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Homeopathy for treatment of irritable bowel syndrome (Review)

Peckham EJ, Cooper K, Roberts ER, Agrawal A, Brabyn S, Tew G

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[Intervention Review]

Homeopathy for treatment of irritable bowel syndrome

Emily J Peckham[1], Katy Cooper[2], E Rachel Roberts[3], Anurag Agrawal[4], Sally Brabyn[1], Garry Tew[5]

[1]Department of Health Sciences, University of York, York, UK. [2]School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK. [3]Homeopathy Research Institute, London, UK. [4]Department of Gastroenterology and Medicine, Doncaster Royal Infirmary, Doncaster, UK. [5]Department of Sport, Exercise and Rehabilitation, Northumbria University, Newcastle Upon Tyne, UK

Contact address: Emily J Peckham, Department of Health Sciences, University of York, Heslington, York, - None -, Y010 5DD, UK. emily.peckham@york.ac.uk.

A B S T R A C T

Background

Irritable bowel syndrome (IBS) is a common, chronic disorder that leads to decreased health-related quality of life and work productivity. A previous version of this review was not able to draw firm conclusions about the effectiveness of homeopathic treatment for IBS and recommended that further high quality RCTs were conducted to explore the clinical and cost effectiveness of homeopathic treatment for IBS. Two types of homeopathic treatment were evaluated in this systematic review: 1. Clinical homeopathy where a specific remedy is prescribed for a specific condition; 2. Individualised homeopathic treatment, where a homeopathic remedy based on a person's individual symptoms is prescribed after a detailed consultation.

Objectives

To assess the effectiveness and safety of homeopathic treatment for IBS.

Search methods

For this update we searched MEDLINE, CENTRAL, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Allied and Complementary Medicine Database (AMED), the Cochrane IBD Group Specialised Register and trials registers from inception to 31 August 2018.

Selection criteria

Randomised controlled trials (RCTs), cohort and case-control studies that compared homeopathic treatment with placebo, other control treatments, or usual care, in adults with IBS were considered for inclusion.

Data collection and analysis

Two authors independently assessed the risk of bias and extracted data. The primary outcome was global improvement in IBS as measured by an IBS symptom severity score. Secondary outcomes included quality of life, abdominal pain, stool frequency, stool consistency, and adverse events. The overall certainty of the evidence supporting the primary and secondary outcomes was assessed using the GRADE criteria. We used the Cochrane risk of bias tool to assess risk of bias. We calculated the mean difference (MD) and 95% confidence interval (CI) for continuous outcomes and the risk ratio (RR) and 95% CI for dichotomous outcomes.

Main results

Four RCTs (307 participants) were included. Two studies compared clinical homeopathy (homeopathic remedy, asafoetida or asafoetida plus nux vomica) to placebo for IBS with constipation (IBS-C). One study compared individualised homeopathic treatment (consultation plus remedy) to usual care for the treatment of IBS in female patients. One study was a three armed RCT comparing individualised home-

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opathic treatment to supportive listening or usual care. The risk of bias in three studies (the two studies assessing clinical homeopathy and the study comparing individualised homeopathic treatment to usual care) was unclear on most criteria and high for selective reporting in one of the clinical homeopathy studies. The three armed study comparing individualised homeopathic treatment to usual care and supportive listening was at low risk of bias in four of the domains and high risk of bias in two (performance bias and detection bias).

A meta-analysis of the studies assessing clinical homeopathy, (171 participants with IBS-C) was conducted. At short-term follow-up of two weeks, global improvement in symptoms was experienced by 73% (46/63) of asafoetida participants compared to 45% (30/66) of placebo participants (RR 1.61, 95% CI 1.18 to 2.18; 2 studies, very low certainty evidence). In the other clinical homeopathy study at two weeks, 68% (13/19) of those in the asafoetida plus nux vomica arm and 52% (12/23) of those in the placebo arm experienced a global improvement in symptoms (RR 1.31, 95% CI 0.80 to 2.15; very low certainty evidence). In the study comparing individualised homeopathic treatment to usual care (N = 20), the mean global improvement score (feeling unwell) at 12 weeks was 1.44 ± 4.55 (n = 9) in the individualised homeopathic treatment arm compared to 1.41 ± 1.97 (n=11) in the usual care arm (MD 0.03; 95% CI -3.16 to 3.22; very low certainty evidence).

In the study comparing individualised homeopathic treatment to usual care, the mean IBS symptom severity score at 6 months was 210.44 ± 112.4 (n = 16) in the individualised homeopathic treatment arm compared to 237.3 + 110.22 (n = 60) in the usual care arm (MD -26.86, 95% CI -88.59 to 34.87; low certainty evidence). The mean quality of life score (EQ-5D) at 6 months in homeopathy participants was 69.07 (SD 17.35) compared to 63.41 (SD 23.31) in usual care participants (MD 5.66, 95% CI -4.69 to 16.01; low certainty evidence).

For In the study comparing individualised homeopathic treatment to supportive listening, the mean IBS symptom severity score at 6 months was 210.44 ± 112.4 (n = 16) in the individualised homeopathic treatment arm compared to 262 + 120.72 (n = 18) in the supportive listening arm (MD -51.56, 95% CI -129.94 to 26.82; very low certainty evidence). The mean quality of life score at 6 months in homeopathy participants was 69.07 (SD 17.35) compared to 63.09 (SD 24.38) in supportive listening participants (MD 5.98, 95% CI -8.13 to 20.09; very low certainty evidence).

None of the included studies reported on abdominal pain, stool frequency, stool consistency, or adverse events.

Authors' conclusions

The results for the outcomes assessed in this review are uncertain. Thus no firm conclusions regarding the effectiveness and safety of homeopathy for the treatment of IBS can be drawn. Further high quality, adequately powered RCTs are required to assess the efficacy and safety of clinical and individualised homeopathy for IBS compared to placebo or usual care.

PLAIN LANGUAGE SUMMARY

Homeopathy for treatment of irritable bowel syndrome

What is irritable bowel syndrome?

Irritable bowel syndrome (IBS) is a common chronic disorder where a person experiences the following symptoms: abdominal pain, discomfort, bloating, constipation or diarrhoea or both. It is difficult to treat because different people experience different symptoms. Some people experience constipation as the main symptom, this form of IBS is known as IBS-C, while others experience diarrhoea as the main symptom. This form of IBS is known as IBS-D. Others experience both constipation and diarrhoea, this form of IBS is known as IBS-M where the M stands for mixed. Currently there is no agreement on the best form of treatment for IBS.This means that it is important to evaluate the effectiveness and safety of treatments, including homeopathic treatment, which some IBS sufferers use.

What is homeopathy?

There are different types of homeopathy. Clinical homeopathy matches a 'remedy' to a specific condition, such as IBS and everybody who has that condition would be given the same remedy. Individualised homeopathy involves a series of in-depth consultations to assess symptoms and other issues that may affect the patient. Following an in-depth consultation the homeopath will select the most appropriate remedy based on the persons' individual symptoms. Individualised homeopathy includes both a consultation and a remedy, whereas clinical homeopathy consists of a remedy without the in-depth consultation.

What did the researchers investigate?

The researchers investigated whether homeopathic treatment led to the improvement of the symptoms of IBS in people with IBS. The researchers

What did the researchers find?

Four randomised controlled trials (RCTs) with 307 participants with IBS were included. Two RCTs (129 participants) compared a homeopathic remedy (asafoetida and asafoetida plus nux vomica) to a placebo remedy for the treatment of people with IBS-C. One study (23 participants) compared individualised homeopathic treatment to usual care in female patients diagnosed with IBS. One study (94 participants) was a three armed study comparing individualised homeopathic treatment plus usual care, supportive listening plus usual care and usual care.

The four trials tested the effects of homeopathic treatment on the severity of IBS symptoms. No conclusions can be drawn from the RCT comparing individualised homeopathic treatment to usual care due to the small number of participants and the low quality of reporting in this trial. This study was carried out in 1990 and usual care for IBS may have changed since then making the results difficult to compare to current treatments.

No conclusions can be drawn from the three armed study comparing individualised homeopathic treatment plus usual care, supportive listening plus usual care and usual care due to the small number of participants in the homeopathic treatment arm (n=16).

The results of two small studies were combined (129 participants) and this suggested that there may be a possible benefit for clinical homeopathy, using the remedy asafoetida, over placebo for patients with IBS-C at a short-term follow-up of two weeks. However both of the studies were carried out in the 1970s when the reporting of trials was not as comprehensive as it is now and we are very uncertain about these results and cannot suggest a possible benefit for clinical homeopathy.

Conclusions

The results for the outcomes assessed in this review are uncertain. Thus no firm conclusions regarding the effectiveness and safety of homeopathy for the treatment of IBS can be drawn. Further high quality RCTs enrolling larger numbers of patients are required to assess the effectiveness and safety of clinical and individualised homeopathy for IBS.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.   Homeopathy versus placebo

Homeopathy versus placebo for the treatment of irritable bowel syndrome

Patient or population: patients with irritable bowel syndrome
Settings: outpatients
Intervention: homeopathy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with homeopathy**				
Global improvement (Asafoetida subgroup) Follow-up: 2 weeks	455 per 1000	732 per 1000 (536 to 991)	**RR 1.61** (1.18 to 2.18)	129 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,3]	Global improvement defined as self improvement on a 3 point Likert scale
Global improvement (Asafoetida + nux vom subgroup) Follow-up: 2 weeks	522 per 1000	683 per 1000 (417 to 1000)	**RR 1.31** (0.8 to 2.15)	42 (1 study)	⊕⊖⊖⊖ **very low**[1,3,4]	Global improvement defined as self improvement on a 3 point Likert scale
Quality of life	Not reported					This outcome was not reported
Abdominal pain	Not reported					This outcome was not reported
Stool frequency	Not reported					This outcome was not reported
Stool consistency	Not reported					This outcome was not reported
Adverse events	Not reported					This outcome was not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] Downgraded one level due to high risk of bias

[2] Downgraded one level due to sparse data (76 events)

[3] Downgraded one level due to the endpoint time (2 weeks). Given the long term nature of IBS it is not clear how useful a two week outcome is for patients' and clinicians' decision making.

[4] Downgraded two levels due to very sparse data (25 events)

Summary of findings 2.   Homeopathy versus usual care

Homeopathy versus usual care for the treatment of irritable bowel syndrome

Patient or population: patients with irritable bowel syndrome
Settings: outpatients
Intervention: homeopathy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	Usual care	**Homeopathy**				
Global improvement (Feeling unwell) Follow-up: 12 weeks	The mean global improvement score was 1.41 (SD = 1.97)	The mean global improvement score was 1.44 (SD = 4.55) MD 0.03 higher (3.16 lower to 3.22 higher)	-	20 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	Global improvement defined as a self reported improvement of symptoms. Scale from: 0 to 5 Higher scores indicate greater improvement
Quality of life	Not reported					This outcome was not reported
Abdominal pain	Not reported					This outcome was not reported
Stool frequency	Not reported					This outcome was not reported

| Stool consistency | Not reported | This outcome was not reported |
| Adverse events | Not reported | This outcome was not reported |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] Downgraded one level due to high risk of bias

[2] Downgraded two levels due to very sparse data (20 participants)

Summary of findings 3.   Homeopathy plus usual care versus usual care

Homeopathy plus usual care versus usual care for the treatment of irritable bowel syndrome

Patient or population: patients with irritable bowel syndrome
Settings: outpatients
Intervention: homeopathy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Homeopathy				
Global improvement (IBS-SSS) Follow-up: 6 months	The mean global improvement score was 237.3 (SD = 110.27)	The mean global improvement score was 210.44 (SD = 112.4) MD 26.86 lower (88.59 lower to 34.87 higher)	-	76 (1 study)	⊕⊕⊖⊖ **low**[1,2]	IBS-SSS. Scale from: 0 to 400 Lower scores indicate less severe disease

Quality of life Follow-up 6 months	The mean quality of life score was 63.41 (SD = 23.31)	The mean quality of life score was 69.07 (SD = 17.35) MD 5.66 higher (4.69 lower to 16.01 higher)	-	76 (1 study)	⊕⊕⊖⊖ low[1,2]	EQ-5D Higher scores indicate better quality of life
Abdominal pain	Not reported					This outcome was not reported
Stool frequency	Not reported					This outcome was not reported
Stool consistency	Not reported					This outcome was not reported
Adverse events	Not reported					This outcome was not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded one level due to sparse data (76 participants)
[2] Downgraded one level due to high risk of bias

Summary of findings 4.   Homeopathy plus usual care versus supportive listening plus usual care

Homeopathy plus usual care versus supportive listening plus usual care for treatment of irritable bowel syndrome

Patient or population: patients with irritable bowel syndrome
Settings: outpatients
Intervention: Homeopathy

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments

	Assumed risk	Corresponding risk				
	Control	Homeopathy				
Global improvement (IBS-SSS) Follow-up: 6 months	The mean global improvement score was 262 (SD = 120.72)	The mean global improvement score was 210.44 (SD = 112.4) MD 51.56 lower (129.94 lower to 26.82 higher)	-	34 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	IBS-SSS. Scale from: 0 to 400 Lower scores indicate less severe disease
Quality of life Follow-up: 6 months	The mean quality of life score was 63.09 (SD = 24.38)	The mean quality of life score was 69.07 (SD = 17.35) MD 5.98 higher (8.13 lower to 20.09 higher)	-	34 (1 study)	⊕⊖⊖⊖ **very low**[1,2]	EQ-5D Higher scores indicate better quality of life
Quality of life	Not reported					This outcome was not reported
Abdominal pain	Not reported					This outcome was not reported
Stool frequency	Not reported					This outcome was not reported
Stool consistency	Not reported					This outcome was not reported
Adverse events	Not reported					This outcome was not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1 Downgraded two levels due to very sparse data (34 participants)
2 Downgraded one level due to high risk of bias

BACKGROUND

Description of the condition

Irritable bowel syndrome (IBS) is a common, chronic disorder that affects 10 to 22% of the population in the UK (Williams 2007). The economic costs of IBS in primary care in the UK are estimated to be over GBP 200 million per year (Akehurst 2002). It is difficult to treat because no single cause has been identified. Treatment is directed at controlling symptoms, using pharmacological and non-pharmacological approaches (Ruepert 2011; Spiller 2007; Zijdenbos 2009).

IBS is characterised by recurrent symptoms (i.e. abdominal pain or discomfort, bloating, constipation, or diarrhoea) that indicate a dysfunctional gastrointestinal tract rather than an organic change or specific diagnosis. It has an uncertain prognosis for recovery (Mearin 2006). Such patients have a plethora of non-colonic symptoms such as back pain, urinary frequency, and chronic fatigue which can lead to the patient being referred to the wrong specialty and having inappropriate investigations and even surgery. This can lower quality of life (Agrawal 2006; Longstreth 2007). In addition, sleep disturbance and depressed mood are common in IBS patients.

Diagnosis of IBS can be made using the Rome IV criteria (Drossman 2016), although this is largely a research tool used to allow common reporting standards of symptoms in trials and other research populations. In clinical practice the diagnosis of IBS is largely based on symptoms and should be positive rather than by exclusion, although the presence of alarm symptoms (e.g. blood in stool, weight loss or family history) should prompt further investigations (Spiller 2007). IBS can be characterised into the following subtypes: IBS with constipation, IBS with diarrhoea, IBS with mixed bowel habits and unspecified.

Usual care for IBS commonly includes advice on lifestyle, including diet and stress reduction, possibly combined with medication. There are a number of different medications used to help treat IBS: antispasmodic medicines, which help to reduce abdominal pain and cramping; laxatives, which help to treat the symptoms of constipation; anti-motility medicines, which help to treat the symptoms of diarrhoea, and neuropathic modulators such as tricyclic antidepressants, which were originally designed to treat depression, but also help to reduce the feeling of abdominal pain and cramping. Alternative treatments such as hypnotherapy, psychotherapy and acupuncture have been tried and have a place in selected patients (Agrawal 2006,McPherson 2012). However these treatments have limited availability and are expensive and labour intensive. Despite much research into both psychological and pharmacological treatments for irritable bowel syndrome no consensus exists on its optimal treatment (Ruepert 2011; Zijdenbos 2009).

Description of the intervention

Homeopathy is a popular, albeit controversial form of complementary and alternative medicine. A UK survey has shown that 1.9% of the population consulted a homeopath in the 12 months prior to the survey and 8.6% had bought an over-the-counter homeopathic remedy (Thomas 2001). Homeopathy is based on treating patients with remedies prepared from substances that have been highly diluted and succussed (shaken). It was first developed by Samuel Hahnemann in the eighteenth century in Germany and works on the principle of "like cures like" whereby a substance that would cause symptoms in a healthy person cures those same symptoms in illness.

Homeopathic treatment varies among different practitioners and four main types can be identified (Linde 1997):

- Individualised (or classical) homeopathy, the type most commonly practised in the UK, involves a consultation followed by the prescription of a homeopathic medicine individualised to the patient;
- Clinical homeopathy, where the same homeopathic medicine is used for a group of patients all presenting with the same clinical condition (e.g. lycopodium for IBS, arnica for bruising);
- Complex homeopathy, where a number of different homeopathic medicines are given either in a fixed combination or concurrently; and
- Isopathy, where the homeopathic medicine is based on the substance which has led to the problem (e.g. grass pollen for hay fever).

Homeopathic medicines when prescribed by trained professionals are generally regarded as safe (Dantas 2000).

How the intervention might work

Homeopathy is based on the 'law of similars' i.e. a substance which causes symptoms in a healthy individual can be used to treat similar symptoms in a diseased person (Vithoulkas 1980).There is significant debate regarding the scientific basis for homeopathy amongst healthcare practitioners, scientists, politicians and policy makers and the mechanism by which homeopathic remedies may work is not completely understood.

The manufacture of homeopathic medicines involves serial dilution alternating with violent agitation (i.e. 'succussion'). The combination of these two processes is referred to as 'potentisation' or 'sequential kinetic activation' (Gariboldi 2009). Many homeopathic medicines are diluted beyond Avogadro's number and therefore fall under the classification of ultra-high dilutions (UHDs). Avogadro's number is the number of molecules in a mole of a substance, approximately 6.0225×10^{23}, which means that a sample diluted beyond 10^{24} would have reached a stage where it is very unlikely that there is even a single molecule of the original substance present. The biological efficacy of UHDs may be dependent on sequential kinetic activation (Gariboldi 2009), but the mechanism by which sequential kinetic activation enables a UHD to be biologically active is unknown. A common theory is that it involves stable water structures, created by interactions between molecules of the biological material and the water it is dissolved in, allowing the water to retain information about the biological material (Montagnier 2009).

Why it is important to do this review

This review is an update of a previously published Cochrane review on homeopathy for irritable bowel syndrome (Peckham 2012). The original review marked a small step forward in establishing whether or not homeopathy is an effective treatment for IBS; however due to the small number of studies, age of the studies and methodological limitations the original review provided only limited information. This updated review is timely not only because of the passage of time but also given the continued lack of effective treatments for IBS and the sustained interest in homeopathy as a potential

treatment option. Lower gastrointestinal tract disorders account for one in 20 of all general practice consultations in the UK (Thompson 2000). In addition, gastroenterology problems are the fourth most common referral to National Health Service (NHS) homeopathic hospitals (Spence 2005) and one of the eight most common conditions treated by NHS homeopaths in general practice (Mathie 2006). The frequency with which people with IBS consult homeopaths may be some indication of the value which they place on the homeopathic approach. Homeopathic treatment may offer a treatment strategy for patients with IBS, but at present it is not clear if it offers any benefit.

OBJECTIVES

The objective of this systematic review is to assess the effectiveness and safety of homeopathic treatment for IBS.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing homeopathic treatment with placebo or active comparators were considered for inclusion regardless of blinding method, publication status and language of publication. Quasi randomised studies were also considered for inclusion, where allocation was achieved by 'quasi-random' methods such as alternation between treatment arms, year of birth, month entered into study. Cohort and case-control studies were also considered for inclusion.

Types of participants

All trials of patients with a diagnosis of IBS were eligible for inclusion in this review regardless of age, gender, race, educational status or duration of IBS. Trials which included IBS patients in whom 10% or more had unstable psychiatric disorders, ulcerative colitis, Crohn's disease, bowel cancer and pregnant and breastfeeding women were excluded from this review.

Types of interventions

Trials were included if one of the groups in the trial received any type of homeopathic treatment involving the delivery of a homeopathic remedy (either by a homeopath following a consultation or studies where a homeopathic remedy was delivered without a consultation) and the other received placebo, an active comparator treatment, or no treatment.

Types of outcome measures

All trials that included any one of the following outcome measures were included in the review.

Primary outcomes

The primary outcome was global improvement of symptoms (patient-reported or clinician-evaluated or both) as measured by a global IBS symptom score (e.g. IBS Severity Scoring System (IBS-SSS), Adequate Relief Measure, GI Symptom Rating Scale, Functional Bowel Disorder Severity Index or IBS Symptom Questionnaire).

Secondary outcomes

Secondary outcomes included:

- Quality of life as measured by validated quality of life measure e.g. EQ5D, SF36, IBS Quality of Life Measure, IBS Quality of Life Questionnaire, Functional Digestive Disorder Quality of Life Questionnaire, IBS Health Related Quality of Life Questionnaire;
- Abdominal pain, discomfort and distension;
- Stool frequency, bowel transit time;
- Stool consistency; and
- Adverse events.

Search methods for identification of studies

Electronic searches

The following electronic databases were searched from inception to 31 August 2018:

The Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library, Ovid MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and the Allied and Complementary Medicine Database (AMED). The Cochrane IBD/FBD Group Specialised Register, Clinical trials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) http://www.who.int/ictrp/en/ were also searched.

Searching other resources

1. Reference searching

The reference lists for all identified studies were inspected for additional studies.

2. Personal contact

The first author of each included study was contacted for information regarding unpublished trials.

Data collection and analysis

Selection of studies

Two authors (EJP and SB) independently reviewed the titles and abstracts of the studies identified by the literature search. Included studies were assessed against the predefined inclusion criteria.

Data extraction and management

Two authors (EP and SB) independently extracted data from the included studies. Authors were contacted to clarify any unclear data. EP who is an author of one of the included studies was not involved in the data extraction or assessment of the risk of bias for the study that she was involved in the conduct of, GT extracted the data for this study.

Assessment of risk of bias in included studies

Two authors (SB and GT) independently assessed the methodological quality of included randomised trials using the Cochrane risk of bias tool (Higgins 2011). The following items were assessed:

- sequence generation (i.e. was allocation sequence adequately generated?);
- allocation sequence concealment (i.e. was allocation adequately concealed?);
- blinding (i.e. was knowledge of the allocated interventions adequately prevented during the study?);

- incomplete outcome data (i.e. were incomplete outcome data adequately addressed?);
- selective outcome reporting (i.e. are reports of the study free of suggestion of selective outcome reporting?); and
- other potential sources of bias (i.e. was the study apparently free of other problems that could lead to a high risk of bias e.g. baseline imbalances, evidence of carry-over in cross-over trials, comparability of groups in cluster trials).

It was intended that, based on these criteria the studies would be subdivided into three categories:

1. Low risk of bias i.e. all quality criteria met;

2. Medium risk of bias i.e. one or more of the quality criteria partly met; and

3. High risk of bias i.e. one or more of the quality criteria not met.

It was intended that the quality of quasi-randomised trials, non-randomised trials, cohort and case control studies would be assessed using a quality instrument designed for assessing the quality of non-randomised studies (Downs 1998).

Using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (Atkins 2004, Schünemann 2011), we will assess the overall quality of the evidence supporting the following outcomes: global improvement of symptoms, quality of life, improvement in abdominal pain, stool frequency, stool consistency and adverse events. The summary of the evidence will be presented in a 'Summary of findings' table, which will provide key information about the best estimate of the magnitude of the effect for each relevant comparison, and the rating of the overall confidence in effect estimates for each outcome. The GRADEpro Guideline Development Tool will be used to create the 'Summary of findings' table.

Measures of treatment effect

Review Manager (RevMan 5.3.5) was used to analyse the data. For continuous outcomes the mean difference (MD) with 95% confidence interval (95% CI) was calculated. For each dichotomous outcome the risk ratio (RR) with 95% CI was calculated.

Unit of analysis issues

We did not anticipate any unit of analysis issues arising from cluster randomisation. In the case of multiple intervention groups each intervention group was analysed separately against the control group and the sample size for the control group was divided proportionately across each intervention group. We noted that if the results were reported at multiple time points in the studies, each outcome would be analysed at pre-defined periods of follow-up in separate meta-analyses. Time points would be grouped as follows: less than three months, three months to one year, longer than one year. These time points were chosen as representing time frames in which a difference in the likelihood of responding could be expected.

Dealing with missing data

We intended to analyse data using the intention to treat (ITT) principle and sensitivity analyses were to be undertaken as appropriate (e.g. ITT versus available case, and study quality). However, da-

ta were analysed on an available case basis as the included studies did not provide enough detail to allow for an ITT analysis.

Assessment of heterogeneity

Statistical heterogeneity was assessed using the Chi² test and the I² statistic. If heterogeneity existed between studies (I² ≥ 50%) for the primary outcome, reasons for the heterogeneity would be explored. Clinical heterogeneity would be assessed through the description of the setting and homeopathic approach used in each study.

Assessment of reporting biases

In the protocol we noted that if more than 10 studies were identified for inclusion in this review, funnel plots would be used to assess publication biases.

Data synthesis

Data from individual trials were combined by meta-analysis if the interventions, outcomes and patient groups were sufficiently similar (determined by consensus). For continuous data the MD with 95% CI was calculated where the same scales have been used. Where studies were deemed sufficiently similar but different scales have been used the standardised mean difference (SMD) would be used to combine data. For dichotomous outcomes the pooled RR and 95% CI were calculated.

In the protocol we specified that data would not be pooled for meta-analysis if a high degree of heterogeneity (I² > 75%) was detected. A fixed-effect model would be used to pool data in the absence of heterogeneity. An I² ≥ 50% is considered to represent moderate heterogeneity and in such cases (I² 50 to 75%) a random-effects model would be used for pooling the data.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was planned between studies that prospectively identified IBS patients using ROME III criteria versus studies that did not use ROME III criteria to prospectively identify IBS patients. In the protocol we also noted that if data were reported separately for the different forms of IBS then a subgroup analysis comparing the different forms would be carried out. A subgroup analysis was also planned for quasi and true randomisation, different comparators (e.g. no treatment, usual care, placebo, or other active treatment) and different homeopathy interventions (e.g. individualised or clinical homeopathy).

Sensitivity analysis

In the protocol we noted that if a sufficient number of trials were identified a sensitivity analysis would be carried out by study quality to determine if the results of the primary analysis change according to which trials are incorporated into the analysis.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies and Characteristics of ongoing studies.

Results of the search

Figure 1 shows details of the search and selection process. From citations initially identified, full text sources were examined (after

removal of duplicates and assessment of abstract), studies were excluded for various reasons (listed in the excluded studies table) and four studies plus two secondary publications from two included studies were included in the review (Owen 1990; Peckham 2014; Rahlfs 1976; Rahlfs 1979). Two studies were included in quantitative synthesis (Rahlfs 1976; Rahlfs 1979). No cohort or case-control studies were identified.

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Figure 1. Study flow diagram.
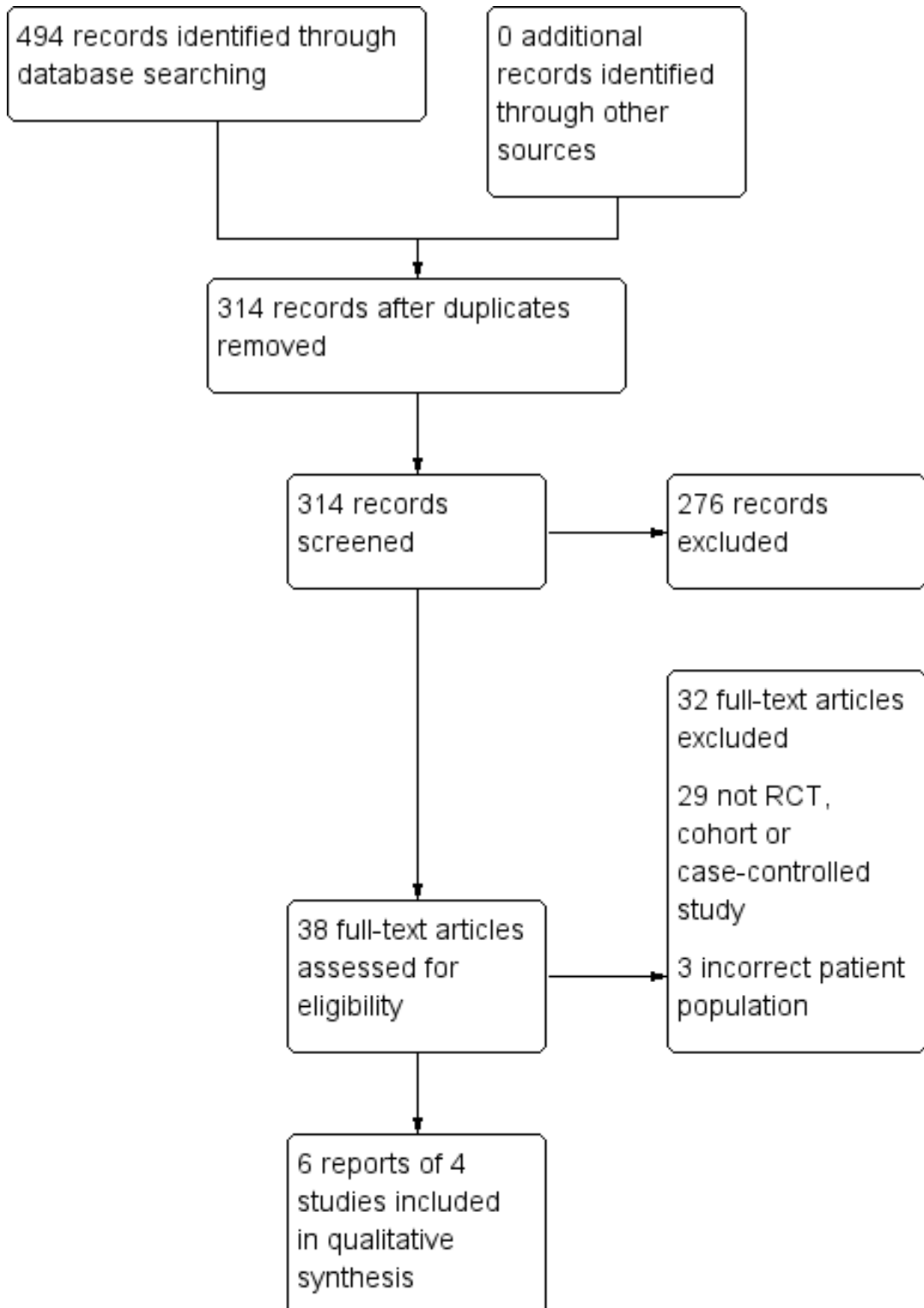
Included studies

Four studies with a total of 307 participants were included (Owen 1990; Peckham 2014; Rahlfs 1976; Rahlfs 1979). See Characteristics of included studies. Owen 1990 and Peckham 2014 were conducted in the UK and published in English. Rahlfs 1976 and Rahlfs 1979 were conducted in the former Federal Republic of Germany and published in German and were translated from German into English. Rahlfs 1976, was a three arm trial comparing asafoetida against asafoetida + nux vomica, against placebo, whereas Rahlfs 1979 compared asafoetida versus placebo (the participants in the two trials are independent). The authors noted that Rahlfs 1976 failed to recruit its target number of participants, hence the (simplified) trial being re-run. There were 23 participants in Owen 1990, 72 participants in Rahlfs 1976, 119 participants in Rahlfs 1979 and 94 participants in Peckham 2014. All included studies were published as full articles.

Owen 1990 compared individualised homeopathic treatment, which involved a homeopathic consultation and an individualised homeopathic remedy, to usual care which consisted of high doses of dicyclomine hydrochloride, faecal bulking agents and diet sheets asking the patient to take a high fibre diet. This study differs from other pragmatic trials of individualised homeopathic treatment, where the more common approach has been to compare individualised homeopathic treatment plus usual care to usual care alone. In Owen 1990 participants were asked to rate how unwell they felt before and after treatment, exact details of how this was scored are not given. Although Owen 1990 did not include a global measurement of IBS as one of the outcomes, we considered the rating of how unwell patients felt to provide a global measurement of the patients' health. The other outcome measures in Owen 1990 involved the patients choosing their own top four worst symptoms and grading these on a visual analogue scale, it was not specified that these symptoms had to be related to IBS, and details of the symptoms patients chose were not reported are not given, hence this outcome measure was not included in this review.

Peckham 2014 was a three armed trial that compared individualised homeopathic treatment plus usual care to supportive listening plus usual care to usual care alone. Unequal randomisation was used in Peckham 2014 with 16 participants allocated to individualised homeopathic treatment, 18 to supportive listening and 60 to usual care. Individualised homeopathic treatment involved a homeopathic consultation and an individualised homeopathic remedy. Supportive listening aimed to control for the time and attention given to the patient in the individualised homeopathic treatment arm and consisted of the same number of sessions of the same duration as the homeopathic consultation. In both the individualised homeopathic treatment and supportive listening arms patients were offered five one hour sessions with a homeopath or counsellor respectively. The primary outcome measure in Peckham 2014 was change in IBS-SSS at 6 months.

None of the included studies reported on adverse events as an outcome.

Excluded studies

The Characteristics of excluded studies table, describes the characteristics of the 32 excluded studies along with the reason for their exclusion.

Ongoing studies

No ongoing studies were identified.

Risk of bias in included studies

The risk of bias in the included studies for each domain are discussed below. See results of the risk of bias analysis are summarized in Figure 2.

Figure 2. Methodological quality summary: review authors' judgments about each methodological quality item for each included study.

Allocation

Owen 1990, Rahlfs 1976, Rahlfs 1979 and Peckham 2014 were described as RCTs. Owen 1990 reported that the participants were stratified and randomised into one of two treatment groups. However, no details were given about the stratification or how randomisation sequence was generated. Rahlfs 1976 reported that a chance code was used for randomisation, although what this entailed and how it was implemented was not described. Rahlfs 1979 did not report any information regarding the method of generation of the randomisation code. Peckham 2014 reported that the random sequence was generated by shuffling of sealed opaque envelopes containing the allocation and was reported as being of low risk of bias for allocation concealment. Rahlfs 1976 and Rahlfs 1979 provided medication in sequentially numbered drug containers and

were rated as low risk for allocation concealment. Owen 1990 did not describe the procedure used for allocation concealment and was rated as unclear for this item.

Blinding

Participants and physicians were not blinded to treatment allocation in the Owen 1990 and Peckham 2014 studies as it was not possible to design a study where participants were not aware of their receiving an individualised homeopathic consultation, supportive listening or usual care. Owen 1990 did not report whether other key study personnel were blinded, or whether outcome assessment was carried out blind. In Peckham 2014 outcomes were participant reported and due to participants being aware of their allocation outcomes were at high risk of bias. In Rahlfs 1976 and Rahlfs 1979 the study participants and the doctors who recruited

the participants were blinded to allocation by the use of an identical placebo. In Rahlfs 1979, the participant blinding was well described. Rahlfs 1976 and Rahlfs 1979 did not report whether other key study personnel were blinded, or if outcome assessment was carried out blind.

Incomplete outcome data

The number of patient withdrawals was reported for Owen 1990, Rahlfs 1976, Rahlfs 1979 and Peckham 2014. Although Owen 1990 reported the number of withdrawals and the arm from which the patients withdrew, the reasons for withdrawal were not reported. In Peckham 2014 the reasons for withdrawal were reported and a comparison of baseline data was made between those who had missing data and those who did not, this indicated that there was a relationship between age, employment status and missing data, hence employment status and age were included in the ANCOVA model for the primary outcome. Rahlfs 1976 did not report which arms that patients withdrew from and therefore it was not clear whether there may be attrition bias in this trial. Rahlfs 1979 reported the number of withdrawals from each treatment group and the reasons for withdrawal. Whilst dropouts appear to be comparable in terms of number and reason for withdrawal across both arms of this study (Rahlfs 1979), it should be remembered that any dropout threatens group comparability at baseline as random allocation seeks to distribute both known and unknown characteristics across groups, and dropouts may differ for unknown characteristics that cannot be measured.

Selective reporting

Due to insufficient reporting in Owen 1990 and Rahlfs 1976 both studies were rated as unclear for the item on selective reporting. Rahlfs 1979 was deemed to be at a high risk of bias due to selective reporting because of evidence of selective choice of data for an outcome. Some participants were excluded from the outcome analyses for not meeting the inclusion criteria while other participants who did not meet the inclusion criteria in terms of age were included in the analyses. Peckham 2014 was deemed to be at low risk of bias for selective reporting due to all the outcomes being reported in the protocol paper being presented in the main paper.

Other potential sources of bias

Due to the low quality of reporting in Owen 1990, Rahlfs 1976 and Rahlfs 1979, the potential for other sources of bias in these studies could not be assessed. No other potential sources of bias were identified in Peckham 2014, however it cannot be certain that there were no other sources of bias so this has been marked as unclear.

Effects of interventions

See: **Summary of findings for the main comparison** Homeopathy versus placebo; **Summary of findings 2** Homeopathy versus usual care; **Summary of findings 3** Homeopathy plus usual care versus usual care; **Summary of findings 4** Homeopathy plus usual care versus supportive listening plus usual care

Clinical homeopathic remedy versus placebo remedy

Rahlfs 1976 and Rahlfs 1979 assessed global improvement in IBS at two weeks as an outcome measure. For this outcome patients were asked to measure their improvement on a three-point scale (Rahlfs 1976) and a four-point scale (Rahlfs 1979). For the Rahlfs 1976 study participants were asked to rate whether they were not or negligi-

bly improved, more than half improved or free of symptoms. Participants in the Rahlfs 1979 study were asked to rate whether they were worse, not or negligibly improved, more than half improved or free of symptoms. For the purposes of this review, we dichotomised these scales into two categories: those who had improved (more than half improved or free of symptoms) versus those who had not improved (those who were worse, or not or negligibly improved).

At short term follow up of two weeks, a pooled analysis (129 participants) indicated that there may be a benefit of the homeopathic treatment asafoetida over placebo. At short-term follow up of two weeks, the RR for global improvement in symptoms for asafoetida versus placebo was 1.61 (95% CI 1.18 to 2.18; very low certainty evidence). Little heterogeneity was detected for this comparison (I^2 = 18%). For the study that compared homeopathic remedy (asafoetida plus nux vomica) to placebo the RR was 1.31 (95% CI 0.80 to 2.15; very low certainty evidence).

Homeopathic treatment versus usual care

In Owen 1990 participants (N = 20) were asked to rate how unwell they felt before and after treatment. The effect of individualised homeopathic treatment was uncertain. The mean global improvement score (i.e. how unwell the participants felt - a lower score indicates feeling more unwell) in the individualised homeopathic treatment arm was 1.44 (SD 4.55) compared to 1.41 (SD 1.97) in the usual care arm (MD 0.03, 95% CI -3.16 to 3.22; very low certainty evidence).

Homeopathic treatment plus usual care versus usual care

In Peckham 2014 participants were asked to complete the IBS-SSS at baseline and at 6 months. The effect of individualised homeopathic treatment at 6 months was uncertain. In the individualised homeopathic treatment plus usual care arm the mean IBS-SSS score was 210.44 (SD 112.4) compared to 237.30 (SD 110.22) in the usual care arm (MD -26.86, 95% CI -88.59 to 34.87; low certainty evidence). A lower score indicates less severity of symptoms.

Homeopathic treatment plus usual care versus supportive listening plus usual care

In Peckham 2014 participants were asked to complete the IBS-SSS at baseline and at 6 months. The effect of homeopathic treatment compared to supportive listening was uncertain. At six months the mean IBS-SSS score in the homeopathic treatment plus usual care arm was 210.44 (SD 112.4) compared to 262.00 (SD 120.72) in the supportive listening plus usual care arm (MD -51.56, 95% CI -129.94 to 26.82; very low certainty evidence). A lower score indicates less severity of symptoms.

Secondary outcome measures

The secondary outcomes quality of life, abdominal pain, stool frequency, stool consistency and adverse events were not reported on in Rahlfs 1976, Rahlfs 1979 or Owen 1990. Quality of life using the EQ-5D was reported on in Peckham 2014. The effect of individualised homeopathic treatment on quality of life was uncertain. In the homeopathic treatment arm the mean EQ-5D visual analogue score (VAS) at six months was 69.07 (SD 17.35) compared to 63.41 (SD 23.31) in the usual care arm (MD 5.66, 95% CI -4.69 to 16.01; low certainty evidence). In the homeopathic treatment arm the mean EQ-5D score at six months was 69.07 (SD 17.35) compared to 63.09 (SD 24.38) in the supportive listening arm (MD 5.98, 95% CI -8.13 to

20.09; very low certainty evidence). A lower score indicates a worse quality of life.

Pooling of results

Outcome data from the Owen 1990 study was not pooled with the data from Rahlfs 1976 and Rahlfs 1979 because of heterogeneity between the studies. The three studies investigated two different types of homeopathy. For the same reason outcome data from Peckham 2014 was not pooled with outcome data from Rahlfs 1976 and Rahlfs 1979. Owen 1990 and Peckham 2014 investigated the effectiveness of individualised (classical) homeopathic treatment, whilst Rahlfs 1976 and Rahlfs 1979 investigated clinical homeopathy. The type of IBS investigated was also potentially different. In the Owen 1990 and Peckham 2014 studies participants were diagnosed with IBS and no further information on type was given, whilst the participants in Rahlfs 1976 and Rahlfs 1979 had constipation-predominant IBS. In addition, the studies measured outcomes at different time points. Peckham 2014 measured outcomes at 26 weeks and Owen 1990 measured outcomes at 12 weeks, whilst Rahlfs 1976 and Rahlfs 1979 measured outcomes at 2 weeks. The primary outcome for the Owen 1990 study was not a global improvement measure and was not comparable with the other three studies. Although it may be tempting to combine studies in a meta-analysis when it is likely to yield a statistically significant result, it is important not to combine studies where there is significant clinical heterogeneity, because these results would not be meaningful due to the large degree of differences between the studies. For these reasons the outcomes from Owen 1990, Peckham 2014, Rahlfs 1976 and Rahlfs 1979 were not combined.

DISCUSSION

Summary of main results

Two RCTs compared a clinical homeopathic remedy (asafoetida and asafoetida plus nux vomica) with placebo for treating IBS-C (Rahlfs 1976; Rahlfs 1979). In a meta-analysis of these studies, the homeopathic remedy found that there may be a benefit of the remedy over placebo for improvement in global IBS symptoms at a short-term follow-up of two weeks. However, this result should be interpreted with caution due to the low quality of the reporting in these studies, a high or unknown risk of bias associated with the trials in this pooled analysis, short-term follow-up, and sparse data.

Two RCTs (Owen 1990; Peckham 2014) compared individualised homeopathic treatment with usual care. In Owen 1990 individualised homeopathic treatment was compared to usual care (dicyclomine hydrochloride, faecal bulking agents, and diet sheets advising a high fibre diet). No conclusions can be drawn from this study due to the small number of participants, the low quality of reporting in this trial and a high risk of bias. Although Peckham 2014 has a low risk of bias and the quality of the reporting is good it is difficult to draw conclusions from this study due to the small number of participants.

Overall completeness and applicability of evidence

Rahlfs 1976 and Rahlfs 1979 assessed the effectiveness of clinical homeopathy for the treatment of constipation-predominant IBS. Therefore this review does not provide information on the effectiveness of clinical homeopathy for the treatment of IBS in general, or diarrhoea-predominant, or mixed typology IBS. Both Rahlfs 1976 and Rahlfs 1979 reported outcomes at two weeks. Given the long

term nature of IBS it is not clear how useful a two-week outcome is for patients', clinicians' and policy makers' decision making. As people live with IBS for years, an evaluation of impact at two weeks fails to take into account possible rebound effects or longer term benefits or adverse events that would be important for patients and practitioners to know about when they consider the potential benefits and harms associated with this intervention.

Two studies that assessed the effectiveness of individualised homeopathic treatment were identified in this review (Owen 1990; Peckham 2014). The number of participants in both these studies were small (N = 23 and N = 94 respectively). Owen 1990 was conducted over 25 years ago. It is likely that there have been changes in usual care for IBS since this time, therefore Owen 1990 may not provide a full picture of the effectiveness of individualised homeopathic treatment compared to usual care. Peckham 2014 was conducted more recently and is likely to compare individualised homeopathic treatment to current usual care however given the small size of this study and the fact that it is underpowered makes it difficult to draw any firm conclusions from the study.

Quality of the evidence

The results from the pooled analysis indicate a possible benefit for homeopathic treatment using clinical homeopathy (non-individualised homeopathic remedies) over placebo for constipation-predominant IBS. However, this result needs to be interpreted with caution. The two studies included in the pooled analysis (Rahlfs 1976 and Rahlfs 1979) were carried out in the 1970s before the introduction of the CONSORT statement (Begg 1996), and the quality of reporting in these studies does not meet currently expected standards (Schultz 2010). The low quality of the reporting means that it is not possible to determine whether or not these studies were carried out in a rigorous manner and thus how likely it is that these results are a true reflection of the treatment effect. Both studies were determined to have an unknown risk of bias for most assessed items and Rahlfs 1979 was at a high risk of reporting bias. The quality of the evidence supporting the primary outcome (i.e. global improvement) was very low due to the low quality of reporting in the included studies, high or unknown risk of bias, sparse data and short-term follow-up.

Participants in the Rahlfs 1976 and Rahlfs 1979 studies were recruited through general practice as having suspected IBS. It is not clear whether diseases such as Crohn's disease or ulcerative colitis were ruled out in these participants and it is possible that some participants had diseases such as Crohn's or ulcerative colitis rather than IBS.

The quality of the reporting in the Owen 1990 study was low, and this study does not meet the current expected standards (Schultz 2010). No conclusions can be drawn from this study due to the small number of participants and risk of bias. Owen 1990 was rated as high risk of bias for blinding of participants and personnel. The study was rated as unknown risk of bias for the other assessed items. The exact details of the medication prescribed in the usual care arm, in terms of dosage and frequency were not reported.

The quality of the reporting in the Peckham 2014 was good and combined with the published protocol it meets the current expected standards (Schultz 2010). Peckham 2014 was rated as being at low risk of bias for selection bias, attrition bias and reporting bias and at high risk of bias for performance bias and detection bias.

However the small number of participants in this study (n = 16 homeopathic treatment, n = 18 supportive listening and n = 60 usual care) and the fact that it was underpowered mean no firm conclusions can be drawn from this study. The quality of the evidence supporting the primary outcome (i.e. global improvement) ranged from very low to low due to sparse data and high risk of bias.

Potential biases in the review process

To avoid potential biases in the review process data extraction was carried out independently by two assessors. In addition, efforts were made to identify all studies that were potentially eligible for this review (see Search methods for identification of studies). However, It is possible that not all potentially eligible studies were identified. This could be because potentially eligible studies have been carried out and then have not been published, or that studies have been published but not in places where they could be accessed, possibly because they were published in little known non-indexed journals or they could have been published in places where they should have been found, but were not found. One of the review authors (EJP) was a trialist for an included study (Peckham 2014). For this study, the assessment of risk of bias and data extraction was performed by other authors. Cohort and case-control studies were considered for inclusion but none were identified by the literature search. In retrospect the inclusion of case-control studies was not appropriate given that the main reason for including case-control studies in a review is when an event is very rare and thus it is unlikely that any RCTs have been carried out (Reeves 2011).

Agreements and disagreements with other studies or reviews

No other systematic reviews of homeopathic treatment for IBS were identified. However non-condition specific systematic reviews of homeopathic treatment that included the Rahlfs 1976 and Rahlfs 1979 studies have been published (Linde 1997; Shang 2005). Neither of these systematic reviews carried out any analyses on homeopathy for the treatment of IBS or specifically commented on homeopathy for IBS.

AUTHORS' CONCLUSIONS

Implications for practice

The results for the outcomes assessed in this review are uncertain. Thus no firm conclusions regarding the effectiveness and safety of homeopathy for the treatment of IBS can be drawn.

In this review of homeopathic treatment for IBS, two of the included studies used clinical (non-individualised) homeopathic remedies to treat patients with constipation-predominant IBS (Rahlfs 1976; Rahlfs 1979). A meta-analysis of these two studies found a possible benefit favouring the homeopathic remedy over placebo. However, these results should be interpreted with caution due to the low quality of reporting in these studies, a high or unknown risk of bias and sparse data. Thus it is not possible to be certain whether or not the trials were able to distinguish between true treatment effects, chance or bias. Furthermore, the low quality of reporting practice means that it is difficult to assess whether the results would be replicated in everyday practice, that is, whether the results are externally valid or generalisable. We are therefore very uncertain about these results and cannot suggest a possible benefit for clinical homeopathy.

It is of note that Rahlfs 1976 and Rahlfs 1979 reported outcomes at two weeks. Given the long term nature of IBS, it is not clear how useful a two-week outcome is for decision making. It is essential that trials have a follow-up period that is clinically meaningful. As people live with IBS for years, an evaluation of impact at two weeks fails to take into account any possible rebound effects, or longer term benefits or adverse events that would be important for patients and practitioners to know about when they consider the potential benefits and harms associated with this intervention.

The results from Owen 1990 are uncertain and no conclusions can be drawn from this study. Owen 1990 compared individualised homeopathic treatment and usual care consisting of dicyclomine hydrochloride and faecal bulking agents. The results from Peckham 2014 are uncertain and no conclusions can be drawn from this study. Peckham 2014 compared individualised homeopathic treatment plus usual care, supportive listening plus usual care and usual care. Individualised homeopathy is the most common form of homeopathy practised in the UK. However due to the poor quality of reporting in Owen 1990 study and the small number of participants in both Owen 1990 and Peckham 2014, no conclusions can be made regarding the usefulness of individualised homeopathic treatment for the treatment of IBS.

None of the included studies reported on adverse events therefore no conclusions can be drawn on the safety of homeopathic treatment for IBS.

Implications for research

Further high quality, adequately powered RCTs are required to assess the efficacy and safety of clinical and individualised homeopathy for IBS compared to placebo or usual care.

Rahlfs 1976 and Rahlfs 1979 evaluated clinical homeopathy involving pre-specified homeopathic remedies for the treatment of IBS-C and were therefore designed to assess the effectiveness of non-individualised homeopathic remedies. However due to the high risk of reporting bias in one of these studies and unclear reporting in both of these studies it is recommended that these trials are repeated using current reporting guidelines (Schultz 2010), to determine whether or not there is any benefit associated with homeopathy for IBS. Future high quality studies should enrol larger numbers of patients and assess longer term efficacy and safety outcomes.

Owen 1990 assessed the effectiveness of individualised homeopathic treatment compared to usual care and Peckham 2014 assessed the effectiveness of individualised homeopathic treatment plus usual care to usual care. Due to the low quality reporting in Owen 1990 and the likelihood that usual care for IBS has changed since this study was conducted, and the fact that Peckham 2014 was underpowered to detect a significant difference, it is recommended that the effectiveness and safety of individualised homeopathic treatment be evaluated in a well-designed, adequately powered trial.

ACKNOWLEDGEMENTS

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Cochrane
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Cochrane Database of Systematic Reviews

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Owen 1990

Methods	RCT, unblinded, parallel study, 12 weeks duration
Participants	Setting; county hospital, UK
	Number of participants; 23 patients were allocated into one of the treatment groups, 20 patients included in analysis
	Recruitment methods; female patients attending the out-patient department at a county hospital in whom a diagnosis of IBS was made
	Diagnosis of IBS; clinical diagnosis by a consultant gastroenterologist and consultant gynaecologist
	Age range of patients; 20-69 years
	Gender (of treated patients); 100% female
	Duration of symptoms > 3 months
Interventions	1. Individualised homeopathic treatment
	2. High doses of Dicyclomine hydrocholoride (exact dose not stated), faecal bulking agents and diet sheets advising a high fibre diet
Outcomes	Patients were asked to grade: their four worst symptoms on a visual analogue scale, dysmenorrhoea, dyspareunia, and feeling unwell at baseline, 2, 6 and 12 weeks
Notes	Detailed information is given on the homeopathic treatment the participants received in terms of; remedy chosen, potency and dosage, whilst no information is given on the strength and dosage of the dicyclomine hydrocholoride and faecal bulking agents prescribed in the usual care arm

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although it is stated that this is a randomised trial no details were given as to how randomisation was achieved
Allocation concealment (selection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition, whilst possible reasons for attrition were discussed for one patient, the reasons for the other two patients leaving the study were not reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information is provided to be able to judge whether the study is at risk from selective reporting
Other bias	Unclear risk	Due to the low quality of the reporting in this study it is unclear whether the study is at risk from any other forms of bias
Blinding of participants and personnel (performance bias)	High risk	Participants and doctors were not blinded to allocation, however it is not stated whether other key study personnel were blinded

Owen 1990 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not reported whether or not the outcome assessment was carried out blind

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Peckham 2014

Methods	Three arm, parallel group non-blinded randomised controlled trial 26 weeks in duration
Participants	Setting: Hospital outpatient, UK
	Number of participants; 94 patients were allocated into one of the treatment groups in a 4:1:1 ratio, 60 patients were allocated to usual care, 16 were offered homeopathic treatment plus usual care and 18 were offered supportive listening plus usual care
	Recruitment methods; GP database recruitment, consultant gastroenterologist in secondary care
	Diagnosis of IBS; diagnosed according to the Rome III criteria, potentially eligible participants were asked to complete a questionnaire which included the Rome III criteria for IBS. Participants had to score a minimum of 100 on the IBS-SSS to be eligible to take part in the trial
	Mean age range of participants; 49 years
	Gender; 83% female
	Duration of symptoms > 3 months
Interventions	1. Individualised homeopathic treatment plus usual care
	2. Supportive listening plus usual care
	3. Usual care
Outcomes	IBS-SSS, EQ-5D, HADS
Notes	This study employed a Trials Within Cohorts design which recruited a cohort of people with IBS. From this cohort people were randomly selected to receive the offer of a treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generated by shuffling of sealed opaque envelopes containing the allocation (protocol paper)
Allocation concealment (selection bias)	Low risk	Questionnaires from participants consenting and meeting the eligibility criteria are taken one at a time, at the same time a sealed opaque envelope containing the allocation is taken from the top of the shuffled pack and opened and the allocation noted. This is carried out by an independent administrator at the University of Sheffield, in the presence of another independent administrator. (protocol paper).
Incomplete outcome data (attrition bias) All outcomes	Low risk	The proportion of patients who dropped out of the usual care and supportive listening arms was similar and the reasons for dropping out were the same in both groups.
		9/60 (15%) participants in the usual care arm did not return the follow-up questionnaire

Peckham 2014 *(Continued)*

		All 16 participants in the homeopathy arm were included in the analysis
		3/18 (17%) participants in the supportive listening arm did not return the questionnaire
Selective reporting (reporting bias)	Low risk	Outcome data presented for those outcome measures stated in the protocol.
Other bias	Low risk	The quality of reporting in this study was good and did not indicate that there were likely to be other forms of bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither the nature of the interventions in this study nor the study design allows for the masking of the therapists or the participants.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were patient-reported outcomes (i.e. the patient was the outcome assessor). As the patients were aware of the group allocation, this domain was judged as high risk of bias.

Rahlfs 1976

Methods	RCT, double blind, parallel study, 2 weeks duration
Participants	Setting; general practice, Germany
	Number of participants; 71 patients treated (number of patients randomised not clearly stated), 63 patients included in analysis
	Recruitment methods; patients presenting in general practice with suspected IBS
	Diagnosis of IBS; Clinical diagnosis plus completion of detailed questionnaire
	Mean age (of treated patients); 43.8 years
	Gender (of treated patients); 50.8% female
	Duration of symptoms > 14 days
Interventions	1. 0.1% asafoetida alcohol solution, 6 x 5 drops daily
	2. 0.1% asafoetida alcohol solution + 0.01% nux vomica alcohol solution, 6 x 5 drops daily
	3. placebo, 45% alcohol solution, 6 x 5 drops daily
Outcomes	Self assessment on a 3 point scale; no or negligible improvement, more than half improved, free of symptoms measured on day 8 and day 15 of the study
	Time to recovery assessed by the patient reporting the day they felt considerable improvement
	Freiburg Personality Inventory
Notes	Analysed participant data were fairly well described, but a lot of pre-randomisation and pre-analysis data were missing

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Homeopathy for treatment of irritable bowel syndrome (Review)

Rahlfs 1976 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	A chance code was used for the randomisation, the exact nature of which was not reported Therefore the risk of bias cannot be determined
Allocation concealment (selection bias)	Low risk	Medication was provided in sequentially numbered drug containers
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition, some reasons for attrition are given, details of allocation are not always given
Selective reporting (reporting bias)	Unclear risk	Insufficient information was provided to be able to judge whether the study was at risk from selective reporting
Other bias	Unclear risk	Insufficient information was provided to assess whether the study was at risk from any other bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and recruiting doctors were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not reported whether outcome assessment was carried out blind

Rahlfs 1979

Methods	RCT, double blind, parallel study, 2 weeks duration
Participants	Setting; general practice, Germany Number of participants; 119 patients treated (number of participants randomised not clearly stated), 89 patients included in analysis Recruitment methods; patients presenting in general practice with suspected IBS Diagnosis of IBS; Clinical diagnosis plus completion of detailed questionnaire Mean age (of patients included in analysis, ages of those not included not stated); 42.5 years Gender (of those included in analysis, gender of those not included not stated); 68.5% female Duration of symptoms > 14 days
Interventions	1. 0.1% asafoetida alcohol solution, 6 x 5 drops daily 2. placebo, 45% alcohol solution, 6 x 5 drops daily
Outcomes	Self assessment on a 4 point scale; worsening of symptoms, no or negligible improvement, more than half improved, free of symptoms, measured on day 8 and day 15 of the study Time to recovery assessed by the patient reporting the day they felt considerable improvement
Notes	Analysed participant data were fairly well described, but a lot of pre-randomisation and pre-analysis data were missing

Rahlfs 1979 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although it was reported that this was a randomised trial no details were given as to how randomisation was achieved
Allocation concealment (selection bias)	Low risk	Medication was provided in sequentially numbered drug containers
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Incomplete outcome data, reasons for missing data, and how incomplete outcome data were addressed was not clearly described
Selective reporting (reporting bias)	High risk	The inclusion and exclusion criteria were applied in a variable manner, some people that were subsequently found not to meet the exclusion and inclusion criteria were removed from the analysis However people who did not meet the inclusion criteria for age, being too old were still included in the analysis This leaves the study at risk of bias due to selective reporting
Other bias	Unclear risk	Due to the low quality of the reporting it was unclear whether the study was at risk from any other forms of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and doctors were blinded to allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not reported whether outcome assessment was carried out blind to treatment allocation

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

Study	Reason for exclusion
Aleem 2000	Discussion piece and not a randomised controlled trial, cohort or case-control study
Anonymous 2005	An initial reading of this Italian article revealed it to be discussing a meta analysis by Shang 2005 Therefore a full translation was not conducted
Anonymous 2009	Discussion piece and not a randomised controlled trial, cohort or case-control study
Bauer 2014	Case studies on the treatment of IBS and not a randomised controlled trial, cohort or case-control study
Bhagat 2010	Case report (n = 1) of homeopathic treatment for IBS
Bhattacharjee 2010	The article was a discussion on the different homeopathic remedies used for the treatment of IBS

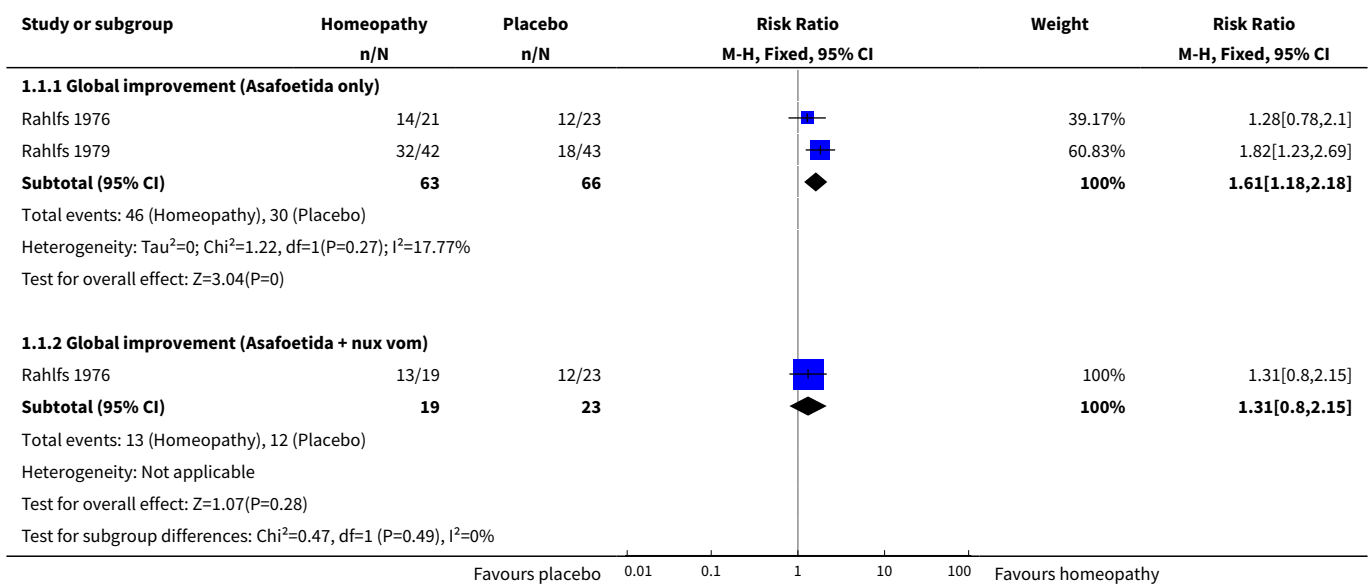| Study	Reason for exclusion
Chen 2015	A discussion on the use of complementary therapies for the treatment of functional gastrointestinal disorders
Cherniack 2013	Not on IBS
Chimthanawala 2004	Case report (n = 2) of homeopathic treatment for IBS
Diamond 2005	A discussion on the use of complementary therapies for the treatment of gastroenterological problems
Elio 2014	Report on a series of patients attending a clinic. Not specific to IBS and not an RCT or case series
Feldhaus 2000	This was a discussion piece on the treatment of IBS
Gamble 2007	Discussion of a potentially new way of assessing and treating IBS, from a homeopathic perspective, using two cases as an example
Gebhardt 1988	Discussion on homeopathic treatment for IBS, not a randomised controlled trial, cohort or case-control study
Gray 1998	This study was a case series of 25 patients with no comparator group
Greeson 2008	Non-randomised observational study of outcomes for patients attending a integrative medical centre where homeopathy was only one of the treatments offered
Grundmann 2014	Review of treatments for IBS does not include homeopathy
Innes 2000	This study was a case series (n = 20) with no comparator group
Jagose 2004	Case report (n = 1) of homeopathic treatment for IBS
Jones 1996	A discussion of the homeopathic treatment of IBS, illustrated by three cases
Jones 1997	Discussion piece on homeopathic treatment of IBS
Jones 1999	Case report study of a woman with IBS treated with homeopathy
Krishendu 2010	A discussion of the different homeopathic remedies used for the treatment of IBS
Lobo 2000	Case report (n = 1) on homeopathic treatment of IBS
Master 2008	Discussion piece on homeopathy for IBS
Mohan 2006	Case report (n = 2) of IBS treated with homeopathy
Pawar 2015	A discussion on homeopathic remedies
Pinto 1999	A selection of case reports on homeopathic treatment for a variety of conditions
Pohl 2013	An overview of treatments for irritable bowel syndrome which does not include homeopathy
Slade 2003	Case report (n = 1) of homeopathic treatment of ulcerative colitis
Turner 2008	Discussion of homeopathic treatment of IBS, illustrated by eight case histories

Study	Reason for exclusion
White 1999	Discussion of homeopathic treatment for IBS, not a randomised controlled trial, cohort or case-control study

DATA AND ANALYSES

Comparison 1.   Homeopathy versus placebo

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Homeopathy versus placebo	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Global improvement (Asafoetida only)	2	129	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.18, 2.18]
1.2 Global improvement (Asafoetida + nux vom)	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.80, 2.15]
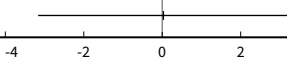
Analysis 1.1.   Comparison 1 Homeopathy versus placebo, Outcome 1 Homeopathy versus placebo.

Study or subgroup	Homeopathy n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Global improvement (Asafoetida only)					
Rahlfs 1976	14/21	12/23		39.17%	1.28[0.78,2.1]
Rahlfs 1979	32/42	18/43		60.83%	1.82[1.23,2.69]
Subtotal (95% CI)	**63**	**66**		**100%**	**1.61[1.18,2.18]**
Total events: 46 (Homeopathy), 30 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.22, df=1(P=0.27); I²=17.77%					
Test for overall effect: Z=3.04(P=0)					
1.1.2 Global improvement (Asafoetida + nux vom)					
Rahlfs 1976	13/19	12/23		100%	1.31[0.8,2.15]
Subtotal (95% CI)	**19**	**23**		**100%**	**1.31[0.8,2.15]**
Total events: 13 (Homeopathy), 12 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.07(P=0.28)					
Test for subgroup differences: Chi²=0.47, df=1 (P=0.49), I²=0%					

Favours placebo   0.01   0.1   1   10   100   Favours homeopathy

Comparison 2.   Homeopathy versus usual care

Outcome or subgroup title	No. of studies	No. of par-ticipants	Statistical method	Effect size
1 Global improvement (feeling unwell)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Homeopathy versus usual care, Outcome 1 Global improvement (feeling unwell).

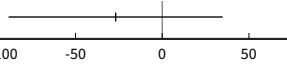| Study or subgroup	Homeopathy		Usual care		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Owen 1990	9	1.4 (4.6)	11	1.4 (2)		0.03[-3.16,3.22]

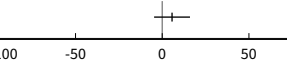Favours usual care -4 -2 0 2 4 Favours homeopathy

Comparison 3. Homeopathy plus usual care versus usual care

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Global improvement (IBS-SSS)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Quality of life	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Homeopathy plus usual care versus usual care, Outcome 1 Global improvement (IBS-SSS).

Study or subgroup	Homeopathy		Usual care		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Peckham 2014	16	210.4 (112.4)	60	237.3 (110.2)		-26.86[-88.59,34.87]

Favours homeopathy -100 -50 0 50 100 Favours usual care
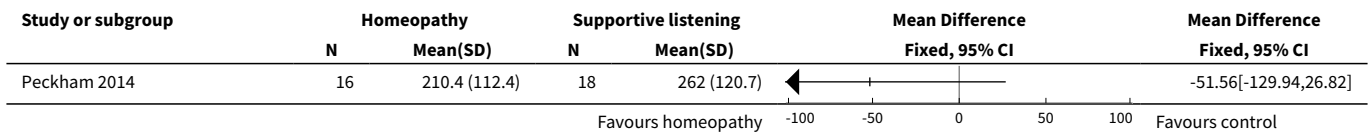
Analysis 3.2. Comparison 3 Homeopathy plus usual care versus usual care, Outcome 2 Quality of life.

Study or subgroup	Homeopathy		Usual care		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Peckham 2014	16	69.1 (17.4)	60	63.4 (23.3)		5.66[-4.69,16.01]

Favours usual care -100 -50 0 50 100 Favours homeopathy

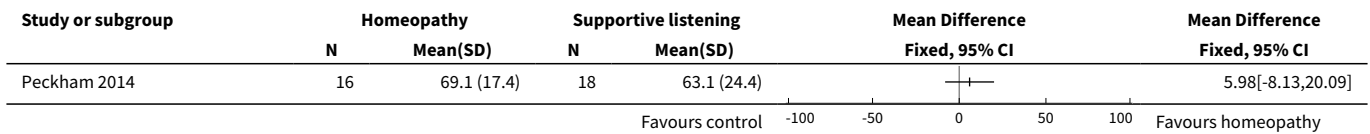## Comparison 4. Homeopathy plus usual care versus supportive listening plus usual care

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Global improvement (IBS-SSS)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Quality of life	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4 Homeopathy plus usual care versus supportive listening plus usual care, Outcome 1 Global improvement (IBS-SSS).

Study or subgroup	Homeopathy		Supportive listening		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Peckham 2014	16	210.4 (112.4)	18	262 (120.7)		-51.56[-129.94,26.82]

Favours homeopathy -100 -50 0 50 100 Favours control

Analysis 4.2. Comparison 4 Homeopathy plus usual care versus supportive listening plus usual care, Outcome 2 Quality of life.

Study or subgroup	Homeopathy		Supportive listening		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Peckham 2014	16	69.1 (17.4)	18	63.1 (24.4)		5.98[-8.13,20.09]

Favours control -100 -50 0 50 100 Favours homeopathy

A P P E N D I C E S

Appendix 1. Search Strategies

Medline

1. Colonic disease*.mp

2. irritable bowel syndrome/

3. colonic diseases, functional/

4. irritable bowel/

5. irritable colon/

6. spastic colon/

7. functional bowel disease*.mp.

8. functional colonic disease*.mp.

9. or/1-8

10. homeopathy/

11. homeopath*.mp.

12. homoeopath*.mp.

13. alternative medicine*.mp.

14. or/10-13

15. 9 and 14

EMBASE

1. Colonic disease*.mp

2. irritable bowel syndrome/

3. colonic diseases, functional/

4. irritable bowel/

5. irritable colon/

6. spastic colon/

7. functional bowel disease*.mp.

8. functional colonic disease*.mp.

9. or/1-8

10. homeopathy/

11. homeopath*.mp.

12. homoeopath*.mp.

13. alternative medicine*.mp.

14. or/10-13

15. 9 and 14

CENTRAL

#1 MeSH: [Irritable bowel syndrome] explode all trees

#2 Colonic disease*

#3 irritable bowel syndrome

#4 colonic diseases, functional

#5 irritable bowel

#6 irritable colon

#7 spastic colon

#8 functional bowel disease*

#9 functional colonic disease*

#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

#11 homeopathy

#12 homeopath*

#13 homoeopath*

#14 alternative medicine*

#15 #11 or #12 or #13 or #14

#16 #10 and #15

Cumulative Index to Nursing and Allied Health Literature (CINAHL)

1. (TI homeopathy or AB homeopathy) OR (TI homeopath* or AB homeopath*) OR (TI homoeopath* or AB homoeopath*) OR (TI alternative medicine* of AB alternative medicine*)

2. (TI Irritable bowel syndrome or AB Irritable bowel syndrome) OR (TI Colonic disease* or AB Colonic disease*) OR (TI irritable colon or AB irritable colon) OR (TI spastic colon or AB spastic colon) OR (TI functional bowel disease* or AB functional bowel disease*) OR (TI functional colonic disease* or AB functional colonic disease*)

Allied and Complementary Medicine Database (AMED)

1. Colonic disease*.mp

2. irritable bowel syndrome/

3. colonic diseases, functional/

4. irritable bowel/

5. irritable colon/

6. spastic colon/

7. functional bowel disease*.mp.

8. functional colonic disease*.mp.

9. or/1-8

10. homeopathy/

11. homeopath*.mp.

12. homoeopath*.mp.

13. alternative medicine*.mp.

14. or/10-13

15. 9 and 14

Clinical trials. Gov

1. Homeopathy and Irritable bowel syndrome

IBD specialized register

1. Irritable bowel syndrome and homeopath

2. Colonic diseases and homeopath

3. Functional bowel and homeopath

WHAT'S NEW

Date	Event	Description
31 August 2018	New search has been performed	New search and one new study added
31 August 2018	New citation required but conclusions have not changed	Updated review, no new conclusions

CONTRIBUTIONS OF AUTHORS

EJP initiated, designed the study and drafted the protocol. EP, SB and GT, extracted the data and conducted the quality assessment. AA and KC arbitrated. KC provided advice on meta analysis. KC, SB, GT and AA all commented on the review.

DECLARATIONS OF INTEREST

EJP has contributed to the design and management of one of the included RCTs. EJP is a homeopath.

GT: None known.

SB: None known.

KC: None known.

AA: None known.

SOURCES OF SUPPORT

Internal sources

- University of Leeds, UK.
- Homeopathy Research Institute, UK.
- ScHARR, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Ferula; Constipation [therapy]; Dicyclomine [therapeutic use]; Dietary Fiber [therapeutic use]; Homeopathy [*methods]; Irritable Bowel Syndrome [*therapy]; Phytotherapy [methods]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans; Male