the use of antispasmodics, although, it is not entirely clear whether one

antispasmodic is more effective than another. Physicians will be limited to those antispasmodics which are locally available.

Antidepressants may also have a role for the treatment of IBS. Antidepressants could be used in patients who seek drug therapy and who have not responded to antispasmodics. The effectiveness of antidepressants may vary with individual patient features.

Implications for research

It is likely that two different disease entities exist: constipation predominant IBS, and diarrhea predominant IBS. There may even be a third entity, patients with an alternating stool pattern. The pharmacological properties of bulking agents, spasmolytic agents and antidepressive medication suggest that different responses might be expected in these patient groups and this issue should be studied in future trials of “classic” drugs.

The variation in methods of outcome assessment in IBS studies is a validity problem. It is uncertain how precisely current outcome measures reflect the actual health status of the IBS patient. The need for more meaningful measures of response to treatment has led to the development of health-related quality of life measures including stool frequency and consistency, social, daily, physical and sexual functioning, sleep, pain, emotion, and change of health. Future research should use validated outcome measures for IBS, such as the IBS Quality of Life Questionnaire (IBSQOL), the IBS Quality of Life Measure (IBS-QOL), the Digestive Health Status Instrument (DHSI), the Functional Digestive Disorder Quality of Life questionnaire (FDDQOL), or the IBS-Q.

The concept of the brain-gut axis invites trials aimed at central and peripheral neural levels; apart from drug trials these may include cognitive behavioural therapy or other psychological interventions (e.g. hypnotherapy).

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aller 2004

Methods	RCT
Participants	56 patients Rome II criteria 53% diarrhea-predominant Setting unclear Mean age 46 years 67% female

Aller 2004 *(Continued)*

Interventions	Bulking agent 30 g fibre of which 25 g insoluble, over the day for 13 weeks
Outcomes	Abdominal pain, continuous Symptom score, continuous
Notes	Half a week run-in

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Single-blind - not described in detail
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients dropped out of the study
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Arthurs 1983

Methods	RCT
Participants	80 patients Setting unclear Diagnostic criteria not defined Mean age 27.7 years 78% female
Interventions	Bulking agent 4 weeks ispaghula husk 2 sachets/day
Outcomes	Global assessment, dichotomous
Notes	Unclear setting No run-in

Arthurs 1983 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind but procedures not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two dropouts
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Awad 1995

Methods	RCT
Participants	40 patients Tertiary care Rome criteria Mean age 31.3 years 100% female
Interventions	Spasmolytic pinaverium 50 mg od for 3 weeks
Outcomes	Abdominal pain, continuous symptom score, continuous
Notes	No run-in

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Adequate

Awad 1995 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical placebo, neither doctors nor patients knew which treatment was given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two dropouts one from each treatment group
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Bahar 2008

Methods	RCT
Participants	33 adolescent patients secondary care Rome criteria mean age 15 years 65% female
Interventions	Antidepressant amitriptyline 10 to 30 mg dd for 8 weeks
Outcomes	Abdominal pain, change score (not included global assessment, change score (not included) and dichotomous
Notes	2 weeks run in period adolescents

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	2 drop-outs

Bahar 2008 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Baldi 1991

Methods	RCT
Participants	71 patients with IBS 8 GI centres Mean age 40 years 60.6% female
Interventions	Spasmolytic 4 weeks otilonium 40 mg tds
Outcomes	abdominal pain
Notes	2 wk run-in with placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, methods not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	One drop-out
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Battaglia 1998

Methods	RCT

Battaglia 1998 *(Continued)*

Participants	325 patients multicentre GI outpatients Rome criteria Mean age 47.7 years 69% female
Interventions	Spasmolytic 15 weeks otilonium 40 mg tds
Outcomes	abdominal pain, dichotomous global assessment, continuous
Notes	2 weeks run-in, with placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, methods not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Bergmann 1991

Methods	RCT
Participants	35 patients Secondary care Clinical diagnosis and investigations
Interventions	Antidepressant 3 months Trimipramine 50 mg OD
Outcomes	Global assessment, dichotomous

Bergmann 1991 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, methods not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Boerner 1988

Methods	RCT
Participants	79 IBS patients partly from primary care
Interventions	Antidepressive doxepine od 50 mg for 8 weeks
Outcomes	Abdominal pain, continuous Global assessment, dichotomous
Notes	No run-in

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Not described

Boerner 1988 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	Not described
Other bias	Unclear risk	Not described

Capanni 2005

Methods	RCT
Participants	178 patients secondary care Rome II criteria Mean age 42 years 75% female
Interventions	Spasmolytics peppermint oil for 3 months, dose not stated
Outcomes	Global assessment, dichotomous IBS-symptoms, dichotomous
Notes	4 weeks run-in Dosage of intervention not clear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 drop-outs from peppermint oil group and 2 drop-outs from placebo

Capanni 2005 *(Continued)*

Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Cappello 2007

Methods	RCT
Participants	57 patients Setting unclear Rome II criteria mean age 41 years 76% female
Interventions	Spasmodic peppermint oil capsules 500 mg for 4 weeks
Outcomes	Abdominal pain, continuous IBS-symptom score, continuous and dichotomous
Notes	No run in

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double blind, methods not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Centonze 1988

Methods	RCT
Participants	48 patients Outclinic 50% female Mean duration of symptoms 4 years
Interventions	Spasmolytic cimetropium tds 50 mg for 6 months
Outcomes	Abdominal pain, continuous Global assessment, dichotomous
Notes	3 weeks run-in without placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, procedures not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Four patients (one in the drug group, three in the placebo group) did not complete the study, three because of noncompliance and one because he moved away.
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Chen 2004

Methods	RCT
Participants	120 IBS patients Setting unclear Rome II criteria Mean age 43 years 48% female

Chen 2004 *(Continued)*

Interventions	Spasmolytic pinaverium bromide 100 mg tds for 8 weeks
Outcomes	Global assessment, dichotomous Symptom score, continuous
Notes	No run-in

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	Not described
Other bias	Unclear risk	Not described

Czalbert 1990

Methods	RCT
Participants	34 IBS Hospital out clinic Mean age 49.3 years
Interventions	Spasmolytic peppermint oil 0.2 ml tds for 10 days
Outcomes	Symptom score, dichotomous
Notes	No run-in

Risk of bias

Bias	Authors' judgement	Support for judgement

Czalbert 1990 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	Not described
Other bias	Unclear risk	Not described

d'Arienzo 1980

Methods	RCT
Participants	28 IBS patients Unclear setting Diagnostic criteria not defined 39% female
Interventions	Spasmolytic otilonium tds 20 mg 4 weeks
Outcomes	Symptom score, continuous
Notes	No run-in

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double blind, procedures not described
Incomplete outcome data (attrition bias)	Unclear risk	Not described

d'Arienzo 1980 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Not described
Other bias	Unclear risk	Not described

Delmont 1981

Methods	RCT
Participants	60 IBS patients Setting unclear Mean age 57 years 67% female
Interventions	Spasmolytic pinaverium tds for 30 days
Outcomes	abdominal pain, dichotomous global assessment, dichotomous
Notes	unclear setting No run-in

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double blind - procedures not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 drop-outs
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Dobrilla 1990

Methods	RCT
Participants	70 IBS patients Hospital out clinic Mean age 45 years 67% female Mean duration of symptoms 3 years
Interventions	Spasmolytic 13 weeks cimetropium tds 50mg
Outcomes	Abdominal pain, continuous Global assessment, dichotomous
Notes	2 weeks run-in without placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind - procedures not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 drop-out
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Drossman 2003

Methods	RCT
Participants	216 patients with functional bowel disorders, 80% with IBS Secondary care Rome criteria Mean age 39.9 years 100% female

Drossman 2003 *(Continued)*

Interventions	Antidepressant desipramine 50-100-150mg od for 12 weeks
Outcomes	Abdominal pain, continuous and dichotomous Global assessment, continuous and dichotomous Symptom score, continuous and dichotomous
Notes	No run-in; minimum duration of symptoms of 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	Investigator-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Dubarry 1977

Methods	RCT
Participants	20 IBS patients Outpatient setting Diagnostic criteria not defined
Interventions	Spasmolytic 6 days pinaverium 50 mg tds
Outcomes	Abdominal pain, dichotomous
Notes	No run-in

Risk of bias

Bias	Authors' judgement	Support for judgement

Dubarry 1977 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, methods not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Fielding 1980

Methods	RCT
Participants	60 IBS patients Unclear setting Diagnostic criteria not defined Mean age 26 years 75% female mean duration of symptoms 2 years
Interventions	Spasmolytic trimebutine tds 200 mg for 6 months
Outcomes	Abdominal pain, dichotomous Global assessment, dichotomous
Notes	No run-in

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Double-blind, identical placebo

Fielding 1980 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 drop-outs
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Fowlie 1992

Methods	RCT
Participants	49 patients Gastro intestinal outpatient clinic Mean age 40 years 65% female Mean duration of symptoms 3.8 years
Interventions	Bulking agent 3 months mixed cereal and fruit fibre 4.1 g/day
Outcomes	Abdominal pain Global assessment Symptom score
Notes	GI Outpatients 1 week run-in

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported

Fowlie 1992 *(Continued)*

Other bias	Low risk	The study appears to be free of other sources of bias

Ghidini 1986

Methods	RCT
Participants	60 IBS patients Hospital setting Mean age 42 years 60% female
Interventions	Spasmolytic rociverine tds 20 mg for 60 days trimebutine 3 dd 100 mg
Outcomes	Abdominal pain, dichotomous Global assessment, dichotomous
Notes	No run-in

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind design with preparations that were outwardly indistinguishable
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Low risk	Expected outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Gilvarry 1989

Methods	RCT
Participants	24 IBS patients Unclear setting

Gilvarry 1989 *(Continued)*

	Diagnostic criteria not defined
	Mean age 32 years
	79% female
Interventions	Antispasmodic pirenzepine 100 mg for 4 weeks
Outcomes	Abdominal pain, dichotomous
	Global assessment, dichotomous
Notes	4 to 8 weeks run-in with high fibre diet (> 30 g/day)
	continued high fibre diet during study period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double blind, methods not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 drop outs
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Heefner 1978

Methods	RCT
Participants	31 patients
	Outpatients clinic
	Diagnostic criteria not defined
	Mean age 48 years
	13% female
Interventions	Antidepressive desipramine od 150 mg, 2months

Heefner 1978 *(Continued)*

Outcomes	Abdominal pain, dichotomous
Notes	No run-in

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double blind, methods not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Jalihal 1990

Methods	RCT with Cross-over design
Participants	20 patients Gastro intestinal outpatients clinic Diagnoses on clinical grounds Mean age 38 years 20% female
Interventions	Bulking agent 4 weeks ispaghula husk 30 g/day
Outcomes	Abdominal pain, dichotomous Global assessment, dichotomous
Notes	GI Outpatients No run-in

Risk of bias

Bias	Authors' judgement	Support for judgement

Jalihal 1990 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, treatment was indistinguishable from the placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs. Two patients were eligible but dropped out before the study.
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Kruis 1986

Methods	RCT
Participants	80 patients Outpatients clinic Mean age 41 years 61% female
Interventions	Bulking agent 16 weeks wheat bran fibre 8 g/day Spasmolitic agent 16 weeks mebeverine 100 mg 4 dd
Outcomes	Global assessment, dichotomous Abdomianl pain, dichotomous
Notes	GI patients No run-in

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Mebeverine and placebo arms were double-blind. Methods not described

Kruis 1986 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Kuiken 2003

Methods	RCT
Participants	40 patients, GI out clinic Rome I criteria Mean age 40 years 55% female Mean duration of symptoms 5.9 years
Interventions	Antidepressive fluoxetine (SSRI) 20 mg od for 6 weeks
Outcomes	Abdominal pain, dichotomous Global assessment, dichotomous
Notes	No run-in

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Centralized randomization by pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 patients dropped out (2 from treatment group and 4 from placebo)
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported

Kuiken 2003 *(Continued)*

Other bias	Low risk	The study appears to be free of other sources of bias

Lech 1988

Methods	RCT
Participants	47 IBS patients Hospitals outpatients clinic Mean age 42 years 76% female
Interventions	Spasmolytic 4 weeks peppermint oil 3 dd 200 mg
Outcomes	Global assessment, dichotomous
Notes	No run-in

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, methods not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Levy 1977

Methods	RCT
Participants	50 IBS patients Unclear setting Diagnostic criteria not defined

Levy 1977 *(Continued)*

	Mean age 48 years 46% female
Interventions	Spasmolytic Pinaverium tds 50 mg 15 days
Outcomes	Global assessment, dichotomous
Notes	No run-in

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, methods not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop outs
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Liu 1997

Methods	RCT
Participants	101 IBS patients Unclear setting 40% females
Interventions	Spasmolytic 4 weeks peppermint oil tds-qid 187 mg
Outcomes	Abdominal pain, dichotomous
Notes	No run-in

Risk of bias

Bias	Authors' judgement	Support for judgement

Liu 1997 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	9 drop-outs: 3 patients on Colpermin and 6 on placebo did not return for follow-up
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Longstreth 1981

Methods	RCT
Participants	77 patients Setting unclear Mean age 38.4 years 83% female Mean duration of symptoms 7.9 years
Interventions	Bulking agent 8 weeks psyllium 19 g/day
Outcomes	Abdominal pain, continuous Global assessment, dichotomous
Notes	Unclear setting 2 weeks run-in

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias)	Low risk	Double-blind, identical sachets

Longstreth 1981 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Lucey 1987

Methods	RCT with Cross-over design
Participants	44 Patients Gastrointestinal outpatient clinic Manning criteria Mean age 32 years 68% female Mean duration of symptoms 60 months
Interventions	Bulking agent 3 months wheat bran fibre 13g/day
Outcomes	IBS symptom score, continuous
Notes	GI Outpatients No run-in

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, methods not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	16 patients dropped out. Reasons for withdrawal not reported
Selective reporting (reporting bias)	Low risk	Expected outcomes reported

Lucey 1987 *(Continued)*

Other bias	Low risk	The study appears to be free of other sources of bias

Masand 2009

Methods	RCT
Participants	72 patient Secondary care Rome II criteria Mean age 49 years 88% female
Interventions	Antidepressant paroxetine 12.5-50 mg for 12 weeks
Outcomes	Global assessment, dichotomous IBS-symptoms, continuous, dichotomous
Notes	run in with placebo, time period not described

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, methods not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Mitchell 2002

Methods	RCT
Participants	107 IBS patients

Mitchell 2002 *(Continued)*

	Secondary care 3 different hospitals
	Rome criteria
	Mean age 53 years
	80% female
Interventions	Antispasmodic
	Alverine citrate 360 mg for 12 weeks
Outcomes	Global assessment
	Abdominal pain
Notes	2 weeks run-in without placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Moshal 1979

Methods	RCT with cross-over design
Participants	20 IBS patients
	Unclear setting
	Diagnostic criteria not defined
	Mean age 27 years
	35% females
	Mean duration of symptoms 1 year
Interventions	Spasmolytic

Moshal 1979 *(Continued)*

	trimebutine tds 200 mg for 4 weeks
Outcomes	Abdominal pain, dichotomous
Notes	No run-in

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Myren 1982

Methods	RCT
Participants	61 patients Primary care setting Mean age 38.9 years 54% female
Interventions	Antidepressive trimipramine 1 dd 50 mg 4 weeks
Outcomes	Global assessment, dichotomous
Notes	No run-in

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described

Myren 1982 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Nigam 1984

Methods	RCT
Participants	168 patients Secondary care Mean age 34.5 years 45% female
Interventions	Bulking agents Ispaghula husk, unclear dose, 12 weeks Spasmolitic agent Hyoscinebutylbromide, unclear dose, 12 weeks
Outcomes	Global assessment, dichotomous
Notes	Inclear dose of intervention No run in

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy

Nigam 1984 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Page 1981

Methods	RCT
Participants	97 patients Unclear setting Mean age 36.7 years 83% females Mean duration of symptoms 2 years
Interventions	Spasmolytic dicyclomine qid 40 mg for 2 weeks
Outcomes	Abdominal pain, dichotomous Global assessment, dichotomous
Notes	2 weeks placebo run-in

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, methods not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Passaretti 1989a

Methods	RCT
Participants	40 patients Out patient clinic Mean age 39 years 60% females
Interventions	Spasmolytic 4 weeks cimetropium tds 50 mg
Outcomes	Abdominal pain, continuous Global assessment, dichotomous
Notes	2 weeks run-in without placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, methods not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Piai 1979

Methods	RCT with cross-over design
Participants	18 patients Unclear setting Diagnostic criteria not defined 56% females
Interventions	Spasmolytic

Piai 1979 *(Continued)*

	prifinium 30 mg tds for 3 weeks
Outcomes	Global assessment, dichotomous
Notes	No run-in

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, methods not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Low risk	All expected outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Prior 1987

Methods	RCT
Participants	80 patients Outpatients 90% female
Interventions	Bulking agents 12 weeks ispaghula husk 19 g/day
Outcomes	Abdominal pain, dichotomous Global assessment, dichotomous
Notes	Outpatients 2 weeks run-in

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described

Prior 1987 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, methods not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Pulpeiro 2000

Methods	RCT
Participants	85 IBS patients Hospital GI department Mean age 45.2 years 69% female
Interventions	Spasmolytic Propinox 4 dd for 4 weeks
Outcomes	Abdominal pain, continuous Global assessment, dichotomous
Notes	No run-in Dose unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical placebo
Incomplete outcome data (attrition bias)	Low risk	No drop-outs

Pulpeiro 2000 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Rajagopalan 1998

Methods	RCT	
Participants	22 patients Outpatients clinic Rome criteria Mean age 35 years 50% female	
Interventions	Antidepressive amitriptyline to 75 mg od for 12 weeks	
Outcomes	Abdominal pain, continuous	
Notes	1 week run-in	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical placebo, all investigators and patients were blind to the treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The same number of patients dropped out from each group. Reasons for drop-out were not reported
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Rees 2005

Methods	RCT
Participants	28 patients GI out clinic Rome criteria Mean age 36.1 years 86% female
Interventions	Bulking agent 10-20 g coarse wheat bran once daily for 8 to 12 weeks
Outcomes	Abdominal pain, continuous Global assessment, dichotomous
Notes	No run in period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind (patients)
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 patients dropped out from treatment group and 4 dropped out from placebo
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Ritchie 1979

Methods	RCT
Participants	24 patients Secondary setting Diagnostic criteria not defined Mean age 38 years

Ritchie 1979 *(Continued)*

	77% female
Interventions	Bulking agent 4 weeks ispaghula husk, 1 sachet 2 dd Spasmolytics hyoscine 4 dd 10 mg 4 weeks
Outcomes	Global assessment, dichotomous
Notes	Hospital setting No run-in

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Centralized randomization by hospital pharmacist
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy. Dummy preparations were identical to active
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 drop-outs
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Schafer 1990

Methods	RCT
Participants	360 IBS pat from various origin (prim care, GI clinic, int med)
Interventions	Spasmolytic 4 weeks butylscopamine 30 mg/day
Outcomes	Abdominal pain Global assessment
Notes	0.5 wk run-in

Risk of bias

Bias	Authors' judgement	Support for judgement

Schafer 1990 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, methods not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop outs not described
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Soltoft 1976

Methods	RCT
Participants	59 patients Setting unclear Mean age 40 years 64% female
Interventions	Bulking agent 6 weeks wheat bran 30 g/day
Outcomes	Global assessment, dichotomous
Notes	Unclear setting >1 week run-in

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo of similar appearance

Soltoft 1976 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Tabas 2004

Methods	RCT
Participants	90 patients Voluntary participants through advertisement Rome I criteria Mean age 46 years 74% female
Interventions	Antidepressant paroxetine (SSRI) 10 or 20 mg od for 12 weeks
Outcomes	Abdominal pain, dichotomous Global assessment, dichotomous
Notes	69 of 81 took part in high-fibre open label trial 7 weeks before

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Centralized randomization by hospital pharmacist
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, researchers and patients were unaware of assignment until the conclusion of the last visit
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Tack 2006a

Methods	Crossoveer with first phase data reported
Participants	23 IBS patients Tertiary setting Rome II criteria Mean age 40 years 78% female
Interventions	Antidepressant citalopram (SSRI) 20-40mg for 6 weeks
Outcomes	Abdominal pain, continuous Global assessment, continuous
Notes	2 weeks run-in

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, matching placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Talley 2008a

Methods	RCT
Participants	51 patients Setting secondary care Rome criteria

Talley 2008a *(Continued)*

	60% female
	70% diarrhea predominant
Interventions	Antidepressive
	Imipramine (TCA) 50 mg dd for 12 weeks
	Citalopram (SSRI) 40 mg dd for 12 weeks
Outcomes	Abdominal pain, changes score (not included)
	global assessment, dichotomous and change score (not included)
Notes	2 weeks run-in period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Centralized randomization by hospital pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy, identical capsules
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reasons for drop-out not provided
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Vahedi 2005

Methods	RCT
Participants	44 IBS patients
	GI clinic
	Rome II criteria
	Mean age 35 years
	61% female
Interventions	Antidepressant fluoxetine(SSRI) 20mg od for 12 weeks
Outcomes	Abdominal pain

Vahedi 2005 *(Continued)*

Notes	Only 44 of 64 eligible patients included. No run-in No run in period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical placebo. Both patients and researchers were unaware of the true identity of the prescribed medicine
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Vahedi 2008

Methods	RCT
Participants	50 diarrhoea-predominant IBS patients Tertiary GI clinic Rome II criteria Mean age 36 years 42% female Mean duration of symptoms 39 months
Interventions	Antidepressant amitriptyline 10 mg for 2 months
Outcomes	Abdominal pain, dichotomous IBS-symptom score, continuous and dichotomous
Notes	No run-in Only diarrhoea-predominant IBS

Risk of bias

Vahedi 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical placebo. Both patients and researchers were unaware of the true identity of the prescribed medicine
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Vij 1991

Methods	RCT
Participants	50 IBS patient Unclear setting Mean age 32 Years 28% female
Interventions	Antidepressive doxepin od 75mg for 6 weeks
Outcomes	Abdominal pain, dichotomous Global assessment, dichotomous
Notes	No run-un

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, identical placebo

Vij 1991 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Virat 1987

Methods	RCT
Participants	78 IBS patients GI Outpatients Diagnostic criteria not defined Mean age 44 years 67% female
Interventions	Spasmolytic pinaverium 50 mg tds 1 week
Outcomes	Abdominal pain, dichotomous Global assessment, dichotomous
Notes	No run-in

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Low risk	Expected outcome reported
Other bias	Low risk	The study appears to be free of other sources of bias

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Achord 1979	Not an RCT
Alevizos 1989	Not appropriate patients: depressive patients with IBS
Andre 1979	Mixed intervention: composite of oxazepam and scopolamine butyl nitrate
Anonymous 1966	Not an RCT
Anonymous 1976	No extractable results
Anonymous 1982	Not an RCT
Anonymous 1986	Not an RCT; a review
Anonymous 1995	Not an RCT
Anonymous 1998	Not an RCT
Anonymous 2002a	Not an RCT
Anonymous 2002b	Not an RCT
Anonymous 2008	Not an RCT; a report from Ford 2008
Arffmann 1985	Cross-over study; no first phase data available
Awad 1997	Not outcome of interest; post-prandial motility
Baldi 1992	Duplicate publication with Baldi 1991
Barbier 1981	Cross-over study; no first phase data available
Bassotti 1988	Not an RCT
Baume 1972	Cross-over study; no first phase data available
Bazzocchi 1992	Not outcome of interest; anorectal function
Berthelot 1981	Only 28% of patients had true IBS. Separate results were not available for these patients
Birt 1989	Not available
Bixquert-Jimenez 2005	Not an RCT
Block 1983	Duplicate publication with Myren 1982
Bosaeus 2004	Not an RCT; a review
Bouchoucha 2000	Not outcome of interest; colonic response to food
Budavari 2002	Not an RCT

Study	Reason for exclusion
Burden 2001	Not an RCT; a review
Camarri 1981	Cross-over study; no first phase data available
Camarri 1986	No placebo group; comparing fenoverine and trimebutine
Camatte 1966	Not an RCT
Cann 1984	Cross-over study; no first phase data available
Capron 1981	Mixed intervention; composite of bulk, sedative and laxative
Capurso 1984	Cross over design with no parallel placebo administration in the first phase
Capurso 1992	Mixed intervention; composite of octylonium bromide and diazepam
Carling 1989	Cross-over study with no reporting of outcomes before first cross-over
Cerrato 2001	Inappropriate patients; children
Chapman 1990	No placebo; comparing mebeverine with high-fibre dietary advice and mebeverine with ispaghula
Chassany 2007	Inapproptiate patients; acute exacerbation
Chen 1999	No placebo; comparing Alverine/dimeticone and nifedipine
Chen 2004a	No placebo
Chevrel 1978	No placebo
Chicharro 2007	Not an RCT
Christen 1990	Not an RCT; a review
Clouse 1994	Not an RCT; a chart review
Clouse 2003	Not an RCT; a review
Cook 1990	Cross-over study; no first phase data available
Copé 1981	No placebo; comparing clidiniumbromide-chlordiazepoxide and trimebutine
Corazza 1983	No placebo; comparing pinaverium bromide and trimebutine
Corazziari 1999	Not an RCT; a review
Creed 2003	No placebo; comparing SSRI and psychotherapy with usual care
Creed 2006	Not an RCT; a review
Crowell 2004	Not an RCT; a review
Curtiss 2008	Not an RCT
Czimmer 2001	Not outcome of interest; sensory thresholds and recto-sigmoideal distention

Study	Reason for exclusion
Darnis 1980	No placebo; comparing bran and kaologenis
De Groote 1968	Not an RCT
de la Garoullaye 1991	No placebo; comparing fenoverine with PVOO and karaya gum
Defrance 1991	No placebo; comparing otilonium and pinaverium bromide
Delvaux 1997	Not an RCT; a review
Dettmar 1998	Not an RCT
Dettmar 1999	No placebo; comparing ispaghula husk with mebeverine and mebeverine with high fibre diet
Dew 1984	Cross-over study; no first phase data available
Diaz-Rubio 1985	Not available
Dioguardi 1991	No placebo; comparing octilonium bromide-diazepam and propantheline bromide-bromazepam
Dubinin 1987	No placebo; comparing bran and bran with other drugs
Ehsanullah 1985	Not outcome of interest; motility index
Eisenburg 1978	Not an RCT
Evangelista 2004	Not an RCT; a review
Evans 1996	Not outcome of interest; motility index
Ferrari 1986	No placebo; comparing octylonium bromide and cimetropium bromide
Fielding 1979	Not an RCT
Fielding 1984	No placebo; comparing different dietary fibres
Fioramonti 1988	Not outcome of interest; colonic motility
Floch 1988	Not an RCT
Francis 1994	Not an RCT
Frexinos 1985	Not outcome of interest; colonic motility
Fritz 1967	Not an RCT
Galeone 1986a	No placebo; comparing tiropramide, trimebutine and octilonium bromide
Galeone 1986b	No placebo; comparing pinaverium bromide and otilonium bromide
Geismar 1971	No extractable results; no clinically relevant data, only preferences
Geoffroy 1977	No placebo
Giaccari 2001	Not an RCT; patients divided in two groups bases on BMI

Study	Reason for exclusion
Giannini 2006	Not an RCT
Gibbons 1979	Not an RCT; a letter
Gilbody 2000	No placebo; comparing two different formulations of mebeverine hydrochloride
Glende 2002	Double-publication with Battaglia 1998
Gnauck 1977	Not an RCT
Golechha 1982	Cross-over study; no first phase data available
Gorard 1994	Not outcome of interest; whole gut and orocaecal transit times
Gorard 1995	Not outcome of interest; small intestinal motility
Greenbaum 1981	Not an RCT; a letter
Greenbaum 1984	Duplicate publication with Greenbaum 1987
Greenbaum 1987	Cross-over study; no first phase data available
Grigoleit 2005	Not an RCT; a review
Guerre 1979	No placebo; comparing karay gum and polyvinylpolypyrrolidone
Halpert 2005	Duplicate publication; paper based on same patients as Drossman 2003
Han 2009	Duplicate publication; same patients as Masand 2009
Hebden 2002	Cross-over study; no first phase data available
Herxheimer 1979	Not an RCT; a letter
Hotz 1994	No placebo
Houghton 1997	Not outcome of interest; colonic motility
Inauen 1994	No placebo; comparing mebeverine slow release and mebeverine tablets
Iwanaga 2002	Not an RCT; a review
Jackson 1998	Not an RCT
Jafri 2006	Not an RCT
Jayanthi 1998	Not an RCT
Ji 2007	Inappropriate patients; patients with functional bowel disorder not specified as IBS
Jing 2004	No placebo
Kaushik 2002	Not an RCT
Kirsch 2000	Not an RCT; a case report

Study	Reason for exclusion
Koch 1998	Double publication with Liu 1997
Koruda 1993	Not an RCT
Kountouras 2002	Inappropriate patients; patients with GERD, who also have IBS
Kumar 1987	No placebo; comparing different doses of ispaghula husk
Kunze 1990	No Placebo; comparing brief psychotherapy, acupuncture and papaverin
Lafon 1982	No data extractable
Lambert 1989	Not an RCT; a survey
Lambert 1991a	Not an RCT
Lambert 1991b	Inappropriate intervention; dietary advice
Lawson 1988	Cross-over study; no first phase data available
Levitan 1981	Inappropriate patients; mixed IBS and diverticulosis
Lin 2003	Not outcome of interest; anorectal visceral sensorimotor functions
Liu 2006	Not an RCT
Locke 2004	Not an RCT; a review article
Lu 2000	No placebo; comparing pinaverlum bromide and mebeverine
Luttecke 1978	Not outcome of interest; only preference
Luttecke 1980	Cross-over study; no first phase data available
Lydiard 2007	Not an RCT
MacRae 1979	Not an RCT; a letter
Manning 1976	No placebo
Manning 1977	No placebo; Comparing high and low-fibre diet
Marks 2008	Duplicate publication; same patients as Masand 2009
Masamune 1998	No placebo; comparing calcium polycarbophil and torimebutine maleate
Masand 2002	Not an RCT
Masand 2005	Not an RCT
Matts 1967	No extractable data
Meier 1996	Mixed intervention; psyllium and Cisapride versus placebo
Miller 2006	Not an RCT

Study	Reason for exclusion
Misra 1989	Not the appropriate patients; patients who had recovered completely after treatment
Modena 1993	No placebo
Mollica 1992	No placebo; comparing Otilonium bromide-diazepam and otilonium bromide
Morgan 2005	Cross-over study; no first phase data available
Morrison 1987	Not outcome of interest; the role of the dietitian
Mortensen 1987	Not outcome of interest; short-chain fatty acids (SCFA) in faeces
Nash 1986	Cross-over study; no first phase data available
Nedogoda 2000	No placebo; comparing pinaverium bromide and otilonium bromide
Noel 1989	Not an RCT
Olden 2005	Not an RCT; a review
Pardell 1982	No placebo; comparing clebopride and hyoscine N-butylbromide
Parisi 2002	No placebo; comparing guargum and wheat bran
Parisi 2005	No placebo group; comparing different doses of guar gum
Passaretti 1985	Not an RCT
Passaretti 1989b	Not outcome of interest; sigmoid-rectal motility
Pearson 2000	Not an RCT
Piai 1987a	Inappropriate patients; mixture of IBS and functional constipation
Piai 1987b	Inappropriate patients; IBS in remission
Pittler 1998	Not an RCT; a meta-analysis
Prior 1986a	Only abstract; full text not available
Prior 1986b	Duplicate publication; abstract publication of Prior 1987
Prout 1983	No placebo; comparing two doses of mebeverine
Quilici 1998	Not an RCT
Quilici 2003	Not an RCT
Rasmussen 1982	Inappropriate intervention; diet
Rees 1979	Cross-over study; no first phase data available
Rhodes 1978	Inaprporiate intervention; sedative-anticholinergic drug combinations
Rhodes 1980	No extractable results

Study	Reason for exclusion
Ritchie 1980	No placebo; comparing psychotropic drug, smooth-muscle relaxant, and bulking agent
Sagduyu 2002	Not an RCT; a letter
Sato 2006	Not an RCT; a review
Schaffstein 1990	No placebo; comparing trimebutine and mebeverine
Schutz 1992	Not an RCT
Secco 1983	Not an RCT
Sharma 1987	Not an RCT
Shaughnessy 2000	Not an RCT
Shrivastava 1984	Not outcome of interest
Singh 2007	Not an RCT
Slawson 2002	Not an RCT
Snook 1994	Cross-over study; no first phase data available
Soifer 1987	Not an RCT
Soifer 1992	Not outcome of interest; colon motility
Soriano 1992	Not an RCT
Stiefelhagen 2008	Not an RCT
Swiatczak 1998	Not an RCT; comparing before and after treatment with bran
Talley 2003	Not an RCT
Talley 2004	Not an RCT
Talley 2008b	Not an RCT; a review
Tan 2007	Not an RCT; a review
Tanum 1996	Inappropriate patients; mixture of IBS and NUD patients
Tanum 2000	Not outcome of interest; assessment of personality traits
Tarpila 2004	No placebo; comparing flaxseed and psyllium
Tarquini 1984	No placebo; comparing octilonium bromide and octilonium bromide with a benzodiazepine
Tasman-Jones 1973	Cross-over study; no first phase data available
Tinozzi 1984	No placebo; comparing tiropramide hydrochloride and octylonium bromide
Tomas-Ridocci 1992	Not the appropriate patients; patients with chronic constipation with or without IBS

Study	Reason for exclusion
Toussaint 1981	No placebo; comparing trimebutine and mebeverine
Tripathi 1983	Duplicate publication with Shrivastava 1984
Tsuneoka 1987	No placebo; comparing trimebutine maleate and mepenzolate bromide
Tudor 1986	No placebo; comparing alverine citrate and mebeverine hydrochloride
van Kerkhoven 2007	Not an RCT; a letter
Van Outryve 1995	No placebo; comparing mebeverine and mebeverine sustained release
Van Steensel 1990	Not an RCT
Villagrasa 1991	No placebo; comparing fibre-rich diet and otilonium bromide
Wald 1990	Not an RCT
Wald 2002	Not an RCT; a review
Wang 2003	No placebo; comparing fluoxetine, paroxetine and doxepin
Wittmann 1999	No RCT; healthy patients compared with IBS patients
Woolner 2000	Not an RCT; preliminary before-after study of low-fibre diet
Yuan 2003	Not an RCT
Yuan 2005	No placebo; comparing trimebutine maleat and pinaveriumbromide
Zhang 2002	No placebo; comparing otilonium bromide, collodal bismuth tartrate and compound diphenoxylate
Zhou 2002	No placebo; comparing paroxetine and pinaverium bromide versus paroxetine versus pinaverium bromide
Zuckerman 2006	Not an RCT; therapeutic recommendations

Characteristics of studies awaiting assessment *[ordered by study ID]*

Abdul-Baki 2009

Methods	RCT
Participants	107 IBS patients
Interventions	Antidepressant imipramine 25 mg versus matched placebo for 12 weeks
Outcomes	Global symptom relief
Notes	

Bijkerk 2009

Methods	RCT
Participants	275 patients with IBS General practice
Interventions	Bulking agent 12 weeks of treatment with: psyllium 10 g or bran 10 g or placebo 10 g (rice flour)
Outcomes	Adequate symptom relief IBS symptom severity score Severity of abdominal pain IBS quality of life scale
Notes	

Everitt 2010

Methods	RCT
Participants	135 IBS patients (Rome III)
Interventions	Antispasmodic and bulking agent mebeverine methylcellulose placebo
Outcomes	IBS severity scale IBS-QOL
Notes	

Khalif 2009

Methods	RCT
Participants	118 IBS patients (Rome II)
Interventions	Antispasmodic oral buscopan (20 mg TID) buscopan suppository (30 mg OD) oral drotaverine (80 mg TID) calcium gluconate tablets (1 TID)

Khalif 2009 *(Continued)*

	calendula suppository (OD)
Outcomes	Pain score
Notes	

Ladabaum 2010

Methods	RCT
Participants	54 non-depressed IBS patients
Interventions	Antidepressant citalopram (20 mg/.day for 4 weeks, then 40 mg/day for 4 weeks) placebo
Outcomes	Adequate relief of IBS symptoms IBS-QOL
Notes	

Merat 2010

Methods	RCT
Participants	90 IBS outpatients
Interventions	Antispasmodic Peppermint oil, colpermin (1 capsule TID for 8 weeks) Placebo (1 capsule TID for 8 weeks)
Outcomes	Abdominal pain QOL
Notes	

Pace 2010

Methods	RCT
Participants	186 IBS patients (Rome II)
Interventions	Antispasmodic octatropine (40 mg BID) and diazepam (2.5 mg BID) or placebo
Outcomes	Satisfactory relief of abdominal pain

Pace 2010 *(Continued)*

	abdominal swelling
	abdominal pain and discomfort
	symptom severity
	number of bowel movements
Notes	

Reme 2010

Methods	RCT
Participants	149 IBS patients
Interventions	Antispasmodic
	mebeverine or mebeverine and cognitive behavior therapy
Outcomes	Psychological distress (anxiety and depression)
Notes	

Saps 2009

Methods	RCT
Participants	90 children with functional gastrointestinal disorders
Interventions	Antidepressant
	amitriptyline (dose based on weight) or placebo
Outcomes	Therapeutic response
Notes	

Wittmann 2010

Methods	RCT
Participants	412 IBS patients (Rome III)
Interventions	Antispasmodic
	alverine citrate (60 mg) with simeticone (300 mg) BID or matching placebo
Outcomes	Abdominal pain
Notes	

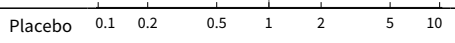
DATA AND ANALYSES

Comparison 1. Bulking agents: Abdominal pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparing nr(%) of successfully treated IBS patients	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.61, 1.36]
1.1 Insoluble fibres	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Soluble fibres	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.61, 1.36]
2 Comparing scores on abdominal pain in IBS patients	4	186	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.34, 0.40]
2.1 Insoluble fibres	3	126	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.52, 0.52]
2.2 Soluble fibres	1	60	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.45, 0.57]

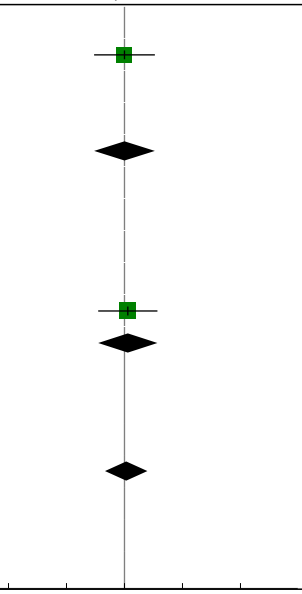
Analysis 1.1. Comparison 1 Bulking agents: Abdominal pain, Outcome 1 Comparing nr(%) of successfully treated IBS patients.

Study or subgroup	Bulking agent n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Insoluble fibres					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Bulking agent), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.1.2 Soluble fibres					
Prior 1987	21/40	23/40		100%	0.91[0.61,1.36]
Subtotal (95% CI)	**40**	**40**		**100%**	**0.91[0.61,1.36]**
Total events: 21 (Bulking agent), 23 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.45(P=0.65)					
Total (95% CI)	**40**	**40**		**100%**	**0.91[0.61,1.36]**
Total events: 21 (Bulking agent), 23 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.45(P=0.65)					
Test for subgroup differences: Not applicable					



Analysis 1.2. Comparison 1 Bulking agents: Abdominal pain, Outcome 2 Comparing scores on abdominal pain in IBS patients.

Study or subgroup	Bulking agent N	Bulking agent Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
1.2.1 Insoluble fibres							
Aller 2004	28	-1.6 (1.5)	28	-1.6 (1.9)		48.73%	0[-0.52,0.52]
Fowlie 1992	23	-5 (0)	19	-5 (0)			Not estimable
Rees 2005	14	-0.8 (0)	14	-0.9 (0)			Not estimable
Subtotal ***	**65**		**61**			**48.73%**	**0[-0.52,0.52]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.2.2 Soluble fibres							
Longstreth 1981	26	-0.6 (0.5)	34	-0.6 (0.5)		51.27%	0.06[-0.45,0.57]
Subtotal ***	**26**		**34**			**51.27%**	**0.06[-0.45,0.57]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.22(P=0.83)							
Total ***	**91**		**95**			**100%**	**0.03[-0.34,0.4]**
Heterogeneity: Tau²=0; Chi²=0.02, df=1(P=0.88); I²=0%							
Test for overall effect: Z=0.16(P=0.87)							
Test for subgroup differences: Chi²=0.02, df=1 (P=0.88), I²=0%							

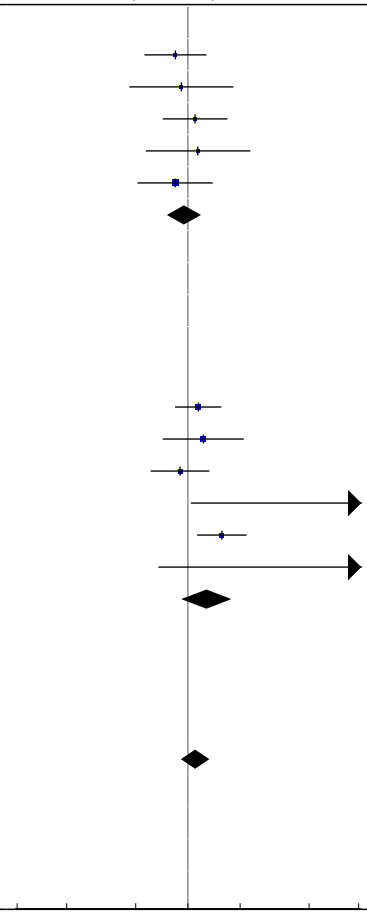


Comparison 2. Bulking agents: Global assessment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparing nr(%) of successfully treated patients with IBS	11	565	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.91, 1.33]
1.1 Insoluble fibres	5	244	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.76, 1.19]
1.2 Soluble fibre	6	321	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.91, 1.78]
2 Comparing scores on global assessment in IBS patients	1	56	Std. Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.74, 0.31]
2.1 Insoluble fibres	1	56	Std. Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.74, 0.31]
2.2 Soluble fibres	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

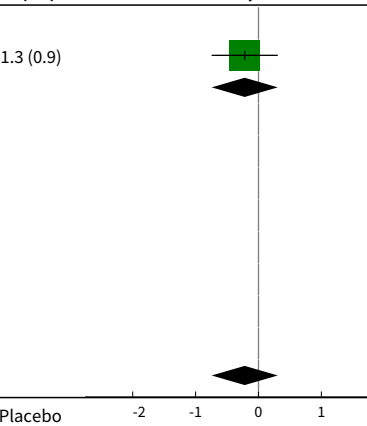
Analysis 2.1. Comparison 2 Bulking agents: Global assessment, Outcome 1 Comparing nr(%) of successfully treated patients with IBS.

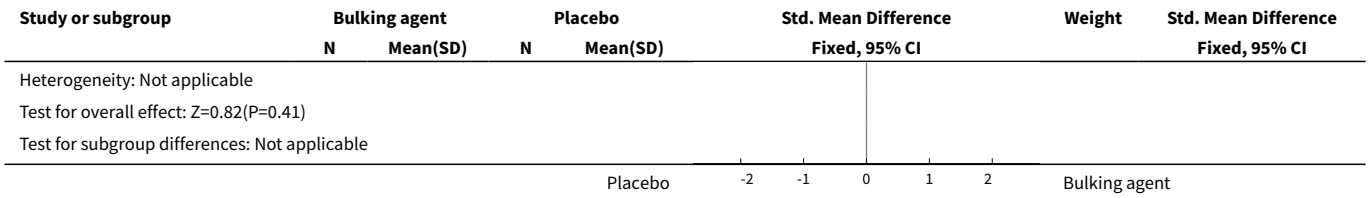
Study or subgroup	Bulking agent n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Insoluble fibres					
Fowlie 1992	15/25	17/24		12.29%	0.85[0.56,1.28]
Kruis 1986	11/40	12/40		6.02%	0.92[0.46,1.83]
Lucey 1987	11/14	10/14		11.65%	1.1[0.72,1.69]
Rees 2005	8/14	7/14		5.99%	1.14[0.57,2.29]
Soltoft 1976	15/32	15/27		9.64%	0.84[0.51,1.39]
Subtotal (95% CI)	**125**	**119**		**45.61%**	**0.95[0.76,1.19]**
Total events: 60 (Bulking agent), 61 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.26, df=4(P=0.87); I^2=0%					
Test for overall effect: Z=0.47(P=0.64)					
2.1.2 Soluble fibre					
Arthurs 1983	29/40	24/38		16.3%	1.15[0.84,1.56]
Jalihal 1990	9/11	6/9		8.7%	1.23[0.72,2.1]
Longstreth 1981	20/37	24/40		13%	0.9[0.61,1.33]
Nigam 1984	8/21	0/21		0.46%	17[1.04,276.85]
Prior 1987	33/40	21/40		15.48%	1.57[1.13,2.18]
Ritchie 1979	5/12	0/12		0.46%	11[0.67,179.29]
Subtotal (95% CI)	**161**	**160**		**54.39%**	**1.28[0.91,1.78]**
Total events: 104 (Bulking agent), 75 (Placebo)					
Heterogeneity: Tau^2=0.08; Chi^2=11.71, df=5(P=0.04); I^2=57.31%					
Test for overall effect: Z=1.43(P=0.15)					
Total (95% CI)	**286**	**279**		**100%**	**1.1[0.91,1.33]**
Total events: 164 (Bulking agent), 136 (Placebo)					
Heterogeneity: Tau^2=0.03; Chi^2=15.49, df=10(P=0.12); I^2=35.43%					
Test for overall effect: Z=1(P=0.32)					
Test for subgroup differences: Chi^2=2.1, df=1 (P=0.15), I^2=52.33%					



Analysis 2.2. Comparison 2 Bulking agents: Global assessment, Outcome 2 Comparing scores on global assessment in IBS patients.

Study or subgroup	Bulking agent N	Bulking agent Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
2.2.1 Insoluble fibres							
Aller 2004	28	-1.5 (0.9)	28	-1.3 (0.9)		100%	-0.22[-0.74,0.31]
Subtotal ***	**28**		**28**			**100%**	**-0.22[-0.74,0.31]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.82(P=0.41)							
2.2.2 Soluble fibres							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**28**		**28**			**100%**	**-0.22[-0.74,0.31]**

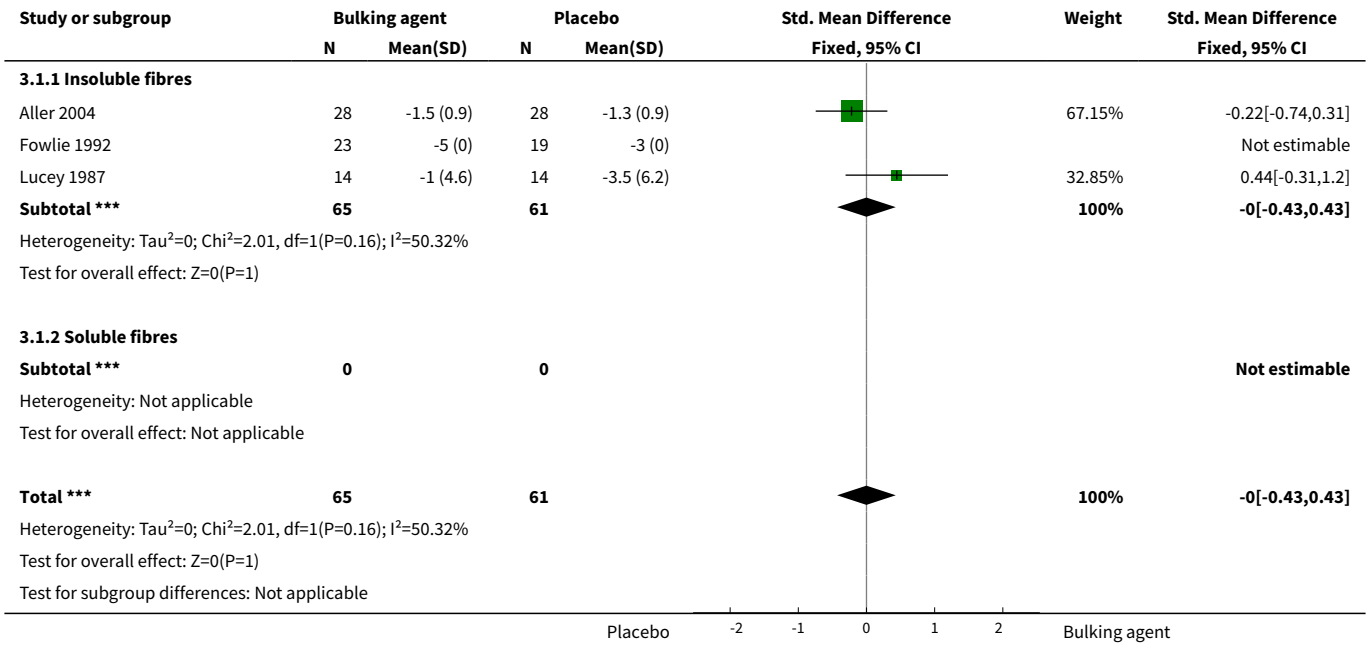




Comparison 3. Bulking agents: Outcome on symptom score

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparing symptom scores in IBS patients	3	126	Std. Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.43, 0.43]
1.1 Insoluble fibres	3	126	Std. Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.43, 0.43]
1.2 Soluble fibres	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Bulking agents: Outcome on symptom score, Outcome 1 Comparing symptom scores in IBS patients.

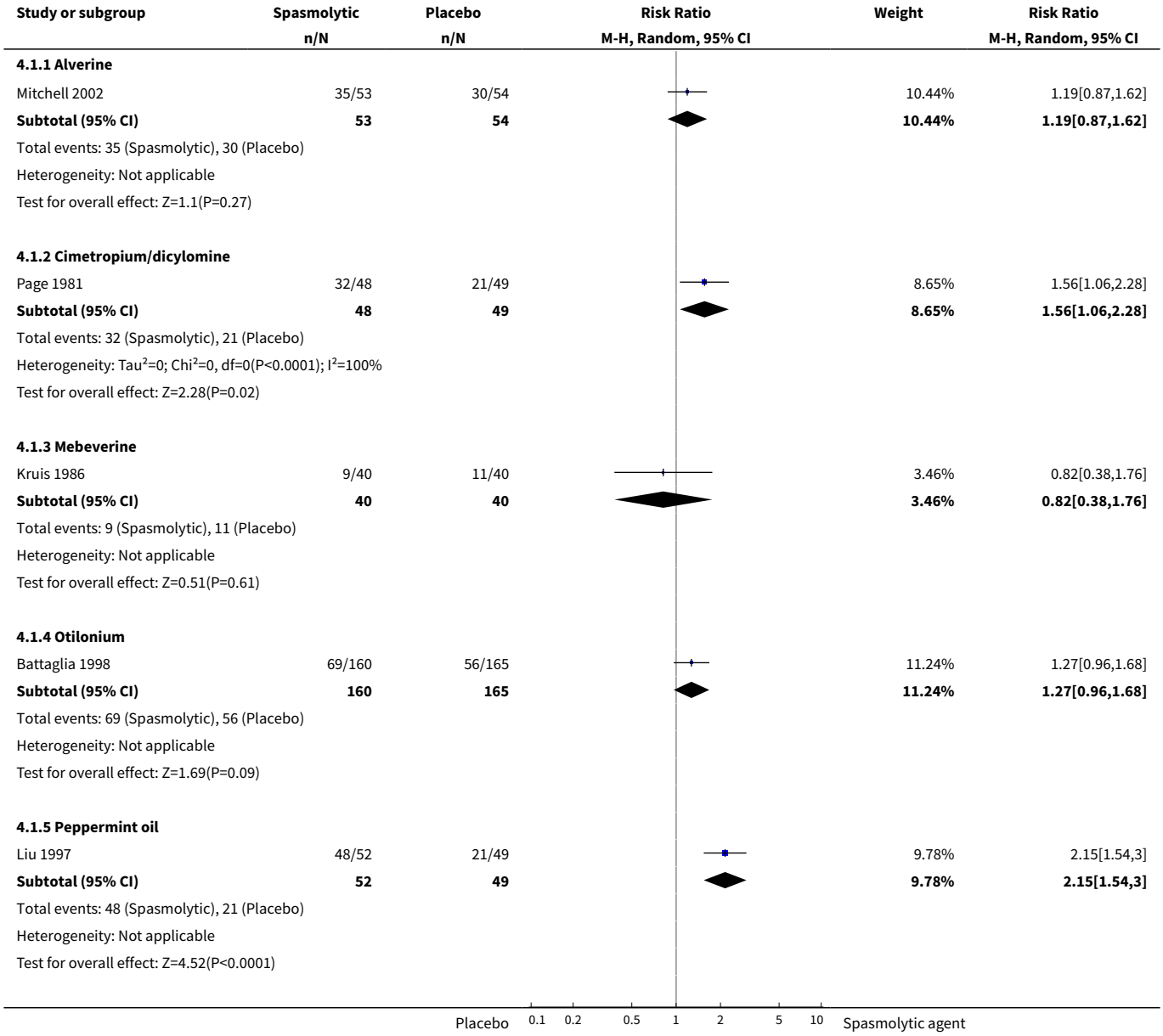


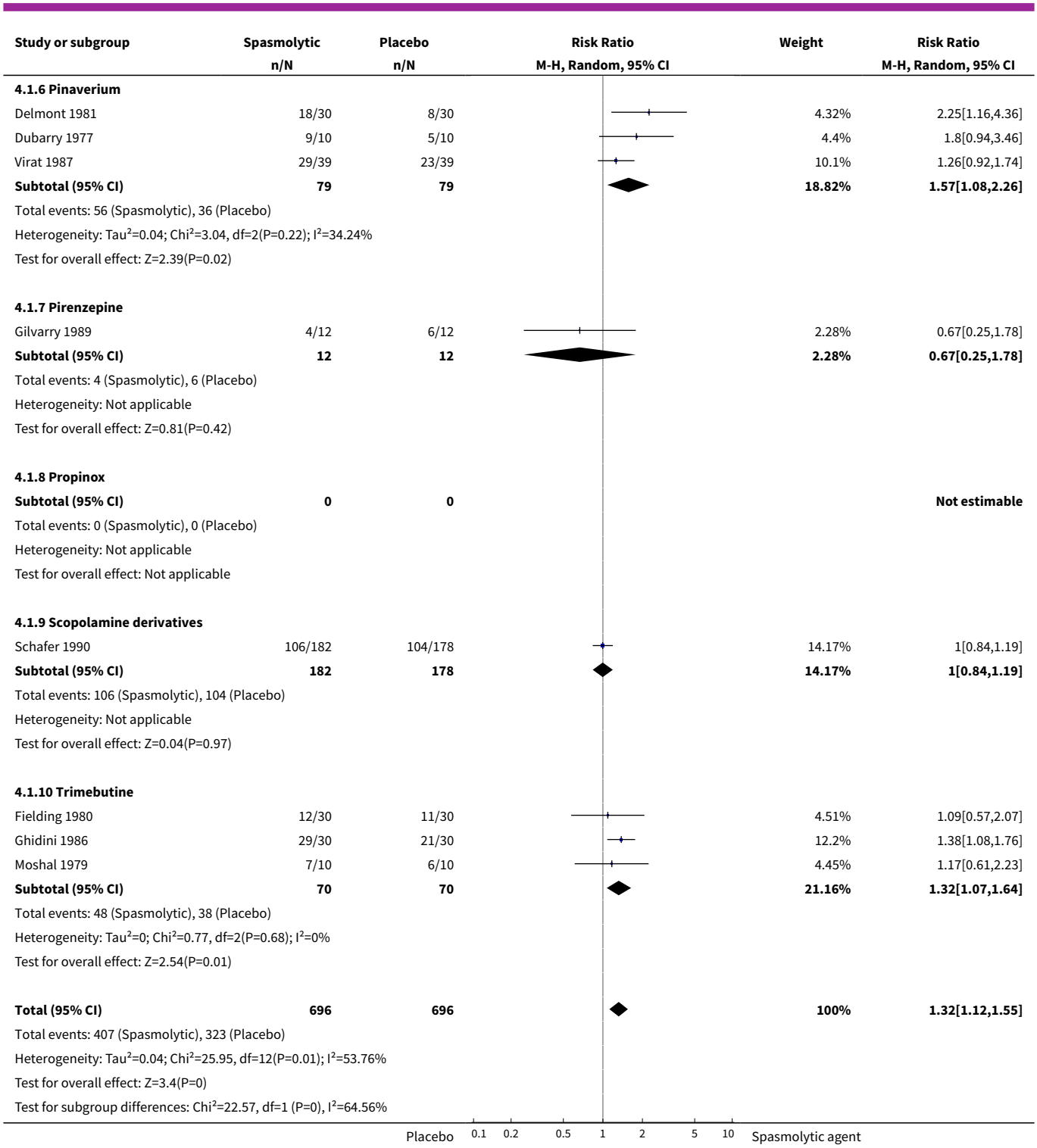
Comparison 4. Spasmolytics: Abdominal pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparing nr(%) of successfully treated IBS patients on Abdominal pain	13	1392	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.12, 1.55]
1.1 Alverine	1	107	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.87, 1.62]
1.2 Cimetropium/dicylomine	1	97	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.06, 2.28]
1.3 Mebeverine	1	80	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.38, 1.76]
1.4 Otilonium	1	325	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.96, 1.68]
1.5 Peppermint oil	1	101	Risk Ratio (M-H, Random, 95% CI)	2.15 [1.54, 3.00]
1.6 Pinaverium	3	158	Risk Ratio (M-H, Random, 95% CI)	1.57 [1.08, 2.26]
1.7 Pirenzepine	1	24	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.25, 1.78]
1.8 Propinox	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.9 Scopolamine derivatives	1	360	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.84, 1.19]
1.10 Trimebutine	3	140	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.07, 1.64]
2 Comparing scores on abdominal pain in IBS patients	8	455	Std. Mean Difference (IV, Random, 95% CI)	1.14 [0.47, 1.81]
2.1 Alvarine	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Cimetropium/dicyclomine	3	146	Std. Mean Difference (IV, Random, 95% CI)	1.08 [0.73, 1.43]
2.3 Mebeverine	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Otilonium	1	70	Std. Mean Difference (IV, Random, 95% CI)	0.43 [-0.04, 0.91]
2.5 Peppermint oil	1	57	Std. Mean Difference (IV, Random, 95% CI)	3.88 [2.98, 4.79]
2.6 Pinaverium	2	114	Std. Mean Difference (IV, Random, 95% CI)	0.44 [-0.20, 1.08]
2.7 Pirenzepine	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.8 Propinox	1	68	Std. Mean Difference (IV, Random, 95% CI)	0.45 [-0.04, 0.93]
2.9 Scopolamine derivatives	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.10 Trimebutine	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

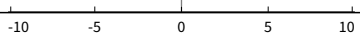
Analysis 4.1. Comparison 4 Spasmolytics: Abdominal pain, Outcome 1 Comparing nr(%) of successfully treated IBS patients on Abdominal pain.

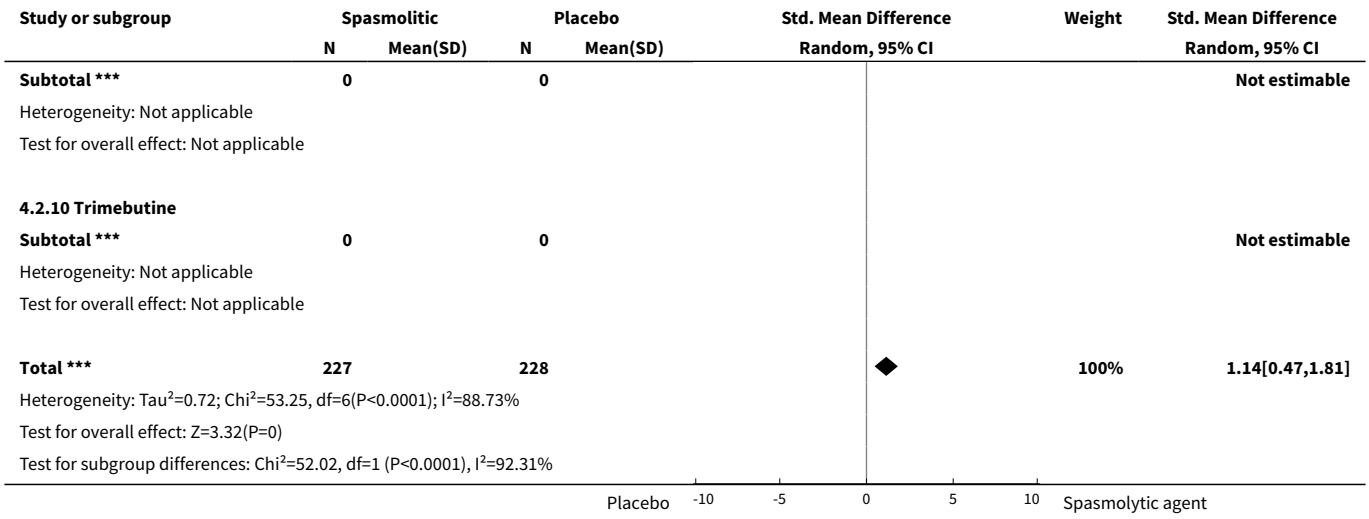




Analysis 4.2. Comparison 4 Spasmolytics: Abdominal pain, Outcome 2 Comparing scores on abdominal pain in IBS patients.

Study or subgroup	Spasmolitic N	Spasmolitic Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
4.2.1 Alvarine							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
4.2.2 Cimetropium/dicyclomine							
Centonze 1988	23	-0.2 (0.5)	21	-1.5 (1.3)		14.17%	1.26[0.6,1.91]
Dobrilla 1990	35	-0.2 (0.5)	34	-0.9 (0.7)		14.94%	1.15[0.64,1.67]
Passaretti 1989a	16	-0.4 (0.5)	17	-0.8 (0.5)		13.84%	0.74[0.03,1.45]
Subtotal ***	**74**		**72**			**42.95%**	**1.08[0.73,1.43]**
Heterogeneity: Tau^2=0; Chi^2=1.23, df=2(P=0.54); I^2=0%							
Test for overall effect: Z=6.06(P<0.0001)							
4.2.3 Mebeverine							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
4.2.4 Otilonium							
Baldi 1991	33	-2.6 (1.7)	37	-3.4 (2.2)		15.12%	0.43[-0.04,0.91]
Subtotal ***	**33**		**37**			**15.12%**	**0.43[-0.04,0.91]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.79(P=0.07)							
4.2.5 Peppermint oil							
Cappello 2007	28	-1.5 (0.3)	29	-2.5 (0.2)		12.63%	3.88[2.98,4.79]
Subtotal ***	**28**		**29**			**12.63%**	**3.88[2.98,4.79]**
Heterogeneity: Not applicable							
Test for overall effect: Z=8.43(P<0.0001)							
4.2.6 Pinaverium							
Awad 1995	19	-2.3 (1.8)	19	-3.1 (1.8)		14.22%	0.44[-0.2,1.08]
Virat 1987	38	-0.8 (0)	38	-1.1 (0)			Not estimable
Subtotal ***	**57**		**57**			**14.22%**	**0.44[-0.2,1.08]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.34(P=0.18)							
4.2.7 Pirenzepine							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
4.2.8 Propinox							
Pulpeiro 2000	35	-1.6 (1)	33	-2.1 (1.1)		15.09%	0.45[-0.04,0.93]
Subtotal ***	**35**		**33**			**15.09%**	**0.45[-0.04,0.93]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.81(P=0.07)							
4.2.9 Scopolamine derivatives							





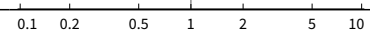
Comparison 5. Spasmolytics: Global assessment

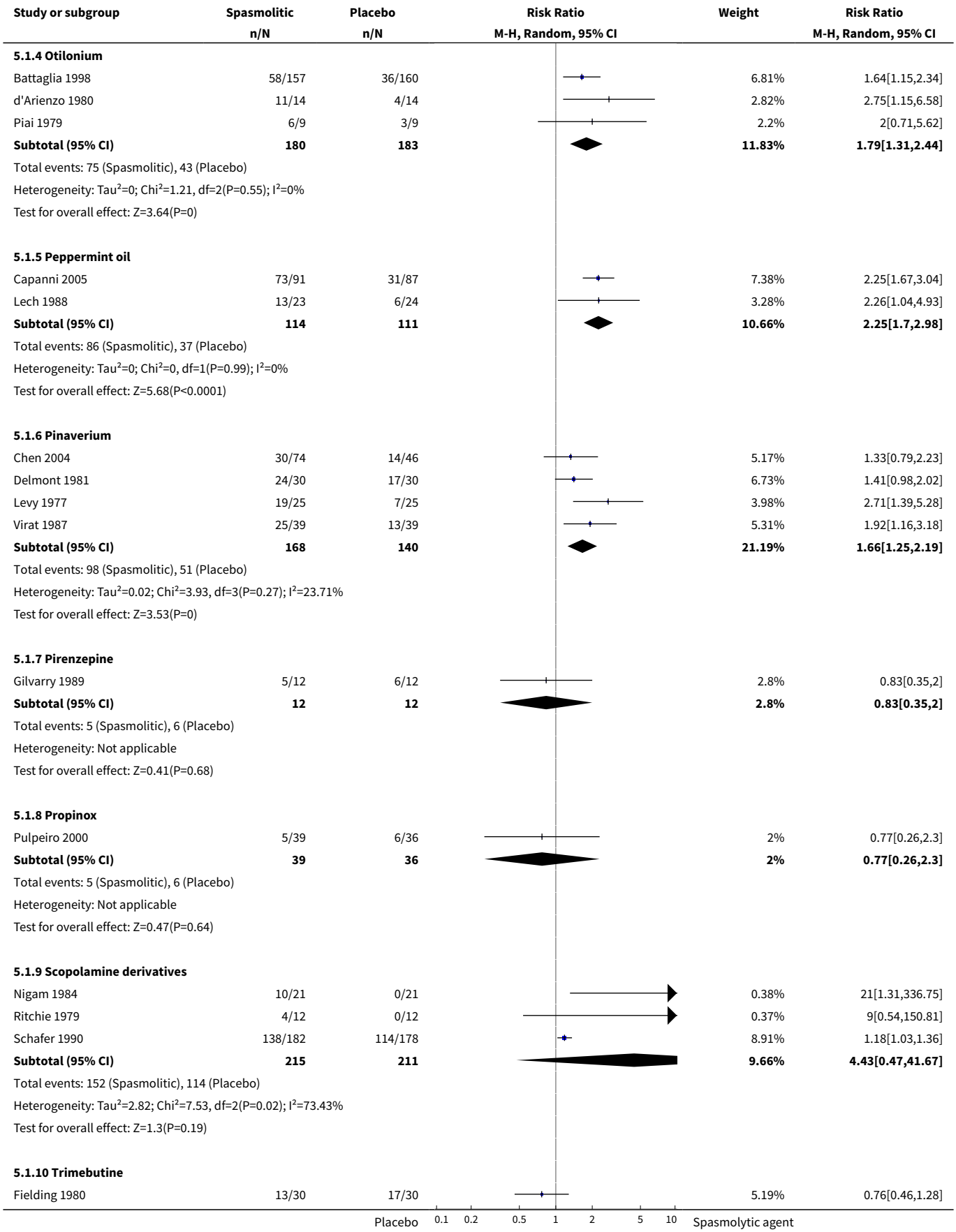
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparing nr (%) of successfully treated patients	22	1983	Risk Ratio (M-H, Random, 95% CI)	1.49 [1.25, 1.77]
1.1 Alverine	1	107	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.80, 1.80]
1.2 Cimtetropium/dicyclomine	4	255	Risk Ratio (M-H, Random, 95% CI)	1.78 [1.15, 2.75]
1.3 Mebeverine	1	80	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.16, 1.07]
1.4 Otilonium	3	363	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.31, 2.44]
1.5 Peppermint oil	2	225	Risk Ratio (M-H, Random, 95% CI)	2.25 [1.70, 2.98]
1.6 Pinaverium	4	308	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.25, 2.19]
1.7 Pirenzepine	1	24	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.35, 2.00]
1.8 Propinox	1	75	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.26, 2.30]
1.9 Scopolamine derivatives	3	426	Risk Ratio (M-H, Random, 95% CI)	4.43 [0.47, 41.67]
1.10 Trimebutine	2	120	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.68, 1.38]
2 Comparing scores on global assessment in IBS patients	2	331	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Alvarine	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Cimetropium/dicyclomine	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Mebeverine	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Otilonium	1	271	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 Peppermint oil	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 Pinaverium	1	60	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.7 Pirenzepine	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.8 Propinox	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.9 Scopolamine derivatives	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.10 Trimebutine	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

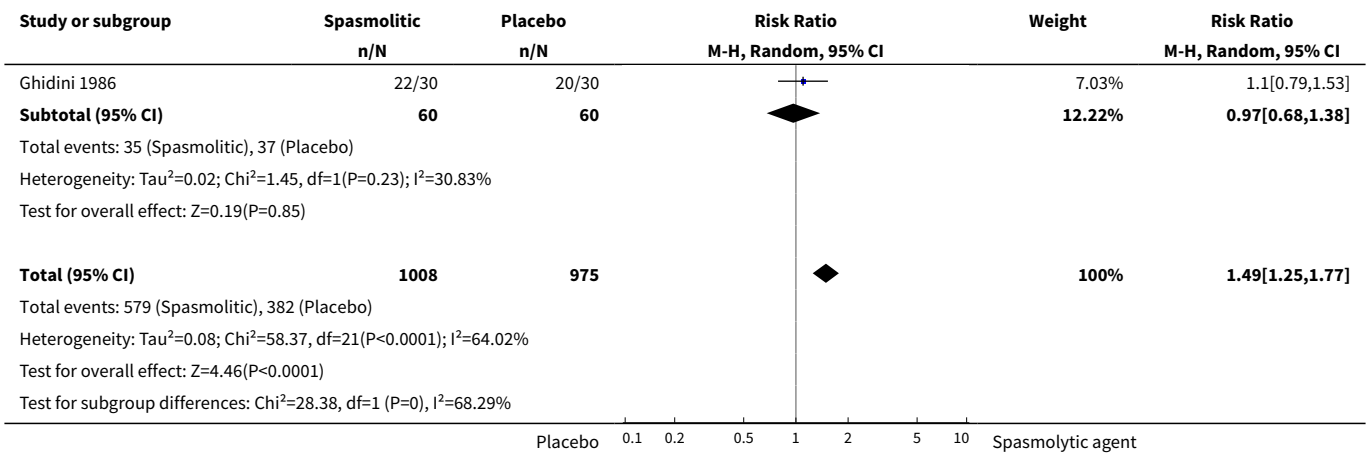
Analysis 5.1. Comparison 5 Spasmolytics: Global assessment, Outcome 1 Comparing nr (%) of successfully treated patients.

Study or subgroup	Spasmolitic n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 Alverine					
Mitchell 2002	27/53	23/54		6.24%	1.2[0.8,1.8]
Subtotal (95% CI)	**53**	**54**		**6.24%**	**1.2[0.8,1.8]**
Total events: 27 (Spasmolitic), 23 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.86(P=0.39)					
5.1.2 Cimtetropium/dicyclomine					
Centonze 1988	20/24	5/24		3.17%	4[1.8,8.9]
Dobrilla 1990	31/35	24/35		7.87%	1.29[1,1.67]
Page 1981	27/48	16/49		5.58%	1.72[1.07,2.77]
Passaretti 1989a	13/20	8/20		4.27%	1.63[0.87,3.04]
Subtotal (95% CI)	**127**	**128**		**20.89%**	**1.78[1.15,2.75]**
Total events: 91 (Spasmolitic), 53 (Placebo)					
Heterogeneity: Tau^2=0.13; Chi^2=9.31, df=3(P=0.03); I^2=67.76%					
Test for overall effect: Z=2.58(P=0.01)					
5.1.3 Mebeverine					
Kruis 1986	5/40	12/40		2.51%	0.42[0.16,1.07]
Subtotal (95% CI)	**40**	**40**		**2.51%**	**0.42[0.16,1.07]**
Total events: 5 (Spasmolitic), 12 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.81(P=0.07)					

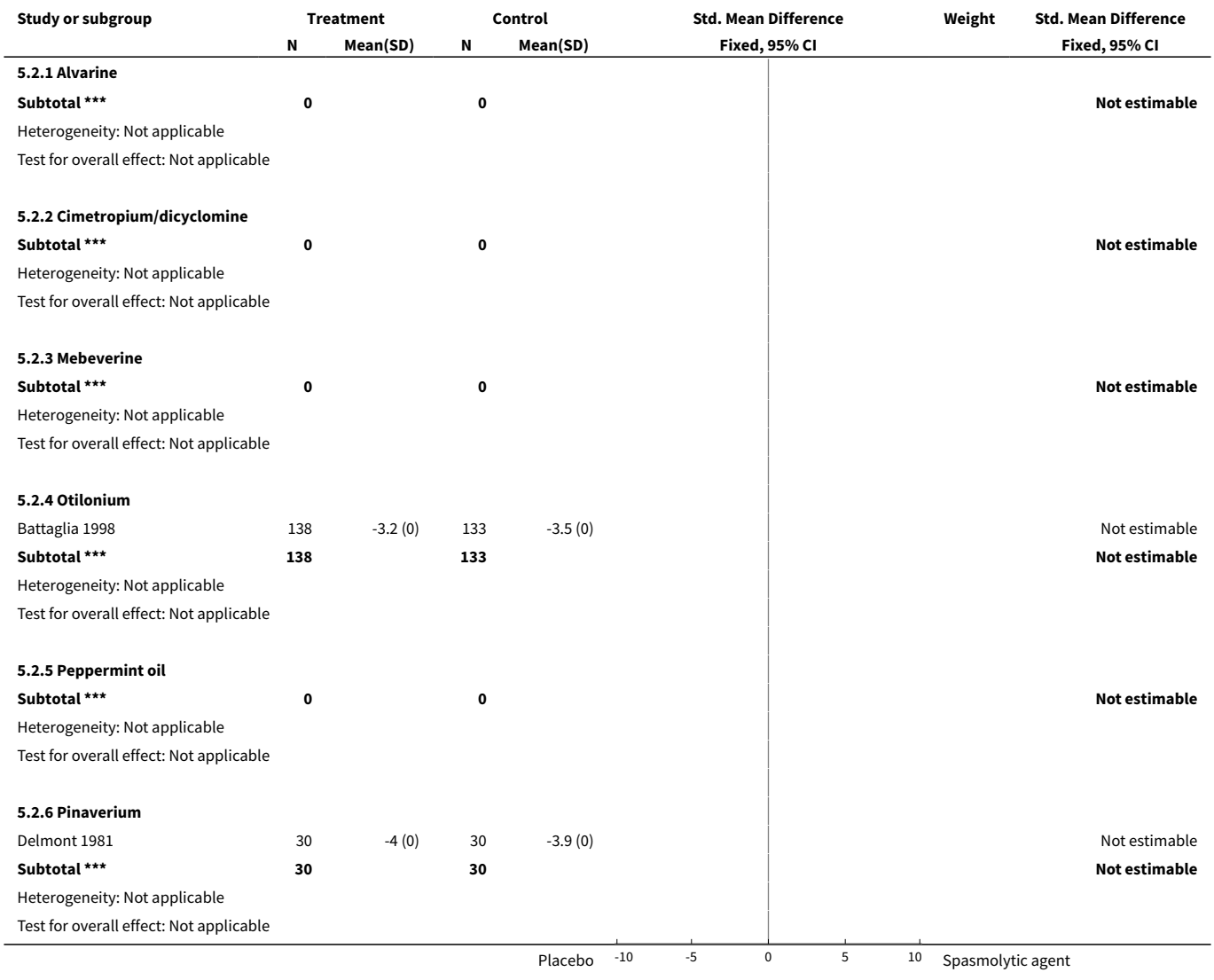




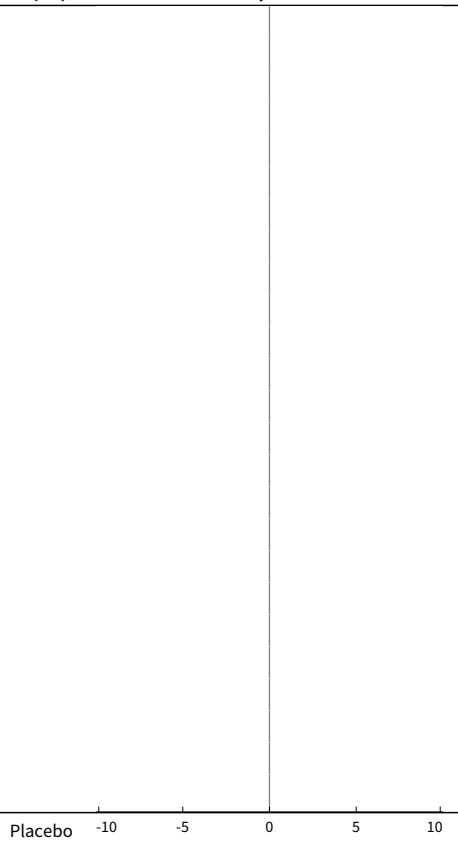
Study or subgroup	Spasmolitic n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.1.4 Otilonium					
Battaglia 1998	58/157	36/160		6.81%	1.64[1.15,2.34]
d'Arienzo 1980	11/14	4/14		2.82%	2.75[1.15,6.58]
Piai 1979	6/9	3/9		2.2%	2[0.71,5.62]
Subtotal (95% CI)	**180**	**183**		**11.83%**	**1.79[1.31,2.44]**
Total events: 75 (Spasmolitic), 43 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.21, df=2(P=0.55); I^2=0%					
Test for overall effect: Z=3.64(P=0)					
5.1.5 Peppermint oil					
Capanni 2005	73/91	31/87		7.38%	2.25[1.67,3.04]
Lech 1988	13/23	6/24		3.28%	2.26[1.04,4.93]
Subtotal (95% CI)	**114**	**111**		**10.66%**	**2.25[1.7,2.98]**
Total events: 86 (Spasmolitic), 37 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=5.68(P<0.0001)					
5.1.6 Pinaverium					
Chen 2004	30/74	14/46		5.17%	1.33[0.79,2.23]
Delmont 1981	24/30	17/30		6.73%	1.41[0.98,2.02]
Levy 1977	19/25	7/25		3.98%	2.71[1.39,5.28]
Virat 1987	25/39	13/39		5.31%	1.92[1.16,3.18]
Subtotal (95% CI)	**168**	**140**		**21.19%**	**1.66[1.25,2.19]**
Total events: 98 (Spasmolitic), 51 (Placebo)					
Heterogeneity: Tau^2=0.02; Chi^2=3.93, df=3(P=0.27); I^2=23.71%					
Test for overall effect: Z=3.53(P=0)					
5.1.7 Pirenzepine					
Gilvarry 1989	5/12	6/12		2.8%	0.83[0.35,2]
Subtotal (95% CI)	**12**	**12**		**2.8%**	**0.83[0.35,2]**
Total events: 5 (Spasmolitic), 6 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.41(P=0.68)					
5.1.8 Propinox					
Pulpeiro 2000	5/39	6/36		2%	0.77[0.26,2.3]
Subtotal (95% CI)	**39**	**36**		**2%**	**0.77[0.26,2.3]**
Total events: 5 (Spasmolitic), 6 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.47(P=0.64)					
5.1.9 Scopolamine derivatives					
Nigam 1984	10/21	0/21		0.38%	21[1.31,336.75]
Ritchie 1979	4/12	0/12		0.37%	9[0.54,150.81]
Schafer 1990	138/182	114/178		8.91%	1.18[1.03,1.36]
Subtotal (95% CI)	**215**	**211**		**9.66%**	**4.43[0.47,41.67]**
Total events: 152 (Spasmolitic), 114 (Placebo)					
Heterogeneity: Tau^2=2.82; Chi^2=7.53, df=2(P=0.02); I^2=73.43%					
Test for overall effect: Z=1.3(P=0.19)					
5.1.10 Trimebutine					
Fielding 1980	13/30	17/30		5.19%	0.76[0.46,1.28]



Analysis 5.2. Comparison 5 Spasmolytics: Global assessment, Outcome 2 Comparing scores on global assessment in IBS patients.



Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
5.2.7 Pirenzepine							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.2.8 Propinox							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.2.9 Scopolamine derivatives							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.2.10 Trimebutine							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**168**		**163**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



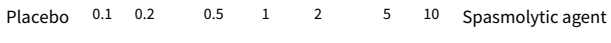
Comparison 6. Spasmolytics: Outcome on symptom score

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparing nr (%) of patients successfully treated	4	586	Risk Ratio (M-H, Random, 95% CI)	1.86 [1.26, 2.76]
1.1 Alvarine	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Cimetropium/dicyclomine	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Mebeverine	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Otilonium	1	317	Risk Ratio (M-H, Random, 95% CI)	1.64 [1.15, 2.34]
1.5 Peppermint oil	3	269	Risk Ratio (M-H, Random, 95% CI)	1.94 [1.09, 3.46]
1.6 Pinaverium	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.7 Pirenzepine	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

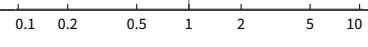
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8 Propinox	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.9 Scopolamine derivatives	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.10 Trimebutine	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Comparing symptom scores in IBS patients	4	243	Std. Mean Difference (IV, Random, 95% CI)	2.39 [0.50, 4.29]
2.1 Alvarine	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Cimetropium/dicyclomine	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Mebeverine	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Otilonium	1	28	Std. Mean Difference (IV, Random, 95% CI)	0.20 [-0.55, 0.94]
2.5 Peppermint oil	1	57	Std. Mean Difference (IV, Random, 95% CI)	9.86 [7.92, 11.81]
2.6 Pinaverium	2	158	Std. Mean Difference (IV, Random, 95% CI)	0.51 [0.19, 0.84]
2.7 Pirenzepine	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.8 Propinox	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.9 Scopolamine derivatives	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.10 Trimebutine	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

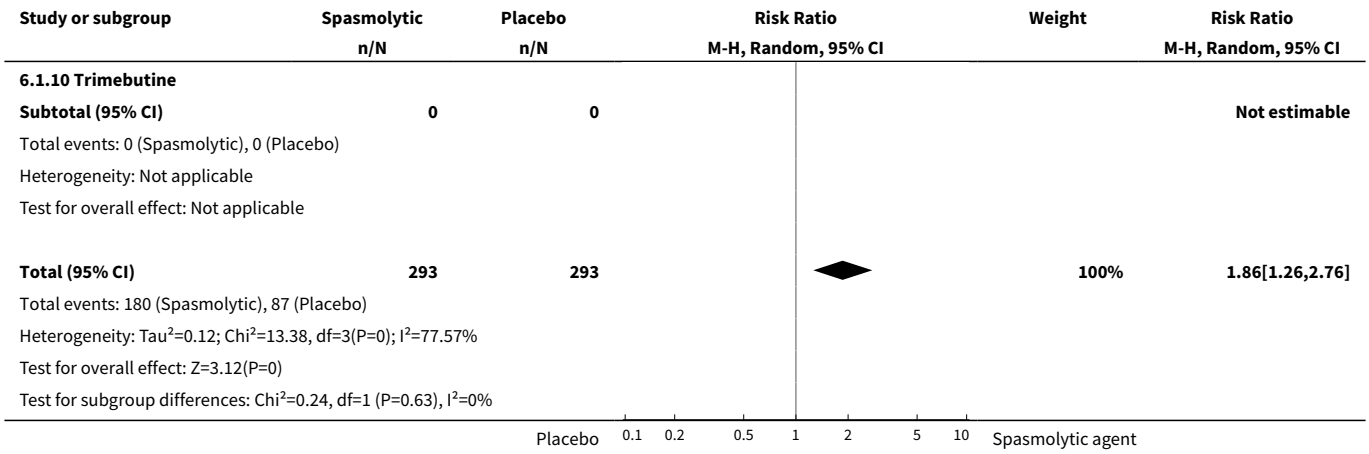
Analysis 6.1. Comparison 6 Spasmolytics: Outcome on symptom score, Outcome 1 Comparing nr (%) of patients successfully treated.

Study or subgroup	Spasmolytic n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Alvarine					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Spasmolytic), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

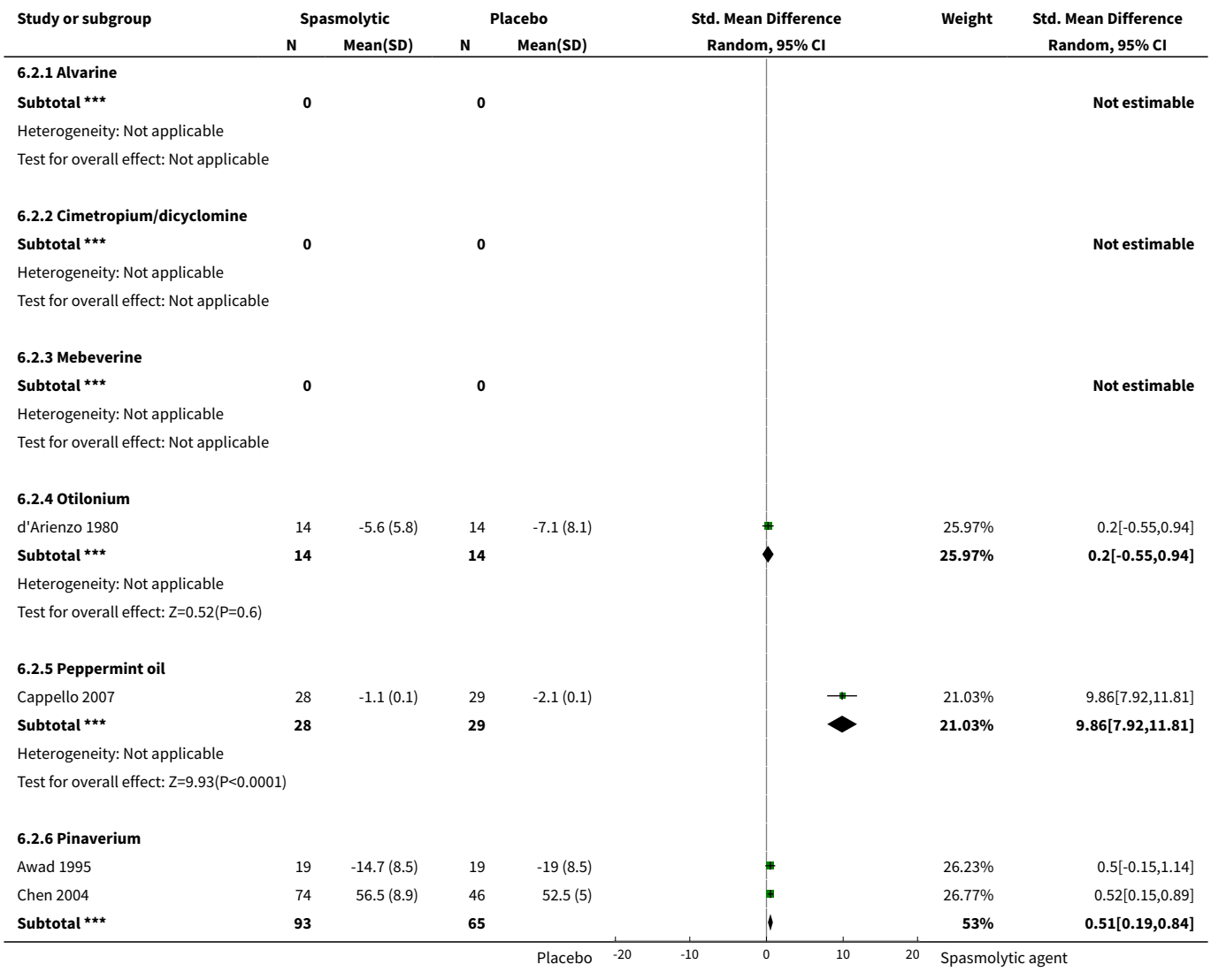


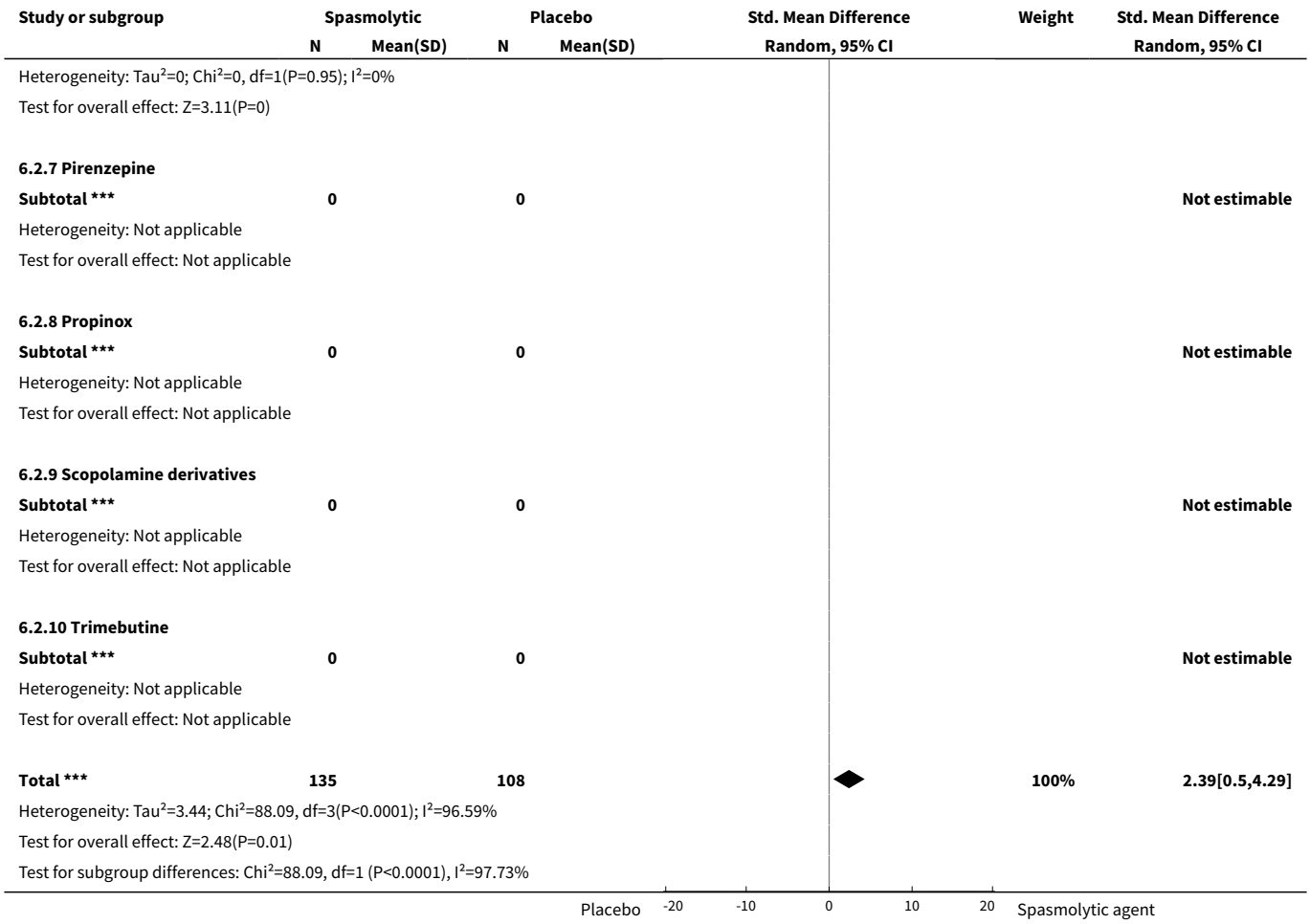
Study or subgroup	Spasmolytic n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.1.2 Cimetropium/dicyclomine					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Spasmolytic), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.1.3 Mebeverine					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Spasmolytic), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.1.4 Otilonium					
Battaglia 1998	58/157	36/160		26.08%	1.64[1.15,2.34]
Subtotal (95% CI)	**157**	**160**		**26.08%**	**1.64[1.15,2.34]**
Total events: 58 (Spasmolytic), 36 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.75(P=0.01)					
6.1.5 Peppermint oil					
Capanni 2005	88/91	29/87		27.72%	2.9[2.15,3.91]
Cappello 2007	18/28	10/29		19.37%	1.86[1.05,3.31]
Czalbert 1990	16/17	12/17		26.82%	1.33[0.96,1.85]
Subtotal (95% CI)	**136**	**133**		**73.92%**	**1.94[1.09,3.46]**
Total events: 122 (Spasmolytic), 51 (Placebo)					
Heterogeneity: Tau^2=0.22; Chi^2=13.78, df=2(P=0); I^2=85.49%					
Test for overall effect: Z=2.25(P=0.02)					
6.1.6 Pinaverium					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Spasmolytic), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.1.7 Pirenzepine					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Spasmolytic), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.1.8 Propinox					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Spasmolytic), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
6.1.9 Scopolamine derivatives					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Spasmolytic), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					





Analysis 6.2. Comparison 6 Spasmolytics: Outcome on symptom score, Outcome 2 Comparing symptom scores in IBS patients.

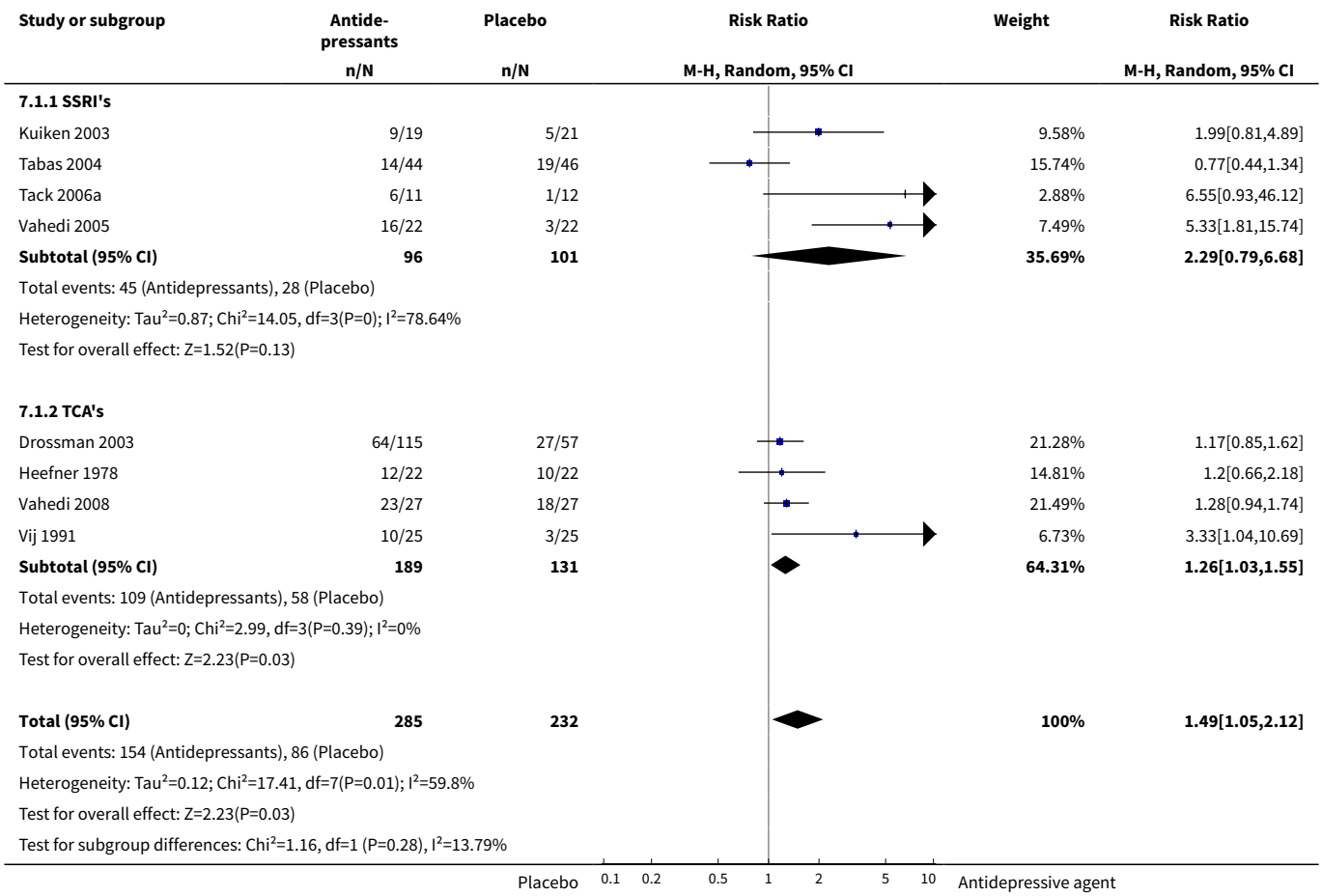




Comparison 7. Antidepressants: Abdominal pain

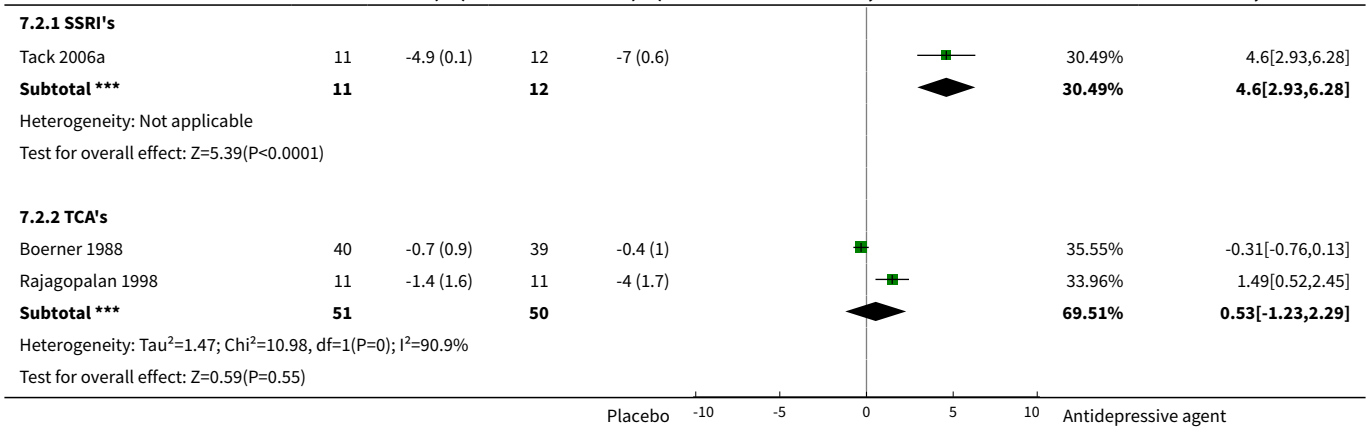
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparing nr(%) of successfully treated patients with IBS	8	517	Risk Ratio (M-H, Random, 95% CI)	1.49 [1.05, 2.12]
1.1 SSRI's	4	197	Risk Ratio (M-H, Random, 95% CI)	2.29 [0.79, 6.68]
1.2 TCA's	4	320	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.03, 1.55]
2 Comparing scores on abdominal pain in patients with IBS	3	124	Std. Mean Difference (IV, Random, 95% CI)	1.80 [-0.57, 4.16]
2.1 SSRI's	1	23	Std. Mean Difference (IV, Random, 95% CI)	4.60 [2.93, 6.28]
2.2 TCA's	2	101	Std. Mean Difference (IV, Random, 95% CI)	0.53 [-1.23, 2.29]

Analysis 7.1. Comparison 7 Antidepressants: Abdominal pain, Outcome 1 Comparing nr(%) of successfully treated patients with IBS.

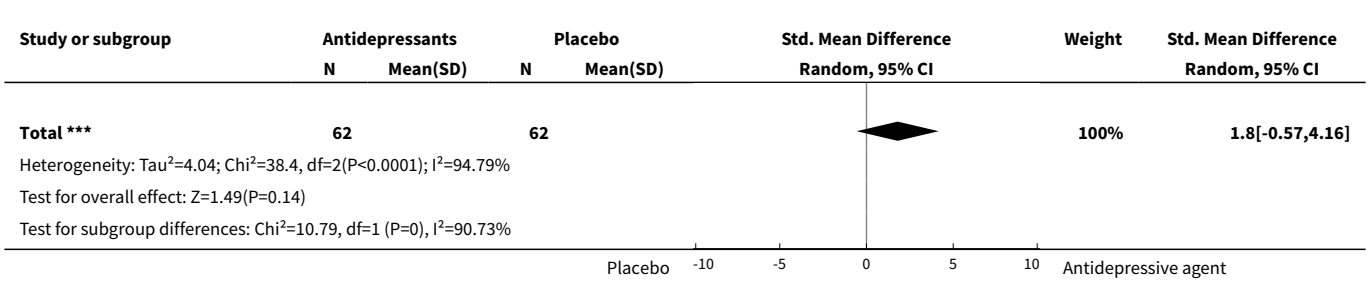


Study or subgroup	Antide-pressants n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 SSRI's					
Kuiken 2003	9/19	5/21		9.58%	1.99[0.81,4.89]
Tabas 2004	14/44	19/46		15.74%	0.77[0.44,1.34]
Tack 2006a	6/11	1/12		2.88%	6.55[0.93,46.12]
Vahedi 2005	16/22	3/22		7.49%	5.33[1.81,15.74]
Subtotal (95% CI)	**96**	**101**		**35.69%**	**2.29[0.79,6.68]**
Total events: 45 (Antidepressants), 28 (Placebo)					
Heterogeneity: Tau²=0.87; Chi²=14.05, df=3(P=0); I²=78.64%					
Test for overall effect: Z=1.52(P=0.13)					
7.1.2 TCA's					
Drossman 2003	64/115	27/57		21.28%	1.17[0.85,1.62]
Heefner 1978	12/22	10/22		14.81%	1.2[0.66,2.18]
Vahedi 2008	23/27	18/27		21.49%	1.28[0.94,1.74]
Vij 1991	10/25	3/25		6.73%	3.33[1.04,10.69]
Subtotal (95% CI)	**189**	**131**		**64.31%**	**1.26[1.03,1.55]**
Total events: 109 (Antidepressants), 58 (Placebo)					
Heterogeneity: Tau²=0; Chi²=2.99, df=3(P=0.39); I²=0%					
Test for overall effect: Z=2.23(P=0.03)					
Total (95% CI)	**285**	**232**		**100%**	**1.49[1.05,2.12]**
Total events: 154 (Antidepressants), 86 (Placebo)					
Heterogeneity: Tau²=0.12; Chi²=17.41, df=7(P=0.01); I²=59.8%					
Test for overall effect: Z=2.23(P=0.03)					
Test for subgroup differences: Chi²=1.16, df=1 (P=0.28), I²=13.79%					

Analysis 7.2. Comparison 7 Antidepressants: Abdominal pain, Outcome 2 Comparing scores on abdominal pain in patients with IBS.



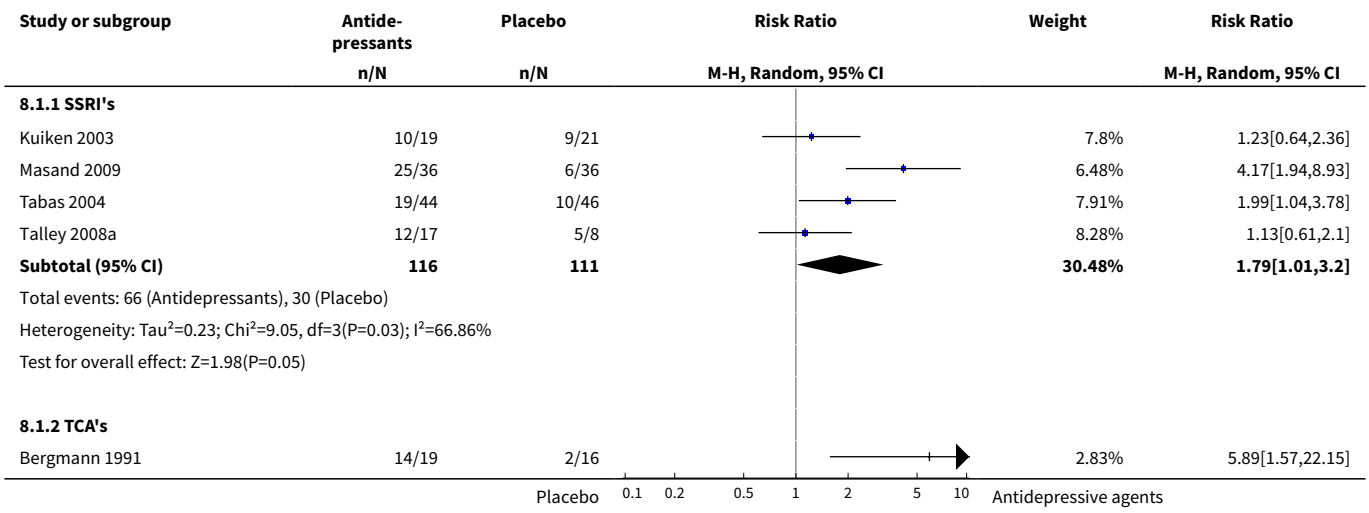
Study or subgroup	Antidepressants N	Antidepressants Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
7.2.1 SSRI's							
Tack 2006a	11	-4.9 (0.1)	12	-7 (0.6)		30.49%	4.6[2.93,6.28]
Subtotal ***	**11**		**12**			**30.49%**	**4.6[2.93,6.28]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.39(P<0.0001)							
7.2.2 TCA's							
Boerner 1988	40	-0.7 (0.9)	39	-0.4 (1)		35.55%	-0.31[-0.76,0.13]
Rajagopalan 1998	11	-1.4 (1.6)	11	-4 (1.7)		33.96%	1.49[0.52,2.45]
Subtotal ***	**51**		**50**			**69.51%**	**0.53[-1.23,2.29]**
Heterogeneity: Tau²=1.47; Chi²=10.98, df=1(P=0); I²=90.9%							
Test for overall effect: Z=0.59(P=0.55)							

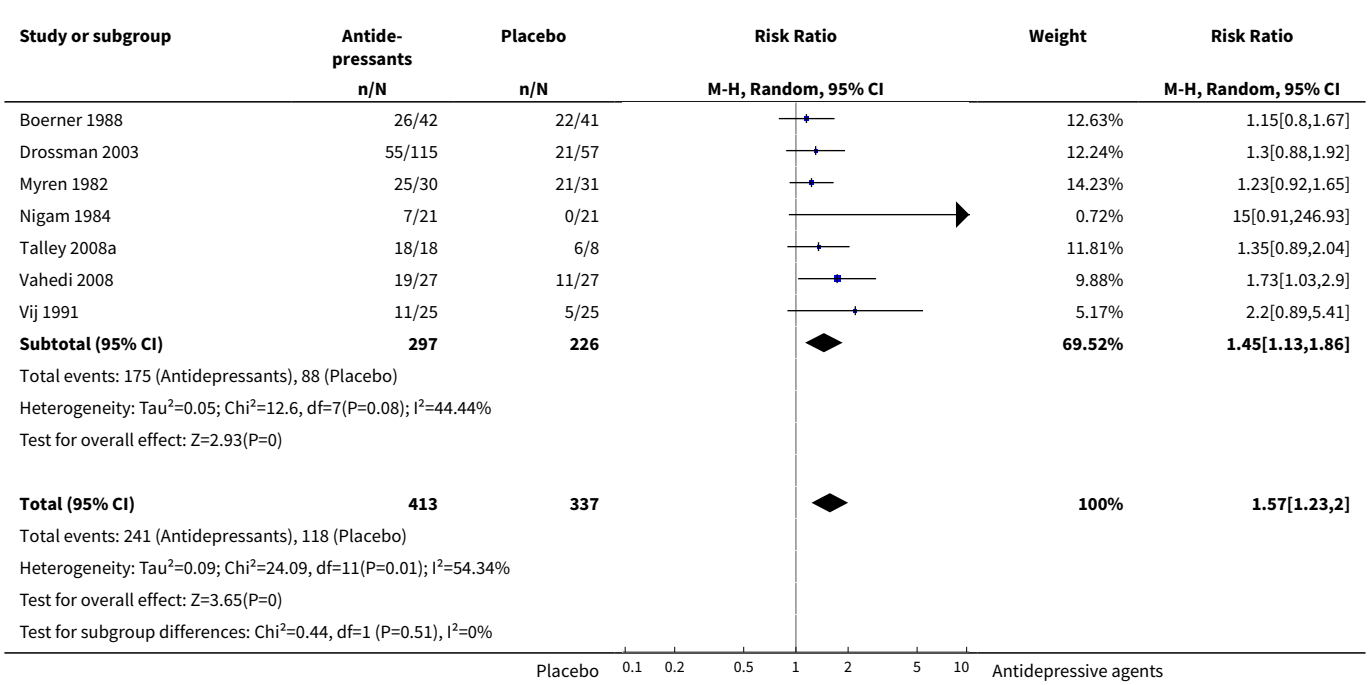


Comparison 8. Antidepressants: Global assessment

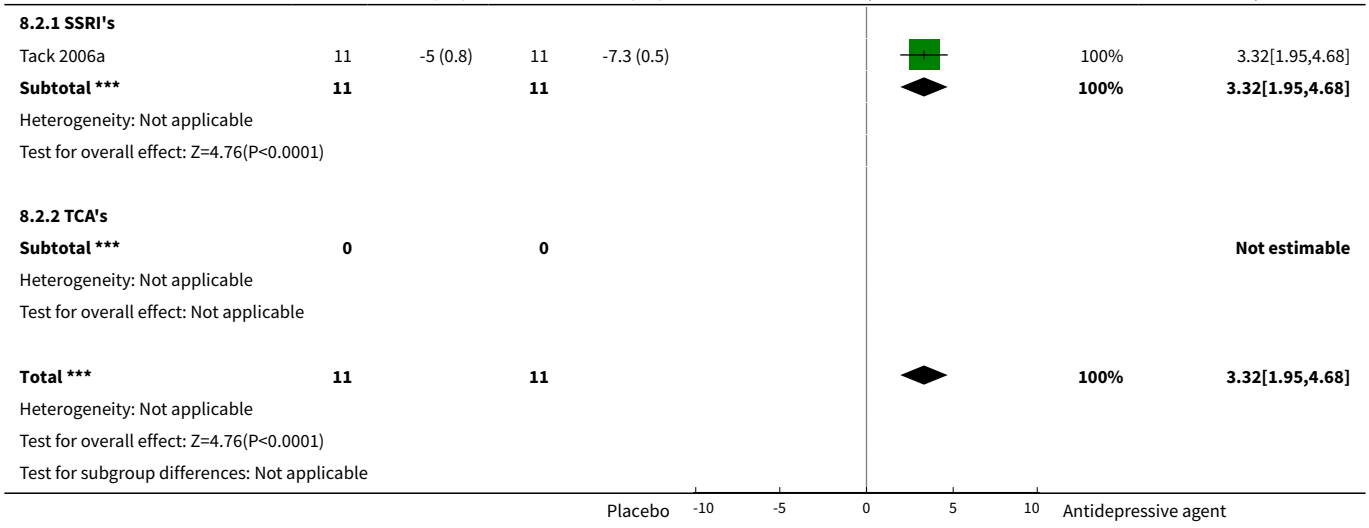
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparing nr (%) of successfully treated patients with IBS	11	750	Risk Ratio (M-H, Random, 95% CI)	1.57 [1.23, 2.00]
1.1 SSRI's	4	227	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.01, 3.20]
1.2 TCA's	8	523	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.13, 1.86]
2 Comparing scores on global assessment in patients with IBS	1	22	Std. Mean Difference (IV, Random, 95% CI)	3.32 [1.95, 4.68]
2.1 SSRI's	1	22	Std. Mean Difference (IV, Random, 95% CI)	3.32 [1.95, 4.68]
2.2 TCA's	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 8.1. Comparison 8 Antidepressants: Global assessment, Outcome 1 Comparing nr (%) of successfully treated patients with IBS.





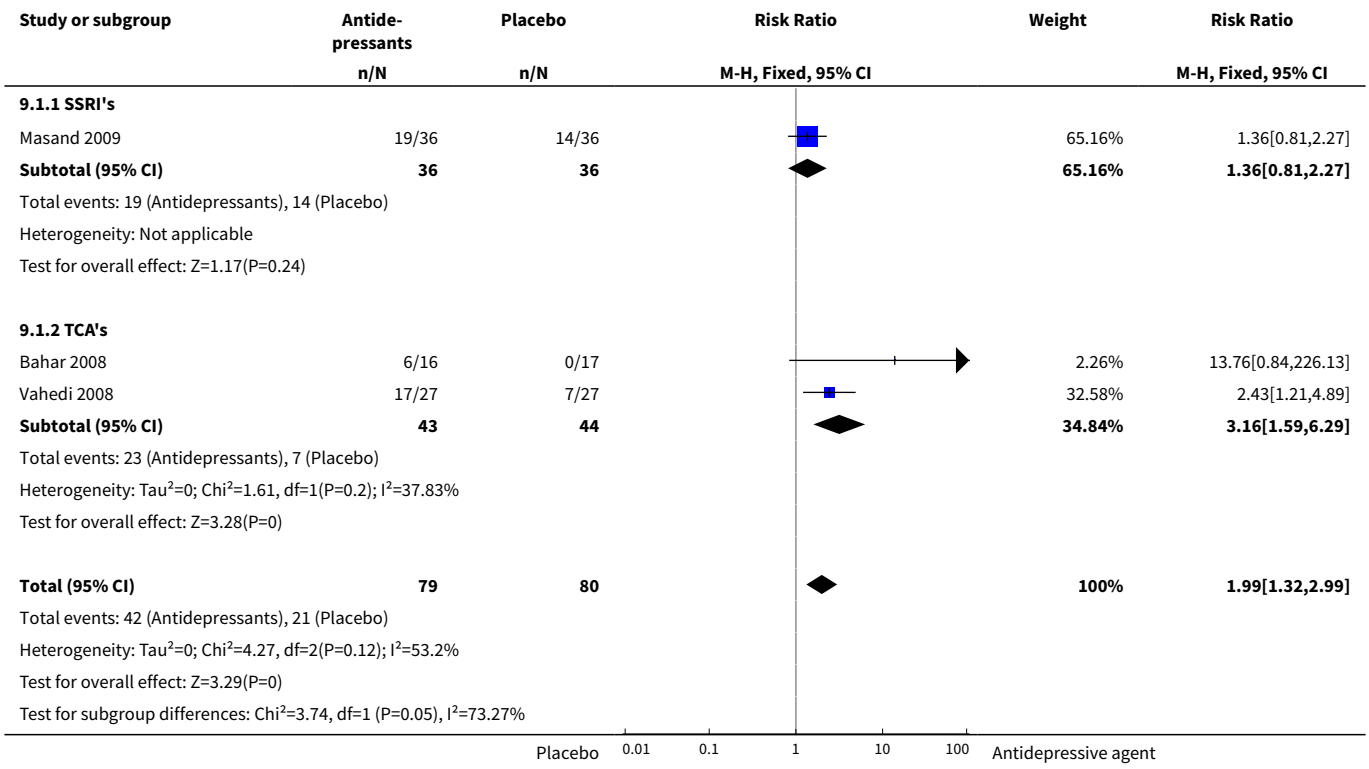
Analysis 8.2. Comparison 8 Antidepressants: Global assessment, Outcome 2 Comparing scores on global assessment in patients with IBS.



Comparison 9. Antidepressants: Outcome on symptom score

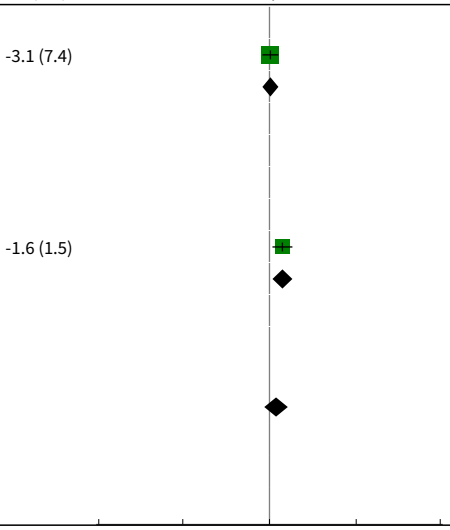
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparing nr (%) of successfully treated IBS patients	3	159	Risk Ratio (M-H, Fixed, 95% CI)	1.99 [1.32, 2.99]
1.1 SSRI's	1	72	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.81, 2.27]
1.2 TCA's	2	87	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [1.59, 6.29]
2 Comparing symptom scores of IBS patients	2	122	Std. Mean Difference (IV, Random, 95% CI)	0.38 [-0.30, 1.06]
2.1 SSRI's	1	72	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.41, 0.52]
2.2 TCA's	1	50	Std. Mean Difference (IV, Random, 95% CI)	0.75 [0.17, 1.32]

Analysis 9.1. Comparison 9 Antidepressants: Outcome on symptom score, Outcome 1 Comparing nr (%) of successfully treated IBS patients.



Analysis 9.2. Comparison 9 Antidepressants: Outcome on symptom score, Outcome 2 Comparing symptom scores of IBS patients.

Study or subgroup	Antidepressants N	Antidepressants Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
9.2.1 SSRI's							
Masand 2009	36	-2.7 (7.4)	36	-3.1 (7.4)		53.17%	0.05[-0.41,0.52]
Subtotal ***	**36**		**36**			**53.17%**	**0.05[-0.41,0.52]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.23(P=0.82)							
9.2.2 TCA's							
Vahedi 2008	25	-0.5 (1.5)	25	-1.6 (1.5)		46.83%	0.75[0.17,1.32]
Subtotal ***	**25**		**25**			**46.83%**	**0.75[0.17,1.32]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.55(P=0.01)							
Total ***	**61**		**61**			**100%**	**0.38[-0.3,1.06]**
Heterogeneity: Tau^2=0.17; Chi^2=3.4, df=1(P=0.07); I^2=70.55%							
Test for overall effect: Z=1.09(P=0.27)							
Test for subgroup differences: Chi^2=3.4, df=1 (P=0.07), I^2=70.55%							

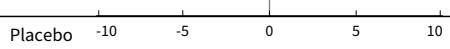


Comparison 10. Adequate concealment bulking agents: abdominal pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparing scores on abdominal pain	2	119	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.32, 0.40]

Analysis 10.1. Comparison 10 Adequate concealment bulking agents: abdominal pain, Outcome 1 Comparing scores on abdominal pain.

Study or subgroup	Bulking agent N	Bulking agent Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Fowlie 1992	23	-5 (16.5)	19	-5 (16.5)		35.13%	0[-0.61,0.61]
Longstreth 1981	37	-0.6 (0.5)	40	-0.6 (0.5)		64.87%	0.06[-0.39,0.5]
Total ***	**60**		**59**			**100%**	**0.04[-0.32,0.4]**
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%							
Test for overall effect: Z=0.2(P=0.84)							

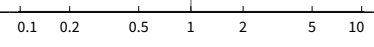


Comparison 11. Adequate concealment bulking agents: global assessment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 comparing nr of successfully treated IBS patient	5	193	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.68, 1.23]

Analysis 11.1. Comparison 11 Adequate concealment bulking agents: global assessment, Outcome 1 comparing nr of successfully treated IBS patient.

Study or subgroup	Bulking agent n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Fowlie 1992	14/23	13/19		31.21%	0.89[0.57,1.39]
Jalihal 1990	9/11	6/9		14.47%	1.23[0.72,2.1]
Longstreth 1981	7/26	14/34		26.6%	0.65[0.31,1.38]
Ritchie 1979	5/7	0/12		0.84%	17.88[1.13,281.81]
Soltoft 1976	7/29	11/23		26.89%	0.5[0.23,1.09]
Total (95% CI)	**96**	**97**		**100%**	**0.91[0.68,1.23]**
Total events: 42 (Bulking agent), 44 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=8.66, df=4(P=0.07); I^2=53.79%					
Test for overall effect: Z=0.59(P=0.56)					

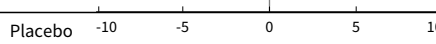


Comparison 12. Adequate concealment spasmolytic agents: abdominal pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparing scores on abdominal pain in IBS patients	2	115	Std. Mean Difference (IV, Fixed, 95% CI)	0.43 [0.06, 0.80]

Analysis 12.1. Comparison 12 Adequate concealment spasmolytic agents: abdominal pain, Outcome 1 Comparing scores on abdominal pain in IBS patients.

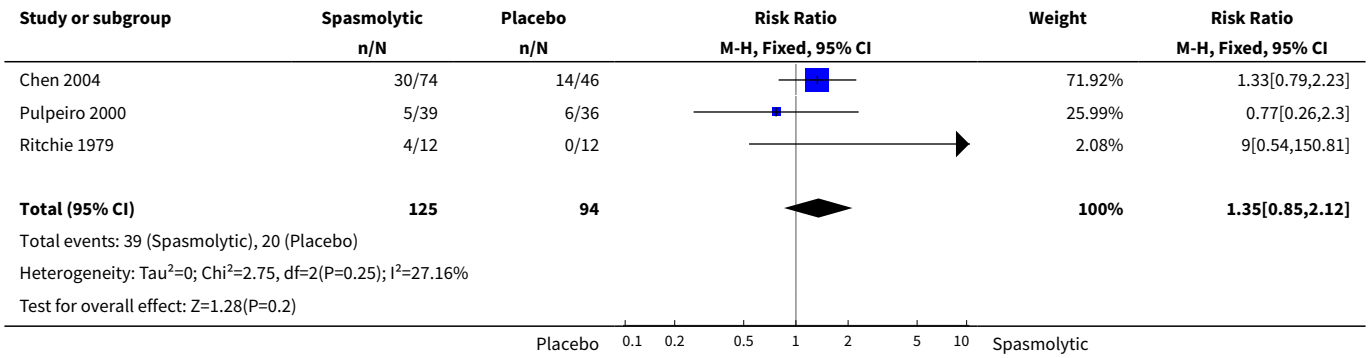
Study or subgroup	Spasmolytic N	Spasmolytic Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Awad 1995	20	-2.3 (1.8)	20	-3 (1.8)		34.95%	0.39[-0.24,1.01]
Pulpeiro 2000	39	-1.6 (1)	36	-2.1 (1.1)		65.05%	0.45[-0.01,0.91]
Total ***	**59**		**56**			**100%**	**0.43[0.06,0.8]**
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%							
Test for overall effect: Z=2.25(P=0.02)							



Comparison 13. Adequate concealment spasmolytic agents: global assessment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 comparing nrs of successfully treated IBS patients with spasmolytic agents	3	219	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.85, 2.12]

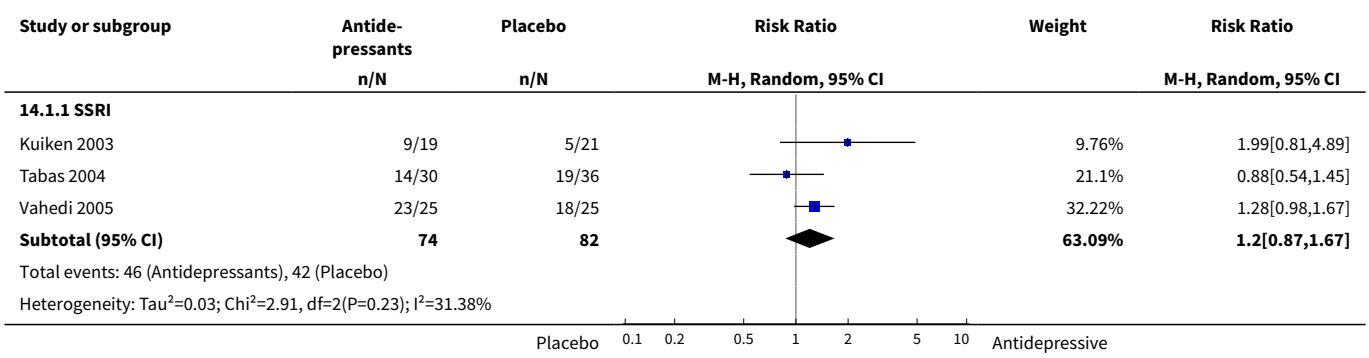
Analysis 13.1. Comparison 13 Adequate concealment spasmolytic agents: global assessment, Outcome 1 comparing nrs of successfully treated IBS patients with spasmolytic agents.

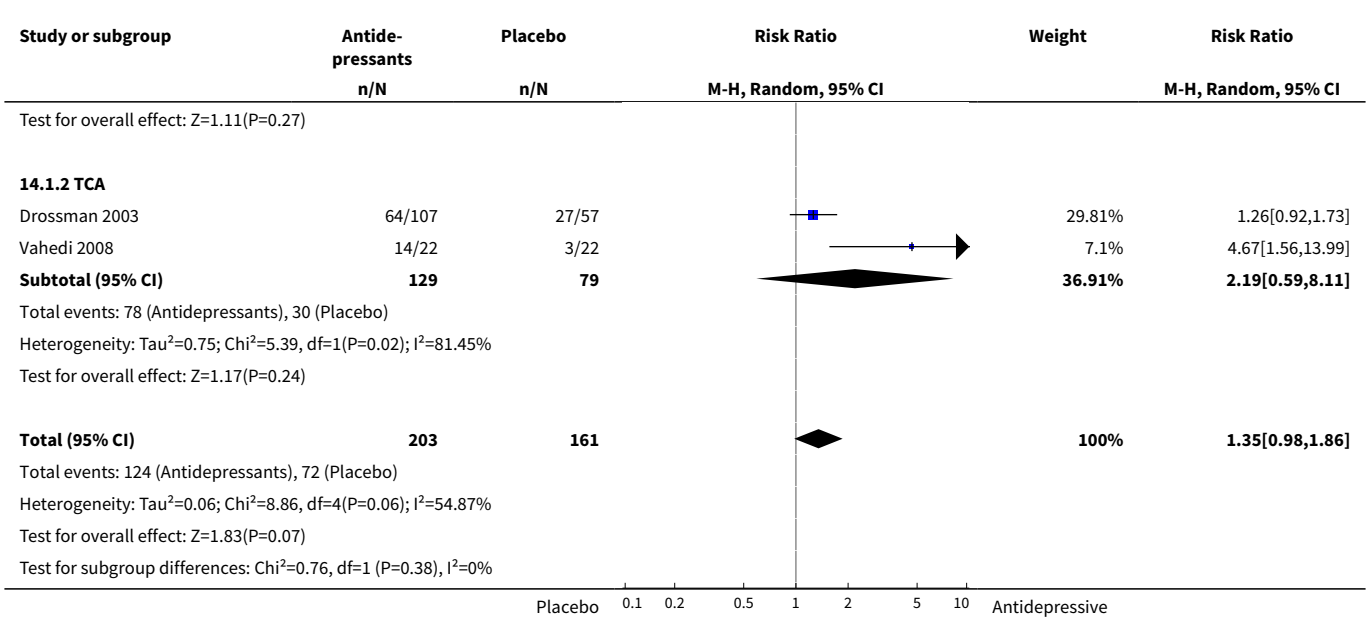


Comparison 14. Adequate concealment antidepressants: abdominal pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparing nr (%) of successfully treated patients	5	364	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.98, 1.86]
1.1 SSRI	3	156	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.87, 1.67]
1.2 TCA	2	208	Risk Ratio (M-H, Random, 95% CI)	2.19 [0.59, 8.11]

Analysis 14.1. Comparison 14 Adequate concealment antidepressants: abdominal pain, Outcome 1 Comparing nr (%) of successfully treated patients.

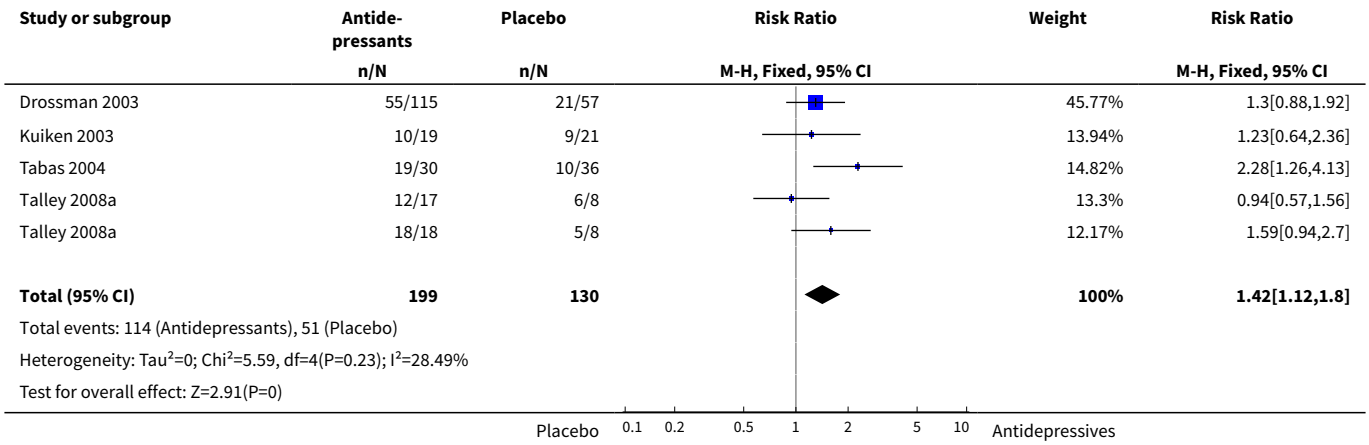




Comparison 15. Adequate concealment antidepressants: global assessment

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Comparing nr (%) of successfully treated IBS patients	4	329	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.12, 1.80]

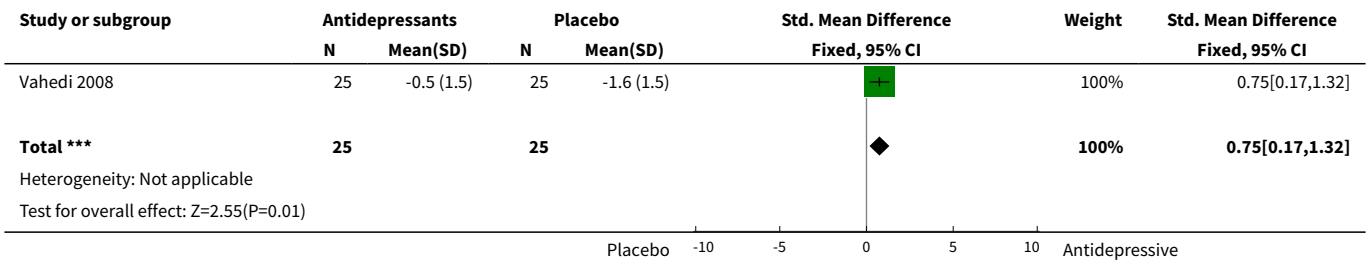
Analysis 15.1. Comparison 15 Adequate concealment antidepressants: global assessment, Outcome 1 Comparing nr (%) of successfully treated IBS patients.



Comparison 16. Adequate concealment antidepressants: Outcome on symptom score

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Comparing symptom scores in IBS patients	1	50	Std. Mean Difference (IV, Fixed, 95% CI)	0.75 [0.17, 1.32]

Analysis 16.1. Comparison 16 Adequate concealment antidepressants: Outcome on symptom score, Outcome 1 Comparing symptom scores in IBS patients.



ADDITIONAL TABLES

Table 1. Bulking agents: main results

	Dichotomous outcomes	Continuous outcomes
	RR (95% CI)	SMD (95% CI)
Abdominal pain	0.91 (0.61 to 1.36)	0.03 (-0.34 to 0.40)
Global assessment	1.11 (0.91 to 1.35)	
Symptom score		0.00 (-0.43 to 0.43)

Table 2. Antispasmodics: main results

	Dichotomous outcomes	Continuous outcomes
	RR (95% CI)	SMD (95% CI)
Abdominal pain	1.32 (1.12 to 1.55)	1.14 (0.47 to 1.81)
Global assessment	1.49 (1.25 to 1.77)	
Symptom score	1.86 (1.26 to 2.76)	2.39 (0.50 to 4.29)

Table 3. Antidepressants: main results

	Dichotomous outcomes	Continuous outcomes
	RR (95% CI)	SMD (95% CI)
Abdominal pain	1.49 (1.05 to 2.12)	1.80 (-0.57 to 4.16)
Global assessment	1.57 (1.23 to 2.00)	3.32 (1.95 to 4.68)
Symptom score	1.99 (1.32 to 2.99)	0.38 (-0.30 to 1.06)

WHAT'S NEW

Date	Event	Description
21 February 2013	Amended	Correction of minor errors in additional tables

HISTORY

Protocol first published: Issue 1, 2002
Review first published: Issue 2, 2005

Date	Event	Description
29 September 2011	Amended	Change in address for contact author
26 April 2011	New citation required and conclusions have changed	Change in authors, conclusions changed due to new data
26 April 2011	New search has been performed	New search, new studies included

CONTRIBUTIONS OF AUTHORS

Preparation of protocol
Coordination of reviewers
Data collection
Data review
Preparation of report

DECLARATIONS OF INTEREST

Greg Rubin owns shares in Glaxo Smith Kline and has received payment for consultancy from pharma companies. The other authors report no known declarations of interest.

INDEX TERMS

Medical Subject Headings (MeSH)

Abdominal Pain [therapy]; Antidepressive Agents [*therapeutic use]; Dietary Fiber [*therapeutic use]; Irritable Bowel Syndrome [*therapy]; Parasympatholytics [*therapeutic use]; Phytotherapy [methods]; Plantago; Randomized Controlled Trials as Topic

MeSH check words

Humans