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Sinopoulou V, Gordon M, Dovey TM., Akobeng AK.
Interventions for the management of abdominal pain in ulcerative colitis.
Cochrane Database of Systematic Reviews 2021, Issue 7. Art. No.: CD013589.
DOI: 10.1002/14651858.CD013589.pub2.

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[Intervention Review]

Interventions for the management of abdominal pain in ulcerative colitis

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Contact address: Morris Gordon, morris@betterprescribing.com.

Editorial group: Cochrane Gut Group.
Publication status and date: New, published in Issue 7, 2021.

Citation: Sinopoulou V, Gordon M, Dovey TM., Akobeng AK. Interventions for the management of abdominal pain in ulcerative colitis. *Cochrane Database of Systematic Reviews* 2021, Issue 7. Art. No.: CD013589. DOI: 10.1002/14651858.CD013589.pub2.

ABSTRACT

Background

Ulcerative colitis (UC) is a chronic inflammation of the colon characterised by periods of relapse and remission. It starts in the rectum and can extend throughout the colon. UC and Crohn's disease (CD) are the most common inflammatory bowel diseases (IBDs). However, UC tends to be more common than CD. It has no known cure but can be managed with medication and surgery. However, studies have shown that abdominal pain persists in up to one-third of people with UC in remission. Abdominal pain could be a symptom of relapse of the disease due to adverse effects of medication, surgical complications and strictures or adhesions secondary to UC.

Objectives

To assess the efficacy and safety of interventions for managing abdominal pain in people with ulcerative colitis.

Search methods

We searched CENTRAL, MEDLINE and five other databases and clinical trials registries on 28 April 2021. We contacted authors of relevant studies and ongoing or unpublished trials that may be relevant to the review. We also searched references of trials and systematic reviews for any additional trials.

Selection criteria

All published, unpublished and ongoing randomised trials that compared interventions for the management of abdominal pain with other active interventions or standard therapy, placebo or no therapy were included. People with both active and inactive disease were included. We excluded studies that did not report on any abdominal pain outcomes.

Data collection and analysis

Two review authors independently conducted data extraction and 'Risk of bias' assessments. We analysed data using Review Manager 5. We expressed dichotomous and continuous outcomes as risk ratios (RRs) and mean differences (MDs), respectively, with 95% confidence intervals. We assessed the certainty of the evidence using the GRADE methodology.

Main results

We included five studies (360 randomised participants). Studies considered mainly participants in an inactive state of the disease.

No conclusions could be drawn about the efficacy of any of the interventions on pain frequency, pain intensity, and treatment success. The certainty of the evidence was very low for all comparisons because of imprecision due to sparse data, and risk of bias.

One study compared a low FODMAPs diet (n=13) to a sham diet (n=13). The evidence is very uncertain about the effect of this treatment on pain frequency (MD -4.00, 95% CI -20.61 to 12.61) and intensity (MD -9.00, 95% CI -20.07 to 2.07). Treatment success was not reported.

One study compared relaxation training (n=20) to wait-list (n=20). The evidence is very uncertain about the effect of this treatment on pain frequency at end of intervention (MD 2.60, 95% CI 1.14 to 4.06) and 6-month follow-up (MD 3.30, 95% CI 1.64 to 4.96). Similarly, the evidence is very uncertain about the effect of this treatment on pain intensity at end of intervention (MD -1.70, 95% CI -2.92 to -0.48) and 6-month follow-up (MD -2.30, 95% CI -3.70 to -0.90). Treatment success was not reported.

One study compared yoga (n=30) to no intervention (n=30). The study defined treatment success as the presence or absence of pain; however, the data they provided was unclear. Pain frequency and intensity were not reported.

One study compared a kefir diet (Lactobacillus bacteria, n=15) to no intervention (n=15). The evidence is very uncertain about the effect of this treatment on pain intensity (MD -0.17, 95% CI -0.91 to 0.57). Pain frequency and treatment success were not reported.

One study compared a stellate ganglion block treatment (n=90) to sulfasalazine treatment (n=30). The study defined treatment success as "stomachache"; however, the data they provided was unclear. Pain frequency and intensity were not reported.

Two studies reported withdrawals due to adverse events. One study reported withdrawals due to adverse events as zero. Two studies did not report this outcome. We cannot draw any conclusions about the effects of any of the interventions on withdrawals due to adverse events because of the very limited evidence.

The reporting of secondary outcomes was inconsistent.

Adverse events tended to be very low or zero. However, we can make no clear judgements about adverse events for any of the interventions, due to the low number of events.

Anxiety was measured and reported at end of intervention in only one study (yoga versus no intervention), and depression was not measured in any of the studies. We can therefore draw no meaningful conclusions about these outcomes.

Authors' conclusions

We found very low-certainty evidence on the efficacy and safety of interventions for the management of abdominal pain in ulcerative colitis. Pervasive issues with very serious imprecision from small samples size and high risk of bias have led to very low-certainty outcomes, precluding conclusions.

While few adverse events and no serious adverse events were reported, the certainty of these findings was again very low for all comparisons, so no conclusions can be drawn.

There is a need for further research. We have identified eight ongoing studies in this review, so an update will be warranted. It is key that future research addresses the issues leading to reduced certainty of outcomes, specifically sample size and reporting that leads to high risk of bias. It is also important that if researchers are considering pain as a critical outcome, they should report clearly if participants were pain-free at baseline; in that case, data would be best presented as separate subgroups throughout their research.

PLAIN LANGUAGE SUMMARY

Therapies for treating pain in ulcerative colitis

What is the aim of this review?

The aim of this Cochrane Review was to find out whether treatments for people with ulcerative colitis (UC) can improve pain.

We analysed data from five studies to answer this question.

Key messages

We cannot draw conclusions about any of these treatments for the management of pain in UC because of the very low certainty of the evidence.

It is unclear whether any of the therapies considered are better than each other, but there is limited evidence due to low numbers of studies and participants, and issues due to low certainty of the reporting of the research studies.

What was studied in the review?

People with ulcerative colitis commonly suffer pain, whether their disease is active on inactive.

Several types of therapies have tried to reduce pain in ulcerative colitis, including diets, psychological therapies, drugs, exercise therapies and brain therapies.

There is currently no agreement amongst clinicians as to which therapy is better.

What are the main results of the review?

We searched for randomised controlled trials (RCTs; clinical studies where people are randomly put into one of two or more treatment groups) comparing any treatment with another or with a dummy/placebo treatment. We found five RCTs looking at 360 participants.

1) Authors reported improvement in pain for a relaxation training compared to no relaxation training, but we cannot draw conclusions about whether this is really the case because of the very low certainty of the evidence.

2) It is unclear whether there is any difference between any of the other therapies studied for the management of pain.

3) It is unclear whether any therapy leads to a difference in adverse events (minor or serious) when compared to any other therapy.

Conclusion

We have very low-certainty evidence for all interventions studied in this review on whether any of them can improve pain in people with ulcerative colitis. We have no confidence that these methods can actually improve pain in ulcerative colitis.

No conclusions can be drawn due to a lack of evidence, and quality issues with the studies that we found. Further research is needed, that addresses the certainty issues that we highlight.

How up-to-date is this review?

This review is up-to-date to April 2021.

Summary of findings 1. Low FODMAPs diet compared to sham diet for the management of abdominal pain in ulcerative colitis

Low FODMAPs diet compared to sham diet for the management of abdominal pain in ulcerative colitis

Patient or population: UC patients
Setting: multicentre, 2 gastroenterology clinics in the UK
Intervention: Low FODMAPs diet
Comparison: Sham diet

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sham diet	Risk with Low FODMAPs diet				
Treatment success as defined by the authors	-	-	-	-	-	Not measured
Pain frequency (measured in days of pain on the IBS-SSS questionnaire)	-	MD 4.00 lower (20.61 lower to 12.61 higher)	-	26 (1 study)	⊕⊖⊖⊖ very low[a,b]	-
Pain intensity (0-10cm visual analogue scale)	-	MD 9.00 lower (20.07 lower to 2.07 higher)	-	26 (1 study)	⊕⊖⊖⊖ very low[a,b]	-
Withdrawal due to adverse events	Study population		RR 1.85 (0.18 to 19.19	52 (1 study)	⊕⊖⊖⊖ very low[a,b]	-
	4 per 1000	0 per 1000 (1 to 77)				

*__The risk in the intervention group__ (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; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded by one level due to high risk of bias.
[b]Downgraded by two levels due to imprecision from very sparse data.

Summary of findings 2. Relaxation training compared to wait-list for the management of abdominal pain in ulcerative colitis

Relaxation training compared to wait-list for the management of abdominal pain in ulcerative colitis

Patient or population: UC patients
Setting: not reported, USA
Intervention: Relaxation training
Comparison: Wait-list

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with wait-list	Risk with relaxation training				
Treatment success as defined by the authors	-	-	-	-	-	Not measured
Pain frequency (end of intervention, hours between pain episodes)	-	MD 2.6 higher (1.14 higher to 4.06 higher)	-	40 (1 study)	⊕⊖⊖⊖ very low[a,b]	-
Pain frequency (6 weeks after end of intervention, hours between pain episodes)	-	MD 3.3 higher (1.64 higher to 4.96 higher)	-	40 (1 study)	⊕⊖⊖⊖ very low[a,b]	-
Pain intensity (end of intervention, unidentified 0-10 scale)	-	MD 1.7 lower (2.92 lower to 0.48 lower)	-	40 (1 study)	⊕⊖⊖⊖ very low[a,b]	-
Pain intensity (6 weeks after end of intervention, unidentified 0-10 scale)	-	MD 2.3 lower (3.7 lower to 0.9 lower)	-	40 (1 study)	⊕⊖⊖⊖ very low[a,b]	-
Withdrawals due to adverse events	-	-	-	-	-	Not measured

***The risk in the intervention group** (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; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded by one level due to high risk of bias.
[b]Downgraded by two levels due to imprecision from very sparse data.

Summary of findings 3. Yoga intervention compared to no intervention for the management of abdominal pain in ulcerative colitis

Yoga intervention plus standard medical therapy compared to standard medical therapy for the management of abdominal pain in ulcerative colitis

Patient or population: UC patients
Setting: New Delhi, India, Single-centre, All India Institute of Medical Science (AIIMS)
Intervention: Yoga intervention plus standard medical therapy
Comparison: Standard medical therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard medical therapy	Risk with yoga intervention plus standard medical therapy				
Treatment success as defined by the authors	-	-	-	-	-	Not measured
Pain frequency	-	-	-	-	-	Not measured
Pain intensity	-	-	-	-	-	Not measured
Withdrawal due to adverse events	Study population		RR 0.50 (0.05 to 5.22)	60 (1 study)	⊕⊖⊖⊖ very low[a,b]	-
	67 per 1000	34 per 1000 (3 to 350)				
State anxiety (20-item State Anxiety Inventory, results range between 20 and 80)	-	MD 6.2 lower (10.57 lower to 1.83 lower)	-	60 (1 study)	⊕⊖⊖⊖ very low[a,b]	-
Trait anxiety (20-item Trait Anxiety Inventory, results range between 20 and 80)	-	MD 1.02 lower (5.25 lower to 3.21 higher)	-	60 (1 study)	⊕⊖⊖⊖ very low[a,b]	-

***The risk in the intervention group** (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; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded by one level due to high risk of bias.
[b]Downgraded by two levels due to imprecision from very sparse data.

Summary of findings 4. Kefir compared to no intervention for the management of abdominal pain in ulcerative colitis

Kefir compared to no intervention for the management of abdominal pain in ulcerative colitis

Patient or population: UC patients
Setting: not reported, single-centre, Turkey
Intervention: Kefir
Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention	Risk with kefir				
Treatment success as defined by the authors	-	-	-	-	-	Not measured
Pain frequency	-	-	-	-		Not measured
Pain intensity (measure on a 0-3 four-point scale)	-	MD 0.17 lower (0.91 lower to 0.57 higher)	-	25 (1 study)	⊕⊝⊝⊝ very low[a,b]	-
Withdrawals due to adverse events	Study population		not estimable	20 (1 study)	-	-
	0 per 1000	0 per 1000 (0 to 0)				

***The risk in the intervention group** (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; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded by one level due to high risk of bias.
[b]Downgraded by two levels due to imprecision from very sparse data.

Summary of findings 5. Stellate ganglion block compared to sulphasalazine for the management of abdominal pain in ulcerative colitis

Stellate ganglion block compared to sulphasalazine for the management of abdominal pain in ulcerative colitis

Patient or population: UC patients
Setting: Cangzhou Central Hospital, China
Intervention: Stellate ganglion block
Comparison: Sulphasalazine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sulphasalazine	Risk with stellage ganglion block				
Treatment success as defined by the authors	-	-	-	-	-	Not measured
Pain frequency	-	-	-	-	-	Not measured
Pain intensity (measure on a 0-3 four-point scale)	-	-	-	-	-	Not measured
Withdrawals due to adverse events	-	-	-	-	-	Not measured

***The risk in the intervention group** (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; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

BACKGROUND

Description of the condition

Ulcerative colitis (UC) is a chronic inflammation of the colon characterised by periods of relapse and remission (Ordas 2012). It starts in the rectum and can extend throughout the colon. UC and Crohn's disease (CD, which can affect the entirety of the gastrointestinal tract) are the two most common inflammatory bowel diseases (IBDs). However, UC tends to be more common than CD, with an estimated prevalence of 90 to 505 cases per 100,000 people in North America and northern Europe (Conrad 2014). Whilst prevalence has been historically higher in Western countries, its incidence in industrialised parts of Asia and Latin America is on the rise. The cause of UC is not known, but is believed to be associated with certain genetic and environmental factors. There is a higher risk in Ashkenazi Jews, people with a family history of the disease, and those who live in Western countries (Da Silva 2014).

Some of the symptoms of active UC include abdominal pain, bloody stools and diarrhoea. These symptoms can be managed using medical interventions such as 5-aminosalicylates, oral corticosteroids, azathioprine or mecarptopurine (Iheozor-Ejiofor 2019; Iskandar 2015) and by surgery in around 20% to 30% of sufferers who do not successfully attain remission with drugs (Ordas 2012). However, studies have shown that abdominal pain persists in up to one-third of people with UC in remission (Coates 2013). This has been attributed to the coexistence of functional bowel disorders such as irritable bowel syndrome (IBS). It is postulated that as the symptoms of IBS and IBD share common underlying psychological (for example, anxiety and depression) and clinical factors (for example, colonic inflammation), an overlap of these factors may trigger a variety of events which result in persistent pain in sufferers (Deberry 2014).

Description of the intervention

Pharmacological interventions

IBD medication can reduce inflammation and associated pain by inducing remission. Where pain persists in the absence of inflammation, it can be managed with pain-relieving medication such as antispasmodics, analgesics such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), cyclo-oxygenate-2 inhibitors (COX-2) and narcotics (Srinath 2012). Short-term use is advised due to the potential adverse effects of some of these drugs.

Antispasmodics are a heterogeneous group of drugs which can relax intestinal muscles. Hyoscyamine and dicycloamine are the most common antispasmodics that are used in IBD. NSAIDs are a group of non-chemically-related compounds which have analgesic effects. They reduce inflammation by inhibiting the production of prostaglandins (Cavkaytar 2019). Examples include ibuprofen, sulphasalazine and indomethacin. Some of these are available as over-the counter drugs. Narcotics are psychoactive compounds with sleep-inducing properties such as opiates and opioids, morphine, codeine, etc. Even though narcotics have historically been viewed in a negative light, observational studies indicate that they are commonly used not only for adults but also in children with IBD (Buckley 2013; Buckley 2015). Finally, neuromodulators, such as gabapentin and tricyclic antidepressants, have been used in functional abdominal pain syndromes and as such for abdominal pain in inflammatory bowel disease (Mikocka-Walus 2020), even though a recent Cochrane Review found no RCTs related to adjuvant treatment with antidepressants for UC (Mikocka-Walus 2019).

Non-pharmacological interventions

Non-pharmacological interventions used in managing abdominal pain may include psychological interventions, lifestyle advice, dietary interventions and alternative medicine. These interventions are generally considered less invasive and may be used as adjuvant treatment.

Psychological therapies are based on theories of human behaviour. Cognitive behavioural therapy, stress management, and coping skills training are the most common psychological interventions used. These are an interesting set of therapies, as the specific interventions delivered can be very heterogeneous; it is therefore key to consider the specific evidence and conceptual alignment of the approach delivered to understand 'what' the therapy was, as well as 'whether' it is effective.

Dietary factors include alcohol elimination and the use of supplements with prebiotic properties. Dietary factors have been considered, with some evidence of impact (Norton 2017). There is also interest in the use of probiotics for functional abdominal pain syndromes, given their impact on the gut microbiome and the reduction in inflammatory processes they may produce (Iheozor-Ejiofor 2019).

Alternative medicine such as acupuncture and transcutaneous electrical nerve stimulation (TENS), which have been used with other conditions such as IBS, are more frequently being used in people with IBD, albeit with limited evidence (Srinath 2012). Acupuncture is a complementary therapy which is generally used for pain unresponsive to standard therapy (Wilkinson 2007). There are various techniques used in acupuncture, such as basic needling, laser acupuncture, and electro-acupuncture.

How the intervention might work

The cause of the abdominal pain could require a targeted approach.

Pharmacological interventions

Antispasmodics often have mixed mechanisms of action, but generally they tend to suppress intestinal spasms resulting from inflammation or obstruction (Srinath 2012). Pharmacological interventions may have associated adverse effects. For example, it is widely thought that NSAIDs may increase the risk of disease flare-up or exacerbation in people with IBD (Klein 2010), but the data that support this contention are sparse. In addition to offering short-term relief, there seem to be concerns among IBD sufferers about the stigma of addiction associated with the use of opioids. The use of psychoactive drugs can also lead to heavy dependence on them and a higher risk of mortality (Coates 2013). In people with IBD, tapering off narcotics could trigger withdrawal symptoms which mimic IBD symptoms (Pauly 2017), thus complicating further treatment. Long-term use for IBD pain relief is therefore not recommended.

Non-pharmacological interventions

Pain resulting from strictures can be eliminated by the introduction of foods which can pass through with ease, thereby preventing intestinal pain (Srinath 2012). It has been postulated that recurrent pain tends to lead to coping behaviours which worsen the

experience of pain. Psychological techniques such as cognitive behavioural therapy work by targeting and stopping these negative coping mechanisms that affect how people deal with pain (Norton 2017). The mechanism of action of alternative and complementary therapies in itself is highly complex, but they are commonly used in wider society and in turn are used by sufferers of UC.

Why it is important to do this review

Abdominal pain is a major driver for the use of healthcare facilities in IBD sufferers. It is the main reason for seeking medical attention for about 70% of people with IBD. This puts a financial strain on healthcare systems amounting to billions of pounds every year (Ghosh 2015). For the patient, it can lead to psychological problems, loss of earnings and a general decline in quality of life. Effective pain management is therefore vital. Pain management has been highlighted as a priority topic for research by IBD patient groups and charities, but is currently not covered in the National Institute for Health and Care Excellence (NICE) or European Crohn's and Colitis Organisation (ECCO) guidelines (ECCO 2010; NICE 2019). Whilst several non-Cochrane systematic reviews have assessed interventions for pain management in IBD, there is currently none which has assessed the efficacy and safety of these interventions specifically in UC. Even though this review covers interventions that have already been assessed in previously-published Cochrane Reviews (Iheozor-Ejiofor 2019; Kafil 2018; Limetkai 2019; Timmer 2011), our focus is solely on studies that have been conducted to provide relief for abdominal pain.

OBJECTIVES

To assess the efficacy and safety of interventions for managing abdominal pain in people with ulcerative colitis.

METHODS

Criteria for considering studies for this review

Types of studies

All published, unpublished and ongoing randomised trials that compare interventions for the management of abdominal pain versus other active interventions or standard therapy, placebo or no therapy. We excluded studies that do not report on any abdominal pain outcomes.

We did not consider induction or maintenance studies for UC that impact abdominal pain as a proxy of disease state. Similarly, we did not consider studies addressing other pain in IBD, such as pain associated with extra-abdominal manifestations.

Studies of people with UC as part of an IBD cohort including CD patients that did not provide separate data for their UC participants are not included in this review. However, they are included in our companion review on Interventions for the management of abdominal pain in Crohn's Disease.

Types of participants

People with UC who are experiencing abdominal pain.

Types of interventions

- Pharmacological treatments (e.g. antispasmodics, antidepressants, laxatives, antidiarrhoeal agents, antibiotics, analgesics, anti-reflux agents, anti-emetic agents, antimigraine agents, antihistaminic agents, serotonergic agents and psychoactive drugs)
- Behaviour therapy (e.g. cognitive behavioural therapy (CBT), hypnotherapy)
- Lifestyle advice (e.g. advice on physical activity including exercise)
- Dietary interventions (e.g. FODMAP, additional fibre intake, decrease in gas-producing foods, extra fluid intake, lactulose- / gluten- / histamine-free diet)
- Prebiotics and probiotics
- Alternative treatments (e.g. acupuncture, homeopathy, body-oriented therapy, musculoskeletal therapy (osteopathy/ chiropractic), yoga)

Types of outcome measures

We considered both dichotomous and continuous outcomes for inclusion.

Primary outcomes

- Treatment success as defined by the authors
- Abdominal pain frequency or change in frequency of pain
- Abdominal pain intensity or change in pain intensity using any validated scale
- Withdrawal due adverse events

Secondary outcomes

- Anxiety/depression
- Adverse events
- Serious adverse events

Search methods for identification of studies

Electronic searches

We searched the following sources from the inception of each database to the date of search. We placed no restrictions on the language of publication:

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO);
- MEDLINE (Ovid MEDLINE ALL from 1946);
- PsycINFO via Ovid;
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO;
- Allied and Complementary Medicine database (AMED) via Ovid;
- ClinicalTrials.gov (www.clinicaltrials.gov)
- World Health Organisation International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch/)

For detailed search strategies, see Appendix 1.

Searching other resources

As complementary search methods, we checked relevant systematic reviews for studies for potential inclusion in our review. We also scrutinised the references of included studies in our review. We sought unpublished trials by contacting experts in the field and we scanned the Internet and abstracts submitted to major international congresses from the three years prior to the search, to capture any studies presented but not yet published in full.

We attempted to obtain translations of papers when necessary.

Data collection and analysis

We carried out data collection and analysis according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

Selection of studies

Two review authors independently screened the titles and abstracts identified from the literature search. We discarded studies which did not meet the inclusion criteria. We obtained the full report of studies which appeared to meet our inclusion criteria or for which there was insufficient information to make a final decision. Two review authors then independently assessed them to establish whether the studies met the inclusion criteria. We resolved disagreements by discussion, with a third review author consulted if resolution was not possible. We entered studies rejected at this or subsequent stages in the Characteristics of excluded studies tables, and recorded the main reason for exclusion.

Data extraction and management

Two review authors carried out data extraction independently, using piloted data extraction forms. We extracted relevant data from full-text articles that met the inclusion criteria. If reported, we collected information on:

- Trial setting: country and number of trial centres
- Methods: study design, total study duration and date
- Participant characteristics: age, socio-demographics, ethnicity, diagnostic criteria and total number
- Eligibility criteria: inclusion and exclusion criteria
- Intervention and comparator
- Outcomes: outcome definition, unit of measurement and time of collection
- Results: number of participants allocated to each group, missing participants, sample size
- Funding source

Assessment of risk of bias in included studies

During data extraction, two review authors independently assessed all studies meeting the inclusion criteria for their risks of bias, using criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). The domains assessed are as follows:

- Sequence generation (selection bias);
- Allocation concealment (selection bias);
- Blinding of participants and personnel (performance bias);
- Blinding of outcome assessment (detection bias);
- Incomplete outcome data (attrition bias);
- Selective reporting (reporting bias);
- Other potential bias.

We judged the studies to be at either low, high or unclear risk of bias for each domain assessed, based on the guidance in Higgins 2021.

After data extraction, the two review authors compared the extracted data to discuss and resolve discrepancies before the data were transferred into the Characteristics of included studies table.

Measures of treatment effect

For the dichotomous outcomes, we expressed treatment effect as risk ratios (RRs) with corresponding 95% confidence intervals (CIs). For continuous outcomes, we expressed the treatment effect as mean differences (MDs) with 95% CIs.

Unit of analysis issues

The participant was the unit of analysis. Cross-over studies would only be included if data were separately reported before and after cross-over, and only data from the first phase would be used. We did not anticipate any cluster-RCTs, but study data would only be used if the authors had used appropriate statistical methods in taking clustering effect into account.

Dealing with missing data

We contacted authors where there were missing data or studies had not reported data in sufficient detail. If there were missing standard deviations, we estimated them using relevant statistical tools and calculators if studies reported standard errors. We judged studies which failed to report measures of variance as being at high risk of selective reporting bias.

Assessment of heterogeneity

We planned to scrutinise studies to ensure that they were clinically homogeneous in terms of participants, intervention, comparator and outcome. Inconsistency was quantified and represented by the I^2 statistic. The thresholds are interpreted as follows (Higgins 2021):

0% to 40%: might not be important;

30% to 60%: may represent moderate heterogeneity;

50% to 90%; may represent substantial heterogeneity;

75% to 100%: considerable heterogeneity.

Assessment of reporting biases

Most reporting biases were minimised by using an inclusive search strategy. We aimed to investigate publication bias using a funnel plot only if there were 10 or more studies, but this was not the case.

Data synthesis

To summarise the study characteristics, we conducted a narrative synthesis of all the included studies.

We used Review Manager 5 (RevMan 2020). Study data were synthesised using the random-effects model. We combined effect estimates of studies which reported data in a similar way in the meta-analysis. We pooled RRs for dichotomous outcomes and MDs for continuous outcomes alongside 95% confidence intervals. Where we were unable to carry out a meta-analysis (e.g. due to lack of uniformity in data reporting), we presented a narrative summary of the included studies.

We had planned to carry out a meta-analysis if there were two or more studies that have assessed similar populations, interventions and outcomes. Studies from paediatric population,

adult population and different sub-intervention types would be analysed separately. However, the data from our included studies were insufficient to do this.

Subgroup analysis and investigation of heterogeneity

If we detected heterogeneity, we had planned to investigate possible causes and address them using methods described in Higgins 2021. We would also undertake subgroup analyses of potential effect modifiers if there were sufficient data. We had identified several potential modifiers of effect:

- Disease activity (active versus inactive disease)
- Pain location
- Disease location

However, the data we obtained were not sufficient to do this.

Sensitivity analysis

We had planned to undertake a sensitivity analysis on the primary outcome of 'treatment success', to assess whether the findings of the review were robust to the decisions made during the review process. However, the data we had were not sufficient for this.

Summary of findings and assessment of the certainty of the evidence

We have presented the main results in a 'Summary of findings' table. Each comparison and primary outcome was exported to GRADEprofiler software (developed by the GRADE working group) for quality assessment (GRADE 2015). We applied GRADE to all comparisons and presented these in additional tables. Based on risk of bias, inconsistency, imprecision, indirectness and publication bias, we rated the quality of the evidence for each outcome as high, moderate, low or very low. These ratings have been defined as follows:

- High: further research is very unlikely to change our confidence in the estimate of effect
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- Low: 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: any estimate of effect is very uncertain

We justified all decisions to downgrade the quality of studies using footnotes and we made comments to aid reader's understanding of the review where necessary.

RESULTS

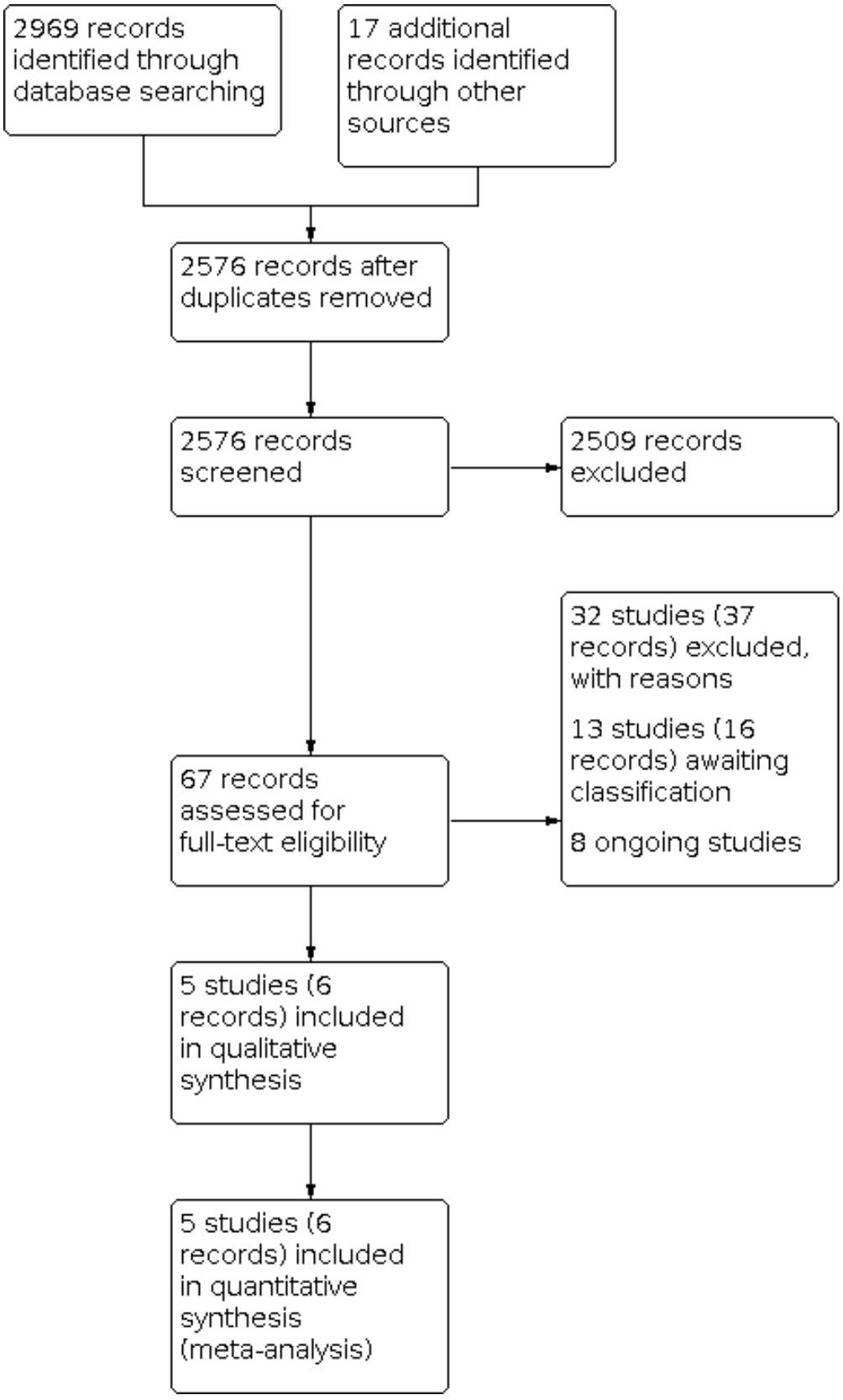
Description of studies

Below we present a description of the studies.

Results of the search

We completed the literature search on the 28 April March 2021 (Appendix 1), identifying a total of 2969 records through database searching. We found 17 additional records from alternative sources. After removal of duplicates 2576 unique records remained. Examination of the titles and abstracts found 67 records for full-text screening. After assessing all 68 records, we identified six records of five studies that met the inclusion criteria and included them in the review. There were also eight records of eight ongoing studies and 16 records of 13 studies awaiting classification. We excluded 37 records of 32 studies for various reasons. We present the results of the search in the PRISMA flow diagram (Figure 1).

Figure 1. Study flow diagram.



Included studies

Setting

We found five RCTs which met our inclusion criteria (360 participants). One was conducted in China (Zhao 2017), one in the UK (Cox 2020), one in the USA (Shaw 1987), one in Turkey (Yilmaz 2019) and one in India (Sharma 2015). All the studies were conducted in hospitals, medical centres or gastroenterology units except for Sharma 2015, which was conducted in an institute of medical science. Two studies (Shaw 1987; Yilmaz 2019) did not provide any information about their setting. Three of the studies were single-centre (Sharma 2015; Yilmaz 2019; Zhao 2017) and one was multi-centre (Cox 2020). One study did not provide this information (Shaw 1987).

Participants

All studies reported mean age (SD) except for one study that reported mean and range of ages (Yilmaz 2019) and one study that only mentioned their accepted age range for participants (Sharma 2015). Average age ranged from 30.4 (Shaw 1987) to 47.6 (Zhao 2017). One study did not mention age in their inclusion/exclusion criteria (Zhao 2017).

Two studies examined exclusively UC populations (Shaw 1987; Zhao 2017), while the rest of the studies examined a mix of people with CD and UC (Cox 2020; Sharma 2015; Yilmaz 2019). Cox 2020 and Yilmaz 2019 had reported separate CD and UC results, while for Yilmaz 2019 we contacted the authors to ask for separate outcome results for their CD and UC participants.

Two studies examined participants in an inactive stage of the disease (Cox 2020; Sharma 2015) and one study participants from inactive to moderate stages of the disease (Yilmaz 2019). Two studies did not report on the activity of the disease (Shaw 1987; Zhao 2017).

Disease duration was reported in three studies (Cox 2020; Yilmaz 2019; Zhao 2017). All three presented disease duration in mean (SD) except for Cox 2020, who only provided the mean and Yilmaz 2019 who provided the mean and range. Average disease duration ranged from three years (Yilmaz 2019) to nine years (Cox 2020).

Interventions

The interventions assessed in the trials were as follows:

- Low FODMAPs diet versus sham diet (Cox 2020);
- Relaxation training versus wait list (Shaw 1987);
- Yoga intervention versus no intervention (Sharma 2015);
- Kefir diet (Kefir is a drink preparation containing Lactobacillus bacteria) versus no intervention (Yilmaz 2019);
- Stellate ganglion block versus sulphasalazine (Zhao 2017).

Primary outcomes:

The length of the interventions ranged from 30 days (Zhao 2017) to eight weeks (Sharma 2015).

The following outcomes were reported:

- Treatment success as defined by the authors. Only one study (Sharma 2015) which measured pain as a dichotomous outcome (presence or absence of pain) clearly defined their success criteria. Zhao 2017 also measured pain as a dichotomous outcome but in an unidentified manner and they only provided result values for "stomachache" without explanation;
- The remaining studies did not explicitly mention treatment success, with authors reporting pain as a continuous outcome and not reporting numbers of responders for their interventions against any definition;
- Abdominal pain frequency or change in frequency of pain. Pain frequency was measured in two studies. Cox 2020 measured pain frequency in days using the IBS-SSS 0 - 100 scoring scale, and in days where pain was reported as moderate or severe in GSRS. Shaw 1987 measured pain frequency in hours between episodes with an unidentified questionnaire;
- Abdominal pain intensity or change in pain intensity using any validated scale. Pain intensity was measured as a continuous outcome in three studies. Yilmaz 2019 used a symptoms diary where participants rated their pain on a scale of 0 - 3 where 0 = none, 1 = mild, 2 = moderate, and 3 = severe; and Cox 2020 used the IBS-SSS 0 - 100 scale and the GSRS scale which measures severity of pain on a scale 0 - 3. Shaw 1987 used an unidentified 0 - 10 scale where a higher score indicates more severe pain.
- Withdrawal due to adverse events. This was reported or could be extracted based on the text in three studies (Cox 2020; Sharma 2015; Yilmaz 2019).

A summary of the interventions and primary pain outcomes can be found in Table 1.

Secondary outcomes:

- Anxiety/depression. Sharma 2015 used the Spielberger's State-Trait Anxiety Inventory to measure anxiety. The other studies did not measure this outcome. Shaw 1987 measured psychological distress due to pain via the Pain and Distress Scale but did not measure anxiety or depression.
- Adverse events (total number of participants with any event). Total number of participants reporting adverse events was reported in two studies (Cox 2020; Sharma 2015).
- Serious adverse events (as defined by good clinical practice reporting within the primary study). The same studies that reported numbers of participants with adverse events also reported numbers of participants with serious adverse events (Cox 2020; Sharma 2015).

Excluded studies

We excluded 33 studies for various reasons. The reasons for exclusion of each study are presented in the excluded studies table and are summarised below.

- 8 studies were excluded as having ineligible outcomes (ACTRN12617000876392; ACTRN12619000150145; Chen 2015b; Dai 2017; Engel 2016; Gibson 2013; Pullan 1994; Tripp 2017)
- 6 studies were excluded for mixed IBD population without separate UC data. We contacted the authors for separate data and they either did not respond or were unable to provide it (Berrill 2014; Mizrahi 2012; Ozgursoy Uran 2019; Tapete 2018; Tapete 2019; Volz 2016)
- 5 studies were excluded for ineligible interventions (Chen 2015a; Collawn 1992; Danese 2019 ; Faghfoori 2014; Ghosh 2018)
- 2 studies were excluded for not being RCTs (McCormick 2010; Spagnuolo 2017)

- 5 studies were excluded for ineligible indication (Hallert 2003; Hanauer 1993; Huang 2013; ISRCTN98226923; Johari 2016)
- 3 studies were excluded for ineligible participant population (Cohen 1999; NCT02763293; Zai 2018)
- 3 studies were excluded for ineligible study design (Bae 2016; Forbes 2019; Gearry 2009)

Risk of bias in included studies

Below we present the results of our 'Risk of bias' assessment (Figure 2; Figure 3). Further details can be found in the 'Risk of bias' tables (beneath Characteristics of included studies tables).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

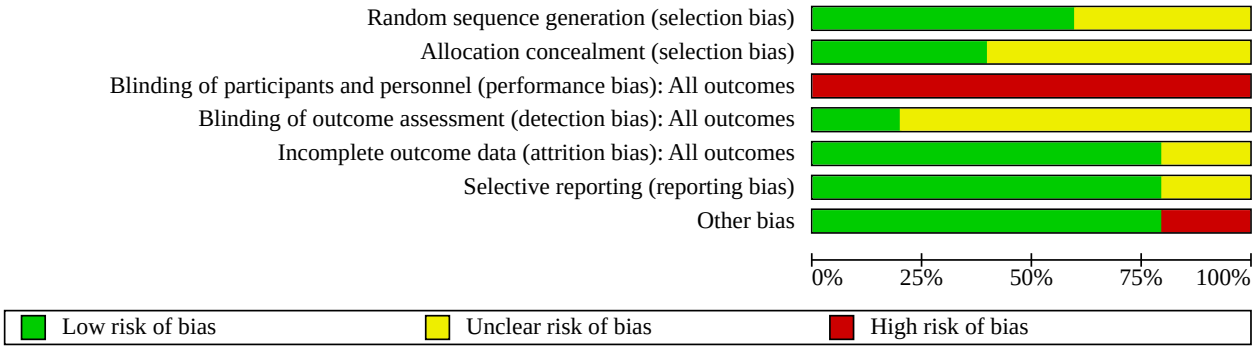
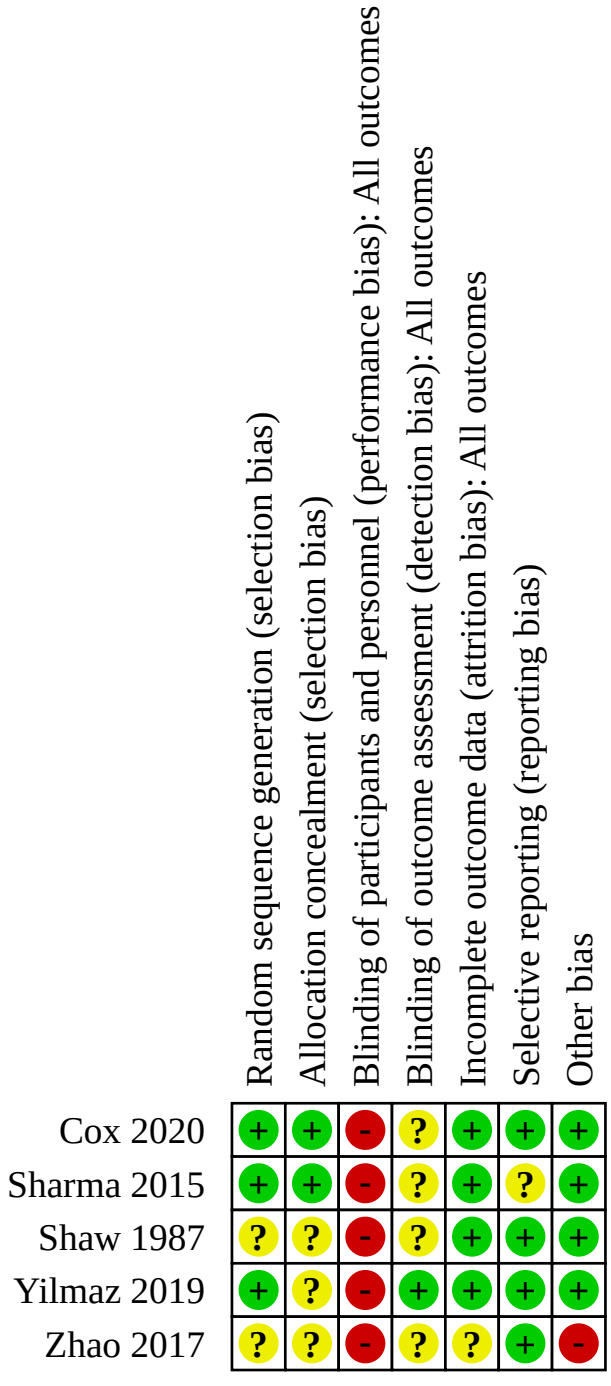


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Randomisation was described clearly in three of the five studies (Cox 2020; Sharma 2015; Yilmaz 2019), which we rated low for risk of bias, and was not sufficiently described in two studies (Shaw 1987; Zhao 2017) which we rated unclear for risk of bias.

We rated two studies at low risk of selection bias (Cox 2020; Sharma 2015), as the method of random allocation of participants to intervention and control groups and allocation concealment was described and we judged it to be adequate. We rated the other three studies at unclear risk of selection bias and allocation concealment (Shaw 1987; Yilmaz 2019; Zhao 2017), as they did not provide enough information (or none at all) about their selection and allocation concealment process.

Blinding

All studies were rated as high in performance bias, as the interventions they studied could not be blinded for both participants and personnel or they were open-label studies. However, Cox 2020 used a sham diet to keep their participants blind to the intervention, which is not typical in diet RCTs due to the difficulties entailed.

Detection bias was rated as low in one study (Yilmaz 2019) which provided details about it, and unclear in the other studies, as they did not provide enough information for a judgement (Cox 2020; Sharma 2015; Shaw 1987; Zhao 2017).

Incomplete outcome data

Attrition bias was judged as low in four studies that provided enough information for judgement (Cox 2020; Sharma 2015; Shaw 1987; Yilmaz 2019). Zhao 2017 was rated as unclear.

Selective reporting

Reporting bias was rated as low in four studies that reported all outcomes they had set out to report (Cox 2020; Shaw 1987; Yilmaz 2019; Zhao 2017). Sharma 2015 lacked enough information in their report to judge whether they had reported all outcomes, and was rated as unclear.

Other potential sources of bias

We rated four studies as low in other potential sources of bias (Cox 2020; Shaw 1987; Sharma 2015; Yilmaz 2019). We rated Zhao 2017 as having high potential for other sources of bias because of significant differences in their participants' baseline characteristics that were highly likely to affect the results (Zhao 2017).

Funding source and conflict of interest

Three studies reported their sources of funding (Cox 2020; Sharma 2015; Yilmaz 2019). Sharma 2015 was funded via a government grant, Cox 2020 was funded by private foundations, and Yilmaz 2019 reported that they received no funding.

Four studies made declarations on conflicts of interest (Cox 2020; Sharma 2015; Yilmaz 2019; Zhao 2017). Three declared no conflicts of interest (Sharma 2015; Yilmaz 2019; Zhao 2017) and Cox 2020 declared industry connections and ownership of an invention connected to their intervention.

Effects of interventions

See: **Summary of findings 1** Low FODMAPs diet compared to sham diet for the management of abdominal pain in ulcerative colitis; **Summary of findings 2** Relaxation training compared to wait-list for the management of abdominal pain in ulcerative colitis; **Summary of findings 3** Yoga intervention compared to no intervention for the management of abdominal pain in ulcerative colitis; **Summary of findings 4** Kefir compared to no intervention for the management of abdominal pain in ulcerative colitis; **Summary of findings 5** Stellate ganglion block compared to sulphasalazine for the management of abdominal pain in ulcerative colitis

A summary of the interventions and key outcome definitions and data are presented in Table 1 and Table 2 and explained below.

1. Low FODMAPs diet versus sham diet

Cox 2020 (n = 52) compared a diet low in FODMAPs to a sham diet. It included participants with either CD or UC who were at an inactive stage of their disease, which was defined by all of the following: physician global assessment, stable medications, no IBD flare in the previous six months, faecal calprotectin less than 250 mg/g, and serum C-reactive protein (CRP) less than 10 mg/L. The intervention lasted for four weeks.

Primary outcomes

Treatment success was not reported.

Pain was measured using the pain subscale of the IBS-SSS that rates pain on a scale of 0 to 100 and the GSRS pain rating scale of 0 to 3.

Pain frequency

Pain frequency was measured.

At end of study, for the 13 UC participants in the 'low FODMAPs' group, the mean (SD) IBS-SSS pain frequency in days was 31 (21.6) days and for the 13 participants in the sham-diet group 35 (21.6). There was no clear difference in days of pain for CD participants when a low FODMAPs diet was compared to a sham diet in Cox 2020 (MD −4.00, 95% CI −20.61 to 12.61). The certainty of evidence was very low, due to risk of bias and imprecision (Analysis 1.1; Summary of findings 1).

Separate UC data for the GSRS scale was requested but not provided by the authors.

Pain intensity

Pain intensity was measured.

At end of study, for the 13 UC participants in the 'low FODMAPs' group the mean (SD) IBS-SSS pain intensity was 20 (14.4) and for the 13 participants in the sham-diet group 29 (14.4). There was no clear difference in intensity of pain for CD participants when a low FODMAPs diet was compared to a sham diet in Cox 2020 (MD −9.00, 95% CI −20.07 to 2.07). The certainty of evidence was very low, due to risk of bias and imprecision (Analysis 1.2; Summary of findings 1).

Separate UC data for the GSRS scale was requested but not provided by the authors.

Withdrawals due to adverse events

There were two withdrawals due to adverse events in the 'low FODMAPs' group (one IBD relapse, one beginning antibiotics) and one in the sham-diet group (IBD relapse). There was no clear difference in withdrawals due to adverse effects between the 'low FODMAPs' and sham-diet groups (RR 1.85, 95% CI 0.18 to 19.19; 52

participants). The certainty of evidence was very low due to risk of bias and imprecision (Analysis 1.3; Summary of findings 1).

Secondary outcomes

Anxiety/depression were not reported.

No serious adverse events were reported. Adverse events were reported in five participants. One participant in the IG group and one in the CG group reported flu-like symptoms and sinusitis, and one reported worsening of abdominal pain in the IG group. Two participants, one in the IG and one in the CG group, reported IBD relapse.

2. Relaxation training versus wait-list

Shaw 1987 compared a relaxation training to a wait-list (n = 40). It included only people with UC at an unclear stage of the disease. The intervention lasted six weeks, with participants followed up for six weeks after the end of the intervention.

Primary outcomes

Treatment success was not reported.

Pain frequency was measured in hours between pain episodes, and pain intensity on an unidentified 0 to 10 scale. Withdrawals due to adverse events were not reported.

Pain frequency

At end of study the mean (SD) score for the 20 UC participants in the relaxation-training group was 5.6 (2.64) and for the 20 UC participants in the wait-list group 3.0 (2.05). There was a difference in hours between pain episodes at end of study in the relaxation training when compared to a wait-list (MD 2.60, 95% CI 1.14 to 4.06). The certainty of evidence was very low, due to imprecision and risk of bias (Analysis 2.1; Summary of findings 2).

Six weeks after end of study the mean (SD) score for the 20 UC participants in the relaxation training group was 6.7 (3.07) and for the 20 UC participants in the wait-list group 3.4 (2.23). There was a small difference in hours between pain episodes six weeks after end of study in the relaxation-training when compared to a wait-list (MD 3.30, 95% CI 1.64 to 4.96). The certainty of evidence was very low, due to imprecision and risk of bias (Analysis 2.2; Summary of findings 2).

Pain intensity

In Shaw 1987 at end of study the mean (SD) score for the 20 UC participants in the relaxation-training group was 5.4 (1.84) and for the 20 UC participants in the wait-list group 7.1 (2.08). There was a difference in pain intensity at end of study in the relaxation-training when compared to a wait-list (MD −1.70, 95% CI −2.92 to −0.48). The certainty of evidence was very low due to imprecision and risk of bias (Analysis 2.3; Summary of findings 2).

Six weeks after end of study the mean (SD) score for the 20 UC participants in the relaxation-training group was 4.5 (2.01) and for the 20 UC participants in the wait-list group 6.8 (2.48). There was a small difference in hours between pain episodes at end of study in the relaxation-training when compared to a wait-list (MD −2.30, 95% CI -3.70 to -0.90). The certainty of evidence was very low due to imprecision and risk of bias (Analysis 2.4; Summary of findings 2).

Withdrawals due to adverse events were not reported.

Secondary outcomes

Anxiety/depression and adverse events or serious adverse events were not reported.

3. Yoga intervention versus no intervention

Sharma 2015 (n = 60) compared a yoga intervention to no intervention (both groups received standard medical therapy). The study included only participants with CD or UC at an inactive stage of the disease with a CDAI score under 150, while UC activity was measured on the Truelove and Witts index (Truelove 1954). The intervention lasted eight weeks. The study reported data for the 30 UC participants in the yoga group and 30 UC participants in the control group.

Primary outcomes

Treatment success in this study was measured as a dichotomous outcome of presence or absence of pain. The types of pain reported were tenesmus, intestinal colic pain, peri-anal pain and arthralgia, of which intestinal colic pain was the most relevant to the topic of this review.

The authors report at baseline that three participants in the yoga group and four in the control group reported the presence of pain, and 23 in the yoga group and 22 in the control group reported absence of pain.

At end of study, in the yoga group five reported presence of pain and in the control group 14 reported presence of pain, while 20 in the yoga group and 12 in the control group reported absence of pain.

After we contacted the authors, they explained that these results are for the 25 UC participants in the yoga group and the 26 participants in the control group who completed the study. However, if the baseline and end-of-study numbers for presence of pain are summed for the yoga group the total is 26. The authors did not provide further clarification on this discrepancy, nor on how presence and absence of pain were defined, and whether this was a yes/no question for participants or a pain scale with a cut-off score.

Due to the reasons outlined above and the fact that we could not determine whether presence and absence of pain were measured for all 60 UC participants randomised to the study at baseline we did not perform an analysis for the results provided for this outcome.

Pain frequency and pain intensity were not reported in this study.

Withdrawals due to adverse events

There were three cases of increased disease activity that led participants to drop out from the study. One occurred in the yoga group and two in the standard medical-therapy group. There was no clear difference in withdrawals due to adverse events between the two groups (RR 0.50, 95% CI 0.05 to 5.22). The certainty of this result is very low due to imprecision and risk of bias (Analysis 3.1; Summary of findings 3).

Secondary outcomes

The authors reported that there were no serious adverse events in either group. Total adverse events were also zero in both groups.

Anxiety level results were reported using the State and Trait Anxiety Inventory, consisting of two 20-item subscales. Participants were asked to mark: not at all, somewhat, moderately, very much, on a scale of 1 to 4. Scoring was done as the sum of these individual scores. The range of anxiety score was 20 to 80.

At end of study the mean (SD) state anxiety score for the 30 UC participants in the yoga group was 32.8 (8.21) and for the 30 UC participants in the standard medical-therapy group 39 (9.05). There was a difference in state anxiety at end of study in the yoga group when compared to standard medical therapy (MD −6.20, 95% CI −10.57 to −1.83). The certainty of evidence was very low due to imprecision and risk of bias (Analysis 3.2; Summary of findings 3).

At end of study the mean (SD) trait anxiety score for the 30 UC participants in the yoga group was 41.24 (8.22) and for the 30 UC participants in the standard medical-therapy group 42.26 (8.29). There was no difference in trait anxiety at end of study in the yoga group when compared to standard medical therapy (MD −1.02, 95% CI −5.25 to 3.21). The certainty of evidence was very low, due to imprecision and risk of bias (Analysis 3.3; Summary of findings 3).

Depression was not measured.

4. Kefir diet (Lactobacillus bacteria) versus no intervention

Yilmaz 2019 (n = 48) compared a Kefir diet with Lactobacillus bacteria versus no intervention. The study included participants with CD or UC whose disease activity ranged from inactive to moderate. The intervention lasted four weeks.

Primary outcomes

Treatment success in Yilmaz 2019 was not reported.

Pain was measured on a four-point rating scale from 0 to 3. Pain frequency was not reported.

Pain intensity

At end of study mean(SD) the score for pain intensity for the 15 participants in the UC Kefir group was 0.33 (0.61) and for the 10 participants in the no-intervention group 0.5 (1.08). No clear difference was detected in pain intensity scores when Kefir diet was compared to no intervention (MD −0.17, 95% CI −0.91 to 0.57). The certainty of the evidence is low due to risk of bias and imprecision (Analysis 4.1; Summary of findings 4)

Withdrawals due to adverse events

There were no withdrawals due to adverse events in either group, so there was no estimable relative effect of the intervention on withdrawals due to adverse events (Summary of findings 4).

Secondary outcomes

Anxiety/depression and adverse events or serious adverse events were not reported.

5. Stellate ganglion block versus sulphasalazine

Zhao 2017 (n = 120) compared stellate ganglion block treatment once a day to four doses of sulphasalazine twice a day orally. The study included UC participants at an unclear stage of the disease. The intervention lasted 30 days. Ninety UC participants were randomised to the intervention group and 30 participants to the control group.

Primary outcomes

Treatment success in Zhao 2017 was not reported. Pain was measured as "stomachache", with no further details.

At baseline, stomachache was experienced by 17 participants in the stellate ganglion block group and by 50 participants in the sulphasalazine group. At end of study, stomachache was experienced by eight participants in the stellate ganglion block group and by 13 participants in the sulphasalazine group.

We contacted the study authors to determine if the end-of-study results were from the same subgroup of participants who reported stomachache at baseline. We received no response and we could not determine if these results were for the participants experiencing stomachache at baseline or if they refer to the whole study cohort. We therefore decided not to perform any meta-analysis for these results.

Pain frequency and intensity were not reported.

Withdrawals due to adverse events were not reported.

Secondary outcomes

Anxiety/depression and adverse events or serious adverse events were not reported.

DISCUSSION

Summary of main results

This review includes a wide range of interventions. Two of them were forms of diet (Cox 2020; Yilmaz 2019), one was a form of psychological management (Shaw 1987), one was a form of exercise (Sharma 2015) and one was a medical treatment (Zhao 2017). Two of them looked exclusively at UC (Shaw 1987; Zhao 2017) while the rest looked at participants with both CD and UC (Cox 2020; Sharma 2015; Yilmaz 2019). The studies included a range of disease states.

Our primary outcome of treatment success was defined or reported in only one study (Sharma 2015), which measured the absence or presence of pain as a dichotomous outcome. Pain was also measured as a dichotomous outcome by Zhao 2017, but the study was unclear about the method they used and reported their results without an explanation.

In the remaining studies pain was measured as a continuous outcome, by improvement on a rating scale: either 0 to 100 (Cox 2020), a 0 to 10 cm VAS scale, a 0 to 10 Likert scale or an unidentified 0 to 10 scale (Shaw 1987), and a four-point 0 to 3 scale (Cox 2020; Yilmaz 2019). In all these studies a lower rating indicated less pain and a higher rating indicated more pain, except for the measurement of pain frequency in Shaw 1987, which measured the time between pain episodes, and in which a higher score indicated less pain frequency. Except for Sharma 2015 and Zhao 2017, all studies measured pain intensity, and only two studies measured pain frequency (Cox 2020; Shaw 1987). Withdrawals due to adverse events were directly or indirectly reported in two studies (Cox 2020; Sharma 2015).

The heterogeneity in outcome measures reported and interventions used severely limited our scope for meta-analysis.

In one study comparing relaxation training to a wait-list, it was reported that relaxation training improved pain intensity and pain frequency in comparison to a wait-list at end of study and at six-week follow-up (Shaw 1987). However, this evidence was of very low certainty, due to imprecision and risk of bias, so we cannot draw any conclusions on the effect of relaxation training on pain intensity for UC.

For two studies, comparing yoga to no intervention and stellate ganglion block to sulphasalazine, whilst their primary outcomes were focused on pain, we could not determine whether they included participants who had both pain and no pain at baseline or only participants with pain. As further data on the subgroup with pain at baseline were not reported, we wrote to the authors for these data but received no response. We were therefore unable to conduct further analysis on these studies.

There were no other direct comparisons that found any clear difference for pain intensity or frequency between interventions, although certainty was very low for all outcomes, due to imprecision from sparse data and risk of bias varying between unclear and high.

Two studies reported withdrawals due to adverse events: Cox 2020: one IBD relapse in each group and one beginning antibiotics in the 'low FODMAPs' group; and Sharma 2015: one case of increased activity in the yoga group and two in the no-intervention group. We could draw no conclusions about the effects of any of the interventions on withdrawals due to adverse events, because of the lack of evidence.

The reporting of serious and total adverse events as secondary outcomes was inconsistent. Cox 2020 and Sharma 2015 reported on serious and total adverse events. Adverse events tended to be very low or zero, while serious adverse events were zero in both. We can make no clear judgements about adverse events for any of the interventions, due to the low number of events. Cox 2020 reported one participant in the intervention and one in the control group with flu-like symptoms and sinusitis, and one case of reported worsening of abdominal pain in the intervention group.

Anxiety was measured only in Sharma 2015, with evidence for an improvement in state anxiety when yoga was compared to no intervention. However, this evidence was of very low certainty due to imprecision and risk of bias, so we cannot draw any conclusions about the effects of yoga on state anxiety in UC. Trait anxiety was also measured, but no clear difference was found when yoga was compared to no intervention.

Depression was not measured in any of the studies.

Overall completeness and applicability of evidence

The studies considered a wide range of interventions, and potentially a mix of disease activity, as two studies did not specify the disease activity of their participants. The number of included studies was also very small, resulting partially from the fact that many studies that examined pain in IBD did not have separate results for their UC population, so we had to exclude them from this review.

It is also very clear that the range of interventions and the small numbers of studies and participants put the evidence at significant risk of imprecision. This is pervasive across the evidence presented in this review, with each comparison at high risk of imprecision.

Quality of the evidence

There were significant issues with risk of bias throughout the studies included in this review. Despite requests to authors of all studies, only one author (Yilmaz 2019) provided data to modify our judgements in some of our 'Risk of bias' assessments.

First, two studies did not clearly describe randomisation (Shaw 1987; Zhao 2017), and three allocation concealment (Shaw 1987; Yilmaz 2019; Zhao 2017).

Secondly, blinding of participants and personnel was understandably not possible in most of the studies, but it was potentially possible for assessors and was either not done or not described in all but one study (Yilmaz 2019). Furthermore, most studies failed to discuss whether their outcome assessors were blinded.

Thirdly, one study had issues with selective reporting (Sharma 2015) which led to further downgrading of the certainty of the evidence.

Finally, other key sources of bias exist, mainly potential imbalance in baseline characteristics which was observed in Zhao 2017, which further impacted the quality of the evidence.

Potential biases in the review process

There is a key area of concern related to the issue of clinical heterogeneity. As discussed, the inclusion of a wide range of interventions, together with uncertainty about the included disease states, reflects the evidence as a whole, but to some extent ignores these issues. However, as further data become available, this potential source of bias may be mitigated in future versions of this review.

It should also be noted that IBS is more common in people with IBD, and it is possible that the interventions that showed some promising results within this review are simply treating IBS and not pain immediately caused by UC.

Agreements and disagreements with other studies or reviews

This is the first Cochrane Review on this topic.

Considering the international guidelines for IBD, few of the major societies mention treating pain in IBD.

The recent UK BSG guidelines (BSG 2019) do make recommendations, citing several of the studies in this review. They state that psychological interventions may be useful as adjunctive therapy, citing this as a weak recommendation with low-quality evidence; this would be supported by the evidence in our review. They do not comment on any of the other intervention types included in this review and do not define such psychological interventions.

The current UK NICE guidelines do not discuss pain relief as a stand-alone treatment goal (NICE 2019). The AGA (AGA 2020) guidelines

make no mention of pain relief in this area. The ECCO (ECCO 2020) guidelines also make no mention of such therapies.

AUTHORS' CONCLUSIONS

Implications for practice

This review found very limited evidence that relaxation training might lead to improvement in pain intensity and pain frequency compared to a wait-list, and that yoga might reduce state anxiety compared to no intervention. However these results are of very low certainty due to imprecision and risk of bias, and we can draw no conclusions about their efficacy.

We found there may be no difference between any of the other treatments in improving pain for people with UC, but we are unable to draw further conclusions as these were very low-certainty results due to low numbers of studies and participants in each comparison area and to clinical heterogeneity within the studies.

Whilst very few adverse events were reported with any of the treatments studied, the certainty of these findings was very low for all comparisons, so we can draw no conclusions.

Even though there was evidence that yoga might reduce state anxiety compared to no intervention, the certainty of this result is very low due to imprecision and risk of bias, so we can draw no conclusions about the effect of yoga on anxiety in UC.

Depression was not reported in any of the studies and once again we can draw no conclusions about the impact of the included interventions on depression.

Implications for research

Given that abdominal pain is a significant problem for a subset of people with UC, there are a number of randomised controlled trials that target it as an independent condition and not as part of inducing or maintaining remission. The need for future research is clear. Many of the interventions studied within this review are anecdotally used by patients and are available without clinician involvement, so clear evidence is vital to inform patients when making these decisions.

Considering the current ongoing trials identified in this review, it seems they are still very heterogeneous in the range of therapies, diverse outcome measures and relatively low sample sizes planned, which will limit the impact that these can have on the evidence base.

We would therefore suggest that key stakeholders, including clinicians, those with understanding of health economics and most importantly patients, should consider which interventions are of interest. They are particularly well-placed to consider feasibility, acceptability and tolerability amongst other factors in targeting future research.

Furthermore, the evidence base would be strengthened if researchers address risk of bias in their reporting and also consider reporting data by disease type or severity, or both. It would also be helpful if studies looking at IBD patients as a whole, report separate results for the IBD conditions included in their studies.

The issue of sample size must be highlighted. All studies included in this review were very small. Authors could consider the use of indicative odds ratios from this review when performing power calculations. Such accurate calculations are vital to halt the large number of low-powered studies and increase the precision of findings.

Another issue is the possibility that pain in UC is not directly caused by the condition, but might be pain associated with IBS, which is more prominent in IBD patients than in the general population. This is something that needs to be clarified further in order to understand which interventions should be targeted for research in the future.

ACKNOWLEDGEMENTS

We would like to thank Dr Chris J. Wallace for copy-editing our work prior to submission.

Funding for VS and partial funding for MG was provided through a larger NIHR Cochrane Programme Grant in the UK.

Maria-Inti Metzendorf (Information Specialist of the Cochrane Metabolic and Endocrine Disorders Group) developed the original search strategies, which were run by Yuhong Yuan (Information Specialist, Cochrane Gut Group).

The review authors would also like to thank the following editors and peer referees who provided comments to improve the review: Dr. Paul Moayyedi (Co-ordinating Editor), Dr. John Marshall (Contact Editor), Dr. Yuhong Yuan and Teo Quay (Managing Editors), Dr. Sarah EI-Nakeep (Peer Reviewer), Dr. Shinichiro Shinzaki (Peer Reviewer), and Douglas MacKay (Consumer Reviewer), and Kate Cahill (Copy Editor).

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CHARACTERISTICS OF STUDIES

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

Cox 2020

Study characteristics	
Methods	RCT, single-blind, placebo-controlled **Setting:** multicentre, 2 gastroenterology clinics in the UK **Study period:** February 2016 - May 2017 The study presents results for the IBD cohort as a whole, does not separate between CD and UC. Where separate data do exist they are presented below
Participants	**Inclusion criteria:** Eligible patients were aged 18 years, with quiescent CD or ulcerative colitis (UC), experiencing ongoing gut symptoms and were naïve to low FODMAP diet. Ongoing gut symptoms were required to meet the Rome III criteria for either diarrhoea predominant (IBS-D), mixed subtype (IBS-M), or un-subtyped IBS (IBS-U), functional bloating, or functional diarrhoea, experiencing abdominal pain, bloating, and/or diarrhoea on 2 days during the baseline screening week and reporting inadequate relief of GI symptoms **Exclusion criteria:** Patients with dose changes of azathioprine, mercaptopurine, methotrexate, or biologics in the preceding 12 weeks; oral 5-aminosalicylic acid in the preceding 4 weeks; or antibiotics, probiotics, or prebiotics in the preceding 8 weeks were excluded. Patients with pure perianal CD, a current stoma, previous extensive GI resection, or a current stricture were excluded. Patients with established bile acid malabsorption were excluded because gut symptoms relating directly to bile acid malabsorption may not be modifiable by low FODMAP diet. Patients with constipation-predominant symptoms were excluded, because low FODMAP diet could exacerbate this symptom. Patients with self-reported lactose intolerance were included if they continued to experience gut symptoms despite low lactose diet. Patients were excluded if they had significant comorbidities, or if they were pregnant or lactating. **Age (mean ± SD):** IG = 33 (11); CG = 40 (13) **Sex (M/F):** IG = 10/17; CG: 13/12 **Site of disease:** IG: proctitis: 6, leftsided: 4, extensive: 3 CG: proctitis: 3, leftsided: 7, extensive: 3 **Use of concurrent medication:** IG: mesalamine 12, thiopurine 9, infliximab 10, adalimumab 2, vedolizumab 0, methotrexate 2

Cox 2020 *(Continued)*

	CG: mesalamine 11, thiopurine 12, infliximab 4, adalimumab 4, vedolizumab 1, methotrexate 1 **Disease activity:** Quiescent. Quiescent IBD was defined by all of the following: physician global assessment, stable medications, no IBD flare in the previous 6 months, faecal calprotectin < 250 mg/g, and serum C-reactive protein (CRP) <10 mg/L. The threshold for faecal calprotectin was chosen according to evidence proposing optimal sensitivity and specificity for detecting endoscopically quiescent disease **Disease duration:** IG = 7 years; CG = 11 years **Number randomised:** IG = 27 (UC = 13, CD = 14) CG = 25 (UC = 13, CD = 12) **Number reaching end of study:** (PP) IG = 24, IG = 22 **Number analysed:** (ITT) IG = 27, IG = 25 **Postrandomisation exclusion:** IG = 3 (1 withdrew consent, 1 antibiotics, 1 steroids); CG = 3 (1 withdrew consent, 1 pregnancy, 1 steroids)
Interventions	**IG:** low FODMAPs. The diet involves the restriction of dietary fructans, GOS, lactose, fructose in excess of glucose, and polyols, including sorbitol and mannitol, and is described in detail elsewhere **CG:** Sham diet. The selection of an appropriate control group and difficulties in masking intervention and control are challenging in dietary intervention studies, but for research on dietary advice (which most closely mimics clinical practice), “sham” dietary advice is considered gold standard. The sham diet in this trial aimed to provide patients in the control group with an exclusion diet of similar intensity and burden to low FODMAP diet, while not affecting nutrient, fibre or FODMAP intakes. Dietary counselling for both low FODMAP diet and sham diet lasted approximately 20 minutes and both groups received written information
Outcomes	**Length of intervention:** 4 weeks **Primary outcomes:** Pain frequency and intensity were measured as IBS-SSS and GSRS scores For the measurements below, as the authors only presented SEM and not SD, we calculated the SD with the formula SD = SEM*√randomised participants Withdrawal due to adverse events **Secondary outcomes:** Serious adverse events Total adverse events
Notes	Funding source: The study was funded by the Kenneth Rainin Foundation (Innovator and Breakthrough awards). The Kenneth Rainin Foundation had no role in the study design, data collection, data analysis, data interpretation or writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. Conflict of interest:

Cox 2020 *(Continued)*

These authors disclose the following: Kevin Whelan and Miranda C. Lomer are the co-inventors of a mobile application to assist patients following the low FODMAP diet. Kevin Whelan has received consultancy fees from Danone, and a research grant from Clasado. The remaining authors disclose no conflicts

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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random allocation sequence was prepared online (www.sealedenvelope.com) by an independent researcher using block randomisation, with a 1:1 ratio of low FODMAP to placebo sham diet. Randomisation was stratified by diagnosis (CD or UC) and faecal calprotectin at screening (100 mg/g and 101 – 249 mg/g)
Allocation concealment (selection bias)	Low risk	Allocation sequences were sealed in opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Participants were blinded to diet allocation and informed that both diets would change the types of carbohydrates consumed, but that one was the diet under investigation, whereas the other was a sham diet. The terms “fermentable carbohydrates,” “low FODMAP diet,” or the mechanisms of the diet were not mentioned to participants." Comment: But personnel were un-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated. Author was contacted and we did not receive a response about this
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data presented for all participants
Selective reporting (reporting bias)	Low risk	Presented as in trial registration and methods
Other bias	Low risk	Authors have disclosed conflicts of interest. Baseline characteristics are balanced.

Sharma 2015

Study characteristics

Methods	RCT **Setting:** New Delhi, India, Single-centre, All India Institute of Medical Science (AIIMS) **Study period:** 2004 - 2008
Participants	**Inclusion criteria:** Only patients between 16 - 60 years who were in the clinical remission phase of the disease were included in the study. UC and CD activity was assessed using the criteria of Truelove and Witts (Truelove

Sharma 2015 *(Continued)*

1954) and the Crohn's Disease Activity Index (CDAI; Best 1976), respectively. The inclusion criteria for UC patients in the remission phase were (a) 1 or 2 stools a day without blood, (b) no fever, (c) no tachycardia, (d) haemoglobin normal or returning towards normal, and (e) erythrocyte sedimentation rate (ESR) normal or returning towards normal. Patients with a CDAI score < 150 were considered in remission

Exclusion criteria:

(a) IBD patients with other chronic diseases like diabetes mellitus, hypertension, or cardiovascular diseases,
(b) any condition known to affect the cardiovascular autonomic functions such as chronic alcoholism or smoking,
(c) patients who have undergone any surgical intervention for IBD,
(d) pregnant women,
(e) patients on any drug regimen affecting autonomic functions,
(f) patients on psychiatric medication, and
(g) patients who have practised yoga within at least 1 year preceding the study

Age (mean ± SD): NS

Sex (M/F): NS

Site of disease: NS

Use of concurrent medication:

NS "There were no significant differences between the medication used by the yoga and control groups"

Disease activity: Clinical remission phase
The diagnosis of UC was established on the basis of clinical evidence of large bowel diarrhoea, haematochezia and tenesmus; endoscopic evidence of diffuse pattern of involvement of the gastrointestinal mucosa characterised by loss of vascular pattern, erythema, friability, or ulcerations; and histological evidence. The diagnosis of CD was established on the basis of the presence of characteristic clinical manifestations (chronic diarrhoea, haematochezia, abdominal pain, and intestinal obstructive manifestations), endoscopic features (skip lesion, asymmetrical involvement, deep ulcers, ileocecal valve involvement, and terminal ileum involvement), together with histological evidence (acute or chronic colitis, presence of inflammation extending beyond muscularis mucosa, lymphoid follicles, and non-caseating granulomas). The involvement of the small intestine was assessed by barium meal follow-through, small bowel enema, and/or retrograde ileoscopy.

Disease duration: NS

Number randomised:

IG: 50 (UC = 30, CD = 20)

CG: 50 (UC = 30, CD = 20)

Number reaching end of study:

IG: UC = 25, CD = 19

CG: UC = 26, CD = 17

Number analysed:

IG: 44 (UC = 25, CD = 19)

CG: 43 (UC = 26, CD = 17)

Postrandomisation exclusion:

IG: UC = 5 (relocation to another city = 1, pregnancy = 2, increased disease activity = 1, lost contact = 1); CD = 1 (bone fracture)

Sharma 2015 *(Continued)*

	CG: UC = 4 (increased disease activity = 2, relocation to another city = 1, started alternative therapy = 1); CD = 3 (lost contact = 1, busy schedule = 1, increased disease activity = 1)
Interventions	**IG:** yoga intervention Along with the standard medical therapy, participants assigned to the yoga group underwent the yoga intervention, which comprised physical postures, pranayama (controlled breathing), and meditation. The supervised yoga intervention (1 week for 1 hour daily) was given under the guidance of a certified yoga trainer. Due to feasibility reasons, the supervised yoga training was provided for 1 week (each session for 1 hour) followed by a daily practice at home continuously over 2 months (1 hour daily). Standard medical treatment was continued by all the participants. A single yoga session was offered individually to the participants during the follow-up visits. During the home practice sessions, participants listened to the audio recording for relaxation; an instruction manual on different postures was also provided to all participants. Telephone support was provided to both groups to motivate a high degree of compliance **CG:** no intervention The standard pharmacological treatment was used by all the participants for maintenance of disease remission. All participants were treated with maintenance doses of mesalamines and azathioprine, along with multivitamins and calcium supplements
Outcomes	**Length of intervention:** 8 weeks (outcomes recorded at baseline, 1 month, 2 months) **Primary outcomes:** Treatment success as defined by the authors: Change from presence to absence of pain Participants were given a symptom diary at the beginning of the study in which they were asked to record the presence or absence of clinical symptoms. In accordance with the wide range of proposals for indices of clinical activity of IBD, the following symptoms were considered: blood, tenesmus, intestinal colic, peri-anal pain, arthralgia, and anorexia Participants were asked to fill the self-report form once a day before going to bed Withdrawal due to adverse events **Secondary outcomes:** Serious adverse events Total adverse events Anxiety levels were assessed by the State and Trait Anxiety Inventory (STAI; Spielberger et al., 1970). It consisted of 2 x 20-item subscales for measuring state and trait anxiety. Participants were asked to mark: not at all, somewhat, moderately, very much, on a scale of 1 – 4. Scoring was done as the sum of these individual scores. The range of anxiety score was 20 – 80
Notes	Funding source: Central Council for Research in Yoga and Naturopathy (CCRYN), New Delhi, India Conflict of interest: The authors declare that they have no competing interests Author contact details: purnimareceives@gmail.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Group assignment was determined by a randomisation scheme devised from computer-generated random-number tables. The tables were prepared by other researchers who were not involved in the study
Allocation concealment (selection bias)	Low risk	The randomisation schedule was concealed in sequentially-numbered, sealed opaque envelopes. Participants were randomised by the research assistant

Sharma 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible for this type of intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned. Author was contacted and we did not receive a response about this
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported for all participants reaching end of study
Selective reporting (reporting bias)	Unclear risk	No pain results for CD reported. All other outcomes mentioned in Methods were reported. Author was contacted and we did not receive a response about this
Other bias	Low risk	No conflict of interest, no differences at baseline

Shaw 1987

Study characteristics	
Methods	RCT **Setting:** not reported**,** USA **Study period:** Not stated
Participants	**Inclusion criteria:** chronic pain for at least 6 months, aged 20 - 60, English-speaking **Exclusion criteria:** History of psychosis and/or psychiatric hospitalisation, Suffering from progressive major medical disorder unrelated to ulcerative colitis, Having concurrent infectious medical disorder, Having history of alcoholism **Age (range):** all participants: 30.4 (6.47) **Sex (M/F):** IG: 10/10; CG: 10/10 **Site of disease:** NS **Use of concurrent medication:** Baseline IG: 15; CG: 16; were taking pain killers or 1 or more anti-inflammatory drugs, or both At end of study: IG: 9; CG: 17 6-month follow-up: IG: 7; CG: 15 **Disease duration:** NS **Disease activity:** NS **Number randomised:** IG: 20; CG: 20 **Number reaching end of study:** NS **Number analysed:** NS

Shaw 1987 *(Continued)*

	Postrandomisation exclusion: NS
Interventions	**IG:** Relaxation training. There were 6 treatment sessions, each 75 min in length, spread out over a 6-week period. Training was done in groups of 5 - 8 individuals. Progressive relaxation was taught. Participants were given audio tapes and were instructed to practice at home with and without the tapes at least once each day. **CG:** Attention control group. Participants in the control group were told that they were on a waiting list for relaxation training. During the training and follow-up periods, the experimenter maintained contact with control participants by telephoning them once a week. The intent was to keep control participants involved, but no direct suggestions were made by the experimenter in these conversations about pain alleviation
Outcomes	**Length of follow-up:** 6 weeks of intervention and follow-up; measured again after 6 weeks from end of intervention **Primary outcomes:** Pain frequency and intensity: The McGill Pain Questionnaire was used to obtain a measure of how participants describe pain; on this test, the higher the score the greater the perceived pain. The Pain and Distress Scale was used to assess the degree of psychological distress caused by chronic pain; on this test, the higher the score the greater the degree of distress. 5 other variables - intensity of present pain (scale of 1 - 10), duration of a pain episode, frequency of a pain episode, amount of pain relief experienced (scale of 1 - 10), and use of medication - were assessed by a questionnaire. **Secondary outcomes:** None reported
Notes	Funding source: NS Conflict of interest: NS Author contact details: annettehrlich@gmail.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned. The author was contacted but we received no response
Allocation concealment (selection bias)	Unclear risk	Not mentioned. The author was contacted but we received no response
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible for this type of intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned. The author was contacted but we received no response
Incomplete outcome data (attrition bias) All outcomes	Low risk	All reported
Selective reporting (reporting bias)	Low risk	All reported

Shaw 1987 *(Continued)*

Other bias	Low risk	Well-controlled baseline, but, there are no declarations about funding or conflicts of interest

Yilmaz 2019

Study characteristics	
Methods	RCT, single-centre **Setting:** not reported, single-centre, Turkey **Study period:** May 2015 - December 2016
Participants	**Inclusion criteria:** Patients with IBD participated in the study. In the trial, CD Activity Index for CD and Truelove-Witts scoring systems for UC were used for disease assessment scores (10 - 11). If the CDAI score was < 450, patients with CD were admitted to the study. If their Truelove-Witts score was severe, patients with UC were not admitted to the study. Volunteers also had to be > 18 years old **Exclusion criteria:** Patients with alcohol consumption > 20 g/day, Allergies or intolerance to milk, Antibiotic treatment within the last 1 month, Column or bowel operation history up to 3 months before the start of the study, and Presence of active infection within 1 month prior to the start of the study or during the study. In addition, if a patient requested to leave of his/her own will, or if kefir was not consumed continuously for 2 weeks, the trial protocol was assessed and was not approved **Age [mean(range)] :** IG: 33 (19 - 68) CG: 43.5 (29 - 76) **Sex (M/F):** IG: 9/6 CG: 4/6 **Site of disease:** IG: colon = 15; ileum = 0; colon+ileum = 0 CG: colon = 10; ileum = 0; colon+ileum = 0 **Use of concurrent medication:** NS **Disease activity:** inactive to moderate **Disease duration:** IG: 4 (1 - 12) CG: NS

Yilmaz 2019 *(Continued)*

	Number randomised: IG: 28 CG: 20 **Number reaching end of study:** IG: 15 CG: 10 **Number analysed:** IG: 15 CG: 10 **Postrandomisation exclusion:** IG: 3 (did not want to drink Kefir); CG:0
Interventions	**IG:** 400 mL/day kefir was administered twice a day to the participants for 4 weeks, which contains a total of 2.0 × 1010 CFU/mL viable Lactobacillus bacteria **CG:** no placebo or other intervention
Outcomes	**Length of intervention:** 4 weeks **Primary outcomes:** Pain intensity: Participants were requested to fill out the symptoms diary that has questionnaires of bowel habits. Abdominal pain was rated on a four-point scale with 0 = none, 1 = mild, 2 = moderate, and 3 = severe (The results were sent to us by the author) **Secondary outcomes:** None reported
Notes	Funding source: The authors declared that this study has received no financial support Conflict of interest: The authors have no conflicts of interest to declare Author contact details: ilkayilmaz001@hotmail.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The author was contacted about this and responded that randomisation was determined via a computer
Allocation concealment (selection bias)	Unclear risk	Not mentioned. The author did not give a response about this
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible for this type of intervention

Yilmaz 2019 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The author responded about this and said that the outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data are presented for all completers
Selective reporting (reporting bias)	Low risk	Aall outcomes are reported and scores were provided to us by the author
Other bias	Low risk	The authors report no conflicts of interest and the baseline characteristics look reasonably balanced, but that is not mentioned in the text

Zhao 2017

Study characteristics	
Methods	RCT **Setting:** Cangzhou Central Hospital, China **Study period:** January 2014 - January 2016
Participants	**Inclusion criteria:** patients with chronic ulcerative colitis **Exclusion criteria:** NS **Age (mean ± SD):** 48.2 (6) years; CG: 47.1 (5.9) years **Sex (M/F):** IG:54/36 CG: 19/11 **Site of disease:** NS **Use of concurrent medication:** NS **Disease duration (mean ± SD):** IG: 4.3 (1.5) years; CG: 4.1 (1.4) years **Disease activity:** NS **Number randomised:** IG: 90; CG: 30 **Number reaching end of study:** NS **Number analysed:** NS **Postrandomisation exclusion:** NS
Interventions	**IG:** stellate ganglion block treatment once a day for 30 days **CG:** 4 doses of sulfasalazine twice a day orally
Outcomes	**Length of follow-up:** 30 days **Primary outcomes:** None reported **Secondary outcomes:**

Zhao 2017 *(Continued)*

	Total adverse events
Notes	Funding source: NS Conflict of interest: "No potential conflicts of interest relevant to this article were reported" Author contact details: zhaonghongying123@21cn.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned. The author was contacted but we received no response
Allocation concealment (selection bias)	Unclear risk	Not mentioned. The author was contacted but we received no response
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned. The author was contacted but we received no response
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is not clear how many participants discontinued and how many were analysed. The author was contacted but we received no response
Selective reporting (reporting bias)	Low risk	All reported
Other bias	High risk	Major differences in the numbers of randomised participants between IG and CG and even though authors mention there were no significant differences at baseline there is a big difference in baseline pain scores

CG: control group; IG: intervention group; UC: ulcerative colitis

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

Study	Reason for exclusion
ACTRN12617000876392	Ineligible outcomes
ACTRN12619000150145	Ineligible outcomes
Bae 2016	Ineligible study design
Berrill 2014	Mixed IBD population without separate UC data
Chen 2015a	Ineligible intervention
Chen 2015b	Ineligible outcomes

Study	Reason for exclusion
Cohen 1999	Ineligible participant population
Collawn 1992	Ineligible intervention
Dai 2017	Ineligible outcomes
Danese 2019	Ineligible intervention (we have not included studies on induction or maintenance of remission)
Engel 2016	Ineligible outcomes
Faghfoori 2014	Ineligible intervention
Forbes 2019	Ineligible study design
Gearry 2009	Ineligible study design
Ghosh 2018	Ineligible intervention (we have not included studies on induction or maintenance of remission)
Gibson 2013	Ineligible outcomes
Hallert 2003	Ineligible indication
Hanauer 1993	Ineligible indication
Huang 2013	Ineligible indication
ISRCTN98226923	Ineligible indication
Johari 2016	Ineligible indication
McCormick 2010	Not an RCT
Mizrahi 2012	Mixed IBD population without separate UC data
NCT02763293	Ineligible participant population
Ozgursoy Uran 2019	Mixed IBD population without separate UC data
Pullan 1994	Ineligible outcomes
Spagnuolo 2017	Not an RCT. According to author no randomisation was performed. They enrolled consecutive patients and, alternating one by one, placed them in the experimental and control arms
Tapete 2018	Mixed IBD population without separate UC data
Tapete 2019	Mixed IBD population without separate UC data
Tripp 2017	Ineligible outcomes
Volz 2016	Mixed IBD population without separate UC data
Zai 2018	Ineligible participant population

IBD: irritable bowel disease; RCT: randomised controlled trial; UC: ulcerative colitis

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

IRCT20120415009475N5

Methods	Study design: RCT, triple-blind, placebo-controlled Setting: Iran
Participants	60 children
Interventions	IG: 2 capsules of 250 mg Saccharomyces Boulardii a day for 2 months CG: 2 placebo capsules a day for 2 months
Outcomes	Start date: 6 March 2018 Estimated completion date: 23 September 2018 Outcomes: • Pain using VAS scales and interviews • Quality of life using interviews and the IMPACT III questionnaire
Notes	Funding: Shahid Beheshti University of Medical Sciences Contact: mirrahimi@sbmu.ac.ir We had no response from the author to determine whether this study meets our inclusion criteria

IRCT20200219046553N1

Methods	Study design: RCT Setting: Iran
Participants	50 IBD patients 18-60 years old
Interventions	IG: mindfulness-based cognitive therapy in addition to their usual medical treatment CG: usual medical treatment
Outcomes	Quality of Life, Depression, Anxiety, Stress, Severity of pain, pain catastrophizing, Dispositional mindfulness and Disease activity
Notes	This study was identified on our updated search and will be included in the next update of this review

Leiby 2014

Methods	Study design: RCT Setting: USA
Participants	12 participants 11 - 17 years old
Interventions	IG: 12 weeks of yoga at 3 months of diagnosis + standard therapy

Leiby 2014 *(Continued)*

	CG: yoga at 6 months of diagnosis + standard therapy
Outcomes	Starting date: NS Estimated completion date: NS Outcomes: Health-related quality of life (PedsQL total score) and self-efficacy using questionnaires
Notes	Funding: NS Contact: 001(973)-971-5676 001(908)-522-8714 We had no response from the author to determine whether this study meets our inclusion criteria

NCT00940576

Methods	Study design: RCT, cross-over Setting: Germany
Participants	15 children and 2 adults
Interventions	Oral Intake of 250 ml per day Mare´s Milk First, then 250 ml per day placebo
Outcomes	Starting date:16 July 2009 Last update: 25 May 2015 Outcomes: • Score of Crohn´s disease or ulcerative colitis, or both • Extra-intestinal pain • Adverse events
Notes	Funding: University of Jena Contact: gerhard.jahreis@uni-jena.de We had no response from the author to determine whether this study meets our inclusion criteria

NCT02963246

Methods	Study design: RCT Setting: Spain
Participants	60 adults
Interventions	IG: Mindfulness intervention (12 months) CG: Treatment-as-usual
Outcomes	Starting date: 5 May 2017 Actual completion date: 14 March 2018

NCT02963246 *(Continued)*

	Outcomes: Primary outcome measures: Quality of life measured with the IBDQ-32 (Inflammatory Bowel Disease Questionnaire); Time frame: Change from baseline IBDQ-32 score at 12 months Secondary outcome measures: Inflammation stress markers (reactive Protein C and faecal calprotectin): Time frame: Change from baseline inflammation stress markers at 12 months
Notes	Funding: Cardenal Herrera University Contact: jose.soria@uchceu.es We had no response from the author to determine whether this study meets our inclusion criteria

NCT04488198

Methods	Study design: RCT
Participants	60
Interventions	IG: acupuncture CG1: placebo CG2: no intervention
Outcomes	Primary: Disease Activity Index Secondary: Quality of Life in Children and Adolescents, pain assessment, C reactive protein, leukocytes, rrythrocyte sedimentation rate
Notes	This study was identified on our updated search and will be included in the next update of this review

NCT04646785

Methods	Study design: RCT
Participants	136
Interventions	IG: mindfulness CBT added to treatment as usual CG: treatment as usual
Outcomes	Primary: Psychological distress Secondary: Objective sleep quality, subjective sleep quality, fatigue, IBD-related quality of life, perceived control over IBD, calprotectin, c reactive protein, clinical disease activity, repetitive negative thinking, mindfulness skills, positive mental health, self compassion, costs, health-related quality of life

NCT04646785 *(Continued)*

Notes	This study was identified on our updated search and will be included in the next update of this review

Neeb 2019

Methods	Study design: phase III, placebo-controlled RCT Setting: Germany
Participants	36 adults
Interventions	IG: transcranial direct current stimulation for 5 days CG: placebo
Outcomes	Outcomes: (i) • High-resolution 3D T1-weighted MRI scans using a magnetisation-prepared rapid gradient echo sequence • DTI sequences using a single-shot echo-planar imaging sequence • BOLD resting-state scans using an echo-planar imaging sequence • 1 mm isotropic T2-weighted fluid-attenuated inversion recovery sequence • T1-and T2-weighted images
Notes	Funding: This study has been supported by the grant "Patientenorientierte Forschung bei CED 2014" of the "Deutsche Morbus Crohn /Colitis ulcerosa Vereinigung e.V." (DCCV e.V.) commissioned to Magdalena Sarah Prüess Contact: magdalena.pruess@charite.de We had no response from the author to determine whether this study meets our inclusion criteria

NTR3414

Methods	Study design: RCT Setting: The Netherlands
Participants	80 people > 11 years old
Interventions	IG: 6 sessions of gut-directed hypnotherapy CG: 6 sessions of standard medical treatment with supportive therapy
Outcomes	Starting date: 1 March 2012 Estimated completion date: 1 September 2013 Outcomes: Primary: The number of participants with > 50% reduction in IBS-SSS pain score Secondary: the effects of therapy on total IBS-SSS score, adequate relief, health-related quality of life, IBD disease activity, health utility index, depression, anxiety, somatisation, abdominal pain related cognitions, absence of school or work, use of healthcare resources and additional costs, use of IBD medication, colonic sensitivity to distension, faecal protease activity and microbiota and the

NTR3414 *(Continued)*

	ability of participant's faecal supernatant to induce colonic hypersensitivity to distension in rats by colonic infusion
Notes	Funding: Zon-Mw, The Netherlands Organisation for Health Research and Development Contact: d.r.hoekman@amsterdamumc.nl Authors are still in the process of publishing the data from this trial. Publication is expected in 2020. Unfortunately, they are unable to provide any reports prior to publication. We could not determine whether this study meets our inclusion criteria

Schoultz 2013

Methods	Study design: RCT, exploratory Setting: Scotland
Participants	40 adults
Interventions	IG: 16 hours of structured group training over an 8-week period CG: 16 hours of structured group training over an 8-week period, 6 months later than the intervention group
Outcomes	Primary outcomes are recruitment, completion/retention rates and adherence and adaptation to the MBCT manual for IBD patients The secondary outcome is to assess the feasibility of collecting reliable and valid data on proposed outcome measures such as quality of life, anxiety, depression, disease activity and mindful awareness
Notes	Funding: This project is funded by University of Stirling, NHS Highland and Crohn's and Colitis UK Contact: ms84@stir.ac.uk We had no response from the author to determine whether this study meets our inclusion criteria

Schoultz 2015

Methods	Study design: RCT, pilot study Setting: Scotland
Participants	44 adults
Interventions	IG: 16 hours of structured group training over 8 consecutive weeks plus guided home practice and follow-up sessions CG: The wait-list group received a leaflet entitled 'Staying well with IBD'
Outcomes	The key objectives were to assess patient eligibility and recruitment/dropout rate, to calculate initial estimates of parameters to the proposed outcome measures (depression, anxiety, disease ac-

Schoultz 2015 *(Continued)*

	tivity, dispositional mindfulness and quality of life) and to estimate sample size for a future large RCT
Notes	Funding: This project is funded by University of Stirling, NHS Highland and Crohn's and Colitis UK. Contact: ms84@stir.ac.uk We had no response from the author to determine whether this study meets our inclusion criteria

Takakura 2020

Methods	Study design: RCT
Participants	33 IBD participants
Interventions	IG: proactive pain protocol CG: standard-of-care reactive pain regimen (as-needed acetaminophen and opioids)
Outcomes	Outcomes included daily pain (assessed by numeric rating scores, 0-10), average daily morphine milligram equivalents (MME), length of stay (LOS), need for surgery during admission, and 30-day readmission rates
Notes	This study was identified on our updated search on 28 April 2021 and will be included in the next update of the review

Tomita 2020

Methods	Study design: RCT Setting: Japan
Participants	70 patients with inactive IBD
Interventions	IG ramosetron (5 μg) was administered orally once daily for 4 weeks CG: placebo
Outcomes	General improvement of IBS-like symptoms were evaluated at the 4-week time point (response rate). Improvements in abdominal pain and discomfort (response rate at 4 weeks) and bowel movement were evaluated at the same time.
Notes	This study was identified on our updated search on 28 April 2021 and will be included in the next update of the review

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

ChiCTR1900024086

Study name	Modified Chinese medicine granule in the treatment of ulcerative colitis in the remission phase: study protocol for a series of N-of-1 randomized, double-blind, controlled trials

ChiCTR1900024086 *(Continued)*

Methods	RCT, cross-over
Participants	20 adults 18 - 75 years old
Interventions	IG: modified Chinese medicine granule CG: mesalazine placebo
Outcomes	Primary outcome: Visual Analogue Scale (diarrhoea, abdominal pain, mucus stool, bloody purulent stool) Secondary outcomes: TCM syndrome scale; The Short Inflammatory Bowel Disease Questionnaire (SIBDQ); The Short Health Scale (SHS); The Rating Form of IBD Patient Concerns (RFIPC)
Starting date	24 June 2019
Contact information	chenxlsums@126.com liufb163@163.com
Notes	Sponsor: National Natural Science Foundation of China (No: 81774451)

ISRCTN71618461

Study name	A supported online self-management for symptoms of fatigue, pain and urgency/incontinence in people with inflammatory bowel disease: the IBD-BOOST trial
Methods	RCT, multicentre
Participants	680 adults aged 18 and above
Interventions	IG: facilitator-supported online self-management CG: care as usual
Outcomes	Primary: UK Inflammatory Bowel Disease Questionnaire (UK-IBDQ) and global rating of symptom relief at 6 months after randomisation Secondary: • UK Inflammatory Bowel Disease Questionnaire (UK-IBDQ) at 12 months • Rating of satisfaction with results of BOOST programme (simple 0 - 100 visual analogue scale) at 6 and 12 months only • Global rating of symptom relief at 12 months • Numerical (0 - 10) pain rating scale at baseline, 6 and 12 months after randomisation • Vaizey (faecal) incontinence score, reflecting participants' perceptions of severity at baseline, 6 and 12 months after randomisation • IBD-Fatigue score at baseline, 6 and 12 months after randomisation

ISRCTN71618461 *(Continued)*

	• IBD-Control score; 8-item self-reported score to measure disease control from the participant's perspective at baseline, 6 and 12 months after randomisation • EQ-5D-5L general health-related quality of life at baseline and 6 and 12 months after randomisation
Starting date	1 October 2019
Contact information	christine.norton@kcl.ac.uk jonathan.syred@kcl.ac.uk
Notes	Sponsor: London North West University Healthcare NHS Trust

NCT03301311

Study name	Personalized Research on Diet in Ulcerative Colitis and Crohn's Disease (PRODUCE)
Methods	RCT, cross-over
Participants	54 patients 7-18 years old
Interventions	IG: Specific Carbohydrate Diet CG: Modified Specific Carbohydrate Diet
Outcomes	Primary outcome measures: Stool frequency: Daily through study completion (34 weeks from randomisation); Self-reported number of stools per day entered as an integer in the study mobile app Stool consistency:Daily through study completion (34 weeks from randomisation); Self-reported assessment of stool consistency using the Bristol Stool Scale entered in the study mobile app Pain interference: Weekly through study completion (34 weeks from randomisation). Participant-reported outcome of pain interference measured using the Patient Reported Outcomes Measurement Information System (PROMIS) Pain Interference Scale on the study app. The scale includes 8 items and responses to each item are on a 0 (never) to 4 (almost always) scale. Higher scores indicate greater pain interference. Look-up tables provided by the PROMIS Assessment Center will be used to transform the raw score to a T-score such that 50 is the mean for the population with a standard deviation of 10 Gastrointestinal Symptoms: Weekly through study completion (34 weeks from randomisation). Self-reported outcome of GI symptom burden measured using the PROMIS GI Symptoms scale on the study app. The scale includes 4 items and responses to each item are on a 1 (never) to 5 (almost always) scale. Higher scores indicate greater GI symptom burden. Look-up tables provided by the measure developers will be used to transform the raw score to a T-score such that 50 is the mean for the population with a standard deviation of 10 Faecal calprotectin: At baseline and once at the end of each treatment period (weeks 10, 18, 26 and 34) for a total of 5 times. Laboratory measurement of intestinal inflammation. Stool will be collected by participants at home and will be mailed to a central lab for processing and analysis Secondary outcome measures: Provider measured disease activity: At baseline, 10 weeks and up to 2 - 4 more times as standard-of-care visits for the duration of the study (34 weeks from randomisation) Pediatric Ulcerative Colitis Index (PUCAI) or Short Pediatric Crohn's Index (sPCDAI) are completed by care providers at all scheduled clinic visits as part of standard of care and are entered into the ImproveCareNow (ICN) registry Laboratory markers of disease activity and inflammation: At baseline, 10 weeks and up to 2 - 4 more times as standard-of-care visits for the duration of the study (34 weeks from randomisation). C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin, and haematocrit collected as part of standard-of-care and are entered into the ImproveCareNow (ICN) registr. Growth: At baseline, week 4, week 10, week 12 and up to 2 - 4 more times as standard-of-care visits for the duration of the study (34 weeks from randomisation) Weight and height are collected at all clinic visits and at the dietitian study follow-up visits (2 weeks into the first diet period of each diet). These data are entered into the ICN registry as part of regular data entry. We will calculate weight-

NCT03301311 *(Continued)*

	for-age Z-scores for all entries during study period. The age-specific mean and standard deviation from U.S. population norms will be used to calculate Z-scores using the Centers for Disease Control Epi-Info program Short Crohn's Disease Activity Index (sCDAI): Weekly through study completion (34 weeks from randomisation). The short Crohn's disease activity index (sCDAI) will be used to assess disease activity based on self-report via the study app. For the sCDAI, items assess general well-being, abdominal pain, and liquid stools. Respondents are asked to report on symptoms for the previous 24 hour period. Scores are calculated based on a published algorithm. Pediatric Ulcerative Colitis Activity Index (PUCAI): Weekly through study completion (34 weeks from randomisation). A self-reported version of the Pediatric Ulcerative Colitis Activity Index (PUCAI) will be used to assess disease activity based on self-report via the study app. For the PUCAI, respondents are asked to report on abdominal pain, bloody stools, stool consistency, stool frequency, nocturnal stools, and activity level over the prior 24-hours. A weighted, summed score is calculated with higher scores indicating worse disease (score range 0 - 85)
Starting date	10 April 2018
Contact information	Heather C Kaplan, MDLisa Opipari-Arrigan, MD
Notes	Sponsor: Children's Hospital Medical Center, Cincinnati, USA

NCT03348852

Study name	Association between functional changes in the brain and the perception of pain in patients with inflammatory bowel diseases (IBD) - measured with functional Magnetic Resonance Imaging
Methods	RCT
Participants	84 adults 18 - 80 years old
Interventions	IG: transcranial direct current stimulation CG: sham transcranial direct current stimulation
Outcomes	Primary Outcome Measures Functional and/or structural changes in the brain measured with cerebral MRI at 2 weeks. Participants will be followed for 2 weeks Changes in pain measured with visual analogue scale at 2 weeks. Participants will be followed for 2 weeks Changes in perception of pain measured with an algometer (pain pressure threshold) at 2 weeks. Participants will be followed for 2 weeks Secondary Outcome Measures: Changes in questionnaire "quality of life" at 2 weeks: questionnaire Changes in functional symptoms at 2 weeks. Questionnaire: irritable bowel syndrome - severity scoring system (IBS-SSS) Changes in activity indices at 2 weeks. Harvey-Bradshaw Index (HBI) or simple clinical colitis activity index Changes in pain catastophising scale at 2 weeks Changes in inflammation biomarker (blood - C-reactive protein) at 2 weeks Changes in inflammation biomarker (stool - calprotectin) at 2 weeks
Starting date	24 January 2017
Contact information	mailto:magdalena.pruess%40charite.de?subject=NCT03348852, EA4/017/16, Association Between Functional Changes in the Brain and the Perception of Pain in Patients With Inflammatory Bowel Diseases (IBD) - Measured With Functional Magnetic Resonance Imaging.

NCT03348852 *(Continued)*

Notes	Sponsor: Charite University, Berlin, Germany

NCT03422861

Study name	Nabilone use for acute pain in inflammatory bowel disease patients
Methods	RCT
Participants	80 adults, aged 25 - 65 years
Interventions	IG: nabilone treatment CG: placebo treatment
Outcomes	Primary outcome measures Total amount of opioid consumption postoperatively up to 72 hours after surgery. All the narcotic consumption will be converted to IV morphine equivalents using standard conversation factors Secondary outcome measures: Pain scores at rest and movement, starting from discharge from post-anaesthetic care unit (PACU), twice a day for 72 hours. Based on visual analogue scale (VAS) scoring system (0 - 10), where score of 0 refers to no pain and a score of 10 refers to the worst pain imaginable Incidence of opioid-related side effects, measured at 24, 48 and 72 hours.]Based on Opioid-Related Symptom Distress Scale Incidence of nabilone side effects at 24, 48, 72 hours. Measured at 24, 48, 72 hours, including drowsiness, vertigo, blurred vision, sensation disturbance, dry mouth, ataxia, anorexia, asthenia, headache, orthostatic hypotension, seizure, syncope, confusion Ulcerative Colitis (UC) symptom severity: measured at baseline (pre-anaesthetic clinic) and at 72 hrs. Based on Simple Clinical Colitis Activity Index (SCCAI) Crohn disease (CD) symptom severity: measured at baseline (pre-anaesthetic clinic) and at 72 hrs. Based on Harvey-Bradshaw Index (HBI) Time to first flatus, assessed on a daily basis for occurrence of first flatus for up to 72 hrs. The number of hours/days elapsed post-surgically when the patient has flatus Number of loose stools: measured on a daily basis for up to 72 hrs after surgery. Predominantly watery/non-formed stool. Bristol stool chart type 6 and 7 Length of hospital stay: measured in hours, starting from arrival to post-anaesthetic care unit (PACU) to the time of discharge from hospital for up to 10 days. The total number of hours the participant is admitted in the hospital
Starting date	April 2020
Contact information	mailto:Naveed.Siddiqui%40uhn.ca?subject=NCT03422861, NAB-2017, Nabilone Use For Acute Pain in Inflammatory Bowel Disease Patients zeev.friedman@sinaihealthsystem.ca
Notes	Sponsor: Samuel Lunenfeld Research Institute, Mount Sinai Hospital

NCT03667586

Study name	Group Cognitive Behavioral Therapy for IBD Patients
Methods	RCT

NCT03667586 *(Continued)*

Participants	130 adults 18-80 years old
Interventions	IG: Cognitive behavioral psychotherapy sessions for 6 months CG: Regular brief follow-ups by the gastroenterologists and the nurse of the research team
Outcomes	Primary Outcome Measures: Health Survey 36 Short Form (SF36) [Time Frame: 18 months] Hospital Anxiety and Depression Scale (HADS) [Time Frame: 18 months] Female Sexual Functioning Index (FSFI) [Time Frame: 18 months] International Index of Erectile Function(IIEF) [Time Frame: 18 months] Secondary outcomes: Crohn's disease activity index [Time Frame: 6 months] Truelove and Witts' severity index [Time Frame: 6 months] Faecal calprotectin [Time Frame: 6 months] Serum cytokines levels [Time Frame: 6 months]
Starting date	21 February 2019
Contact information	mariakalogeropoulou@yahoo.com chtriantos@hotmail.com We had no response from the author to determine whether this study meets our inclusion criteria
Notes	Sponsor: University Hospital of Patras

NCT03798405

Study name	Reactive vs. proactive pain control in IBD (PAIN-Sparing)
Methods	RCT
Participants	166 adults aged 18+
Interventions	IG: Proactive Analgesic Inpatient Narcotic-Sparing CG: Reactive traditional prescribing habits
Outcomes	Primary outcome measures Patient-Reported Pain Scores: Difference in the average daily pain score from the first to the last day of hospitalisation, typically 7 days. Visual Analog Pain Numeric Rating Scale (Scale range 0 (no pain) to 10 (severe pain)) Secondary outcome measures: Healthcare Utilisation: From hospital admission until hospital discharge, typically 7 days. Hospital length of stay (in days) Functional Activity from hospital admission until hospital discharge, typically 7 days. FitBit activity (number of steps per day) Opioid consumption: From hospital admission until hospital discharge, typically 7 days. Milligram morphine-equivalents consumed per day

NCT03798405 *(Continued)*

Starting date	1 January 2019
Contact information	mailto:gil.melmed%40cshs.org?subject=NCT03798405, Pro00050742, Reactive vs. Proactive Pain Control in IBD
Notes	Sponsor: Cedars-Sinai Medical Center

NCT03825900

Study name	Transcranial direct current stimulation and the interaction between chronic pain and the intestinal epithelial barrier in patients with chronic inflammatory bowel diseases (IBD)
Methods	RCT
Participants	84 adults aged 18 - 80 years old
Interventions	IG: active transcranial direct current stimulation CG: sham transcranial direct current stimulation
Outcomes	Primary outcome measures Functional changes in the brain measured with cerebral MRI at 6 weeks. Exploratory analyses of resting-state fMRI Structural changes in the brain measured with cerebral MRI at 6 weeks. Exploratory analyses of MRI with respect to DTI (diffusions tensor imaging) and VBM (voxel based morphometry) Functional and/or structural changes in the Intestinal Epithelial Barrier measured with endoscopy of the rectum with sample-taking at 6 weeks. Changes in pain measured with visual analogue scale at 6 weeks. VAS scale from 0 - 10 Changes in perception of pain measured with an algometer (pain pressure threshold) at 6 weeks. Continuous scale from 0 kg Secondary outcome measures Changes in questionnaire "quality of life" at 6 weeks. Questionnaire "quality of life" analyses daily activities, scale running from 32 points (worse outcome) to 224 points (best outcome) Changes in functional symptoms using IBS-SSS at 6 weeks. IBS-SSS: irritable bowel syndrome - severity score system, questionnaire analyses functional symptoms, score running from 0 (best outcome) to 600 points (worst outcome) Changes in activity indices using HWI questionnaire or SCCAI questionnaire at 6 weeks. HWI: Harvey-Bradshaw-Index, SCCAI: Simple Clinical Colitis Activity Index, scale: points: 0 - 20 points (low points are best outcome, high points are worst outcome) Changes in pain catastrophising scale questionnaire at 6 weeks. Pain catastrophising scale questionnaire analyses subjective catastrophising due to pain, score running from 0 - 52 points (low points are best outcome, high points are worst outcome) Changes in inflammation biomarker (blood - C-reactive protein) at 6 weeks. Unit: mg/dl Changes in inflammation biomarker (stool - calprotectin) at 6 weeks. Unit: mg/g
Starting date	1 June 2018
Contact information	mailto:magdalena.pruess%40charite.de?subject=NCT03825900, EA4/221/17, Transcranial Direct Current Stimulation and the Interaction Between Chronic Pain and the Intestinal Epithelial Barrier in Patients With Chronic Inflammatory Bowel Diseases (IBD)
Notes	Sponsor: Charite University, Berlin, Germany

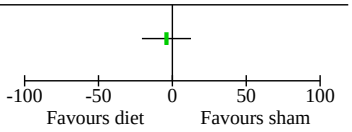
DATA AND ANALYSES

Comparison 1. Low FODMAPs diet vs sham diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Pain frequency	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.2 Pain intensity	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.3 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

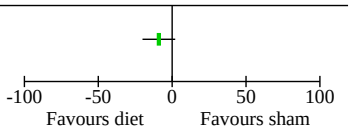
Analysis 1.1. Comparison 1: Low FODMAPs diet vs sham diet, Outcome 1: Pain frequency

	Low FODMAPs			Sham diet			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Cox 2020	31	21.6	13	35	21.6	13	-4.00 [-20.61 , 12.61]	



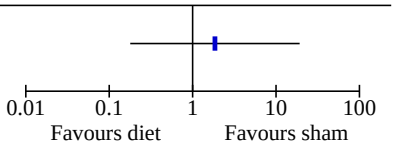
Analysis 1.2. Comparison 1: Low FODMAPs diet vs sham diet, Outcome 2: Pain intensity

	Low FODMAPs			Sham diet			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Cox 2020	20	14.4	13	29	14.4	13	-9.00 [-20.07 , 2.07]	



Analysis 1.3. Comparison 1: Low FODMAPs diet vs sham diet, Outcome 3: Withdrawal due to adverse events

	Low FODMAPs		Sham diet		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Cox 2020	2	27	1	25	1.85 [0.18 , 19.19]	

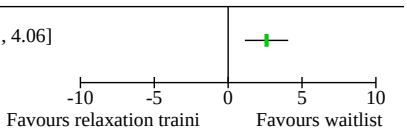


Comparison 2. Relaxation training vs wait-list

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Pain frequency (end of intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.2 Pain frequency (6 weeks after end of intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.3 Pain intensity (end of intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.4 Pain intensity (6 weeks after end of intervention)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

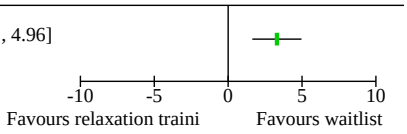
Analysis 2.1. Comparison 2: Relaxation training vs wait-list, Outcome 1: Pain frequency (end of intervention)

	Relaxation training			Wait-list			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Shaw 1987	5.6	2.64	20	3	2.05	20	2.60 [1.14 , 4.06]	



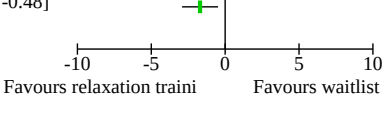
Analysis 2.2. Comparison 2: Relaxation training vs wait-list, Outcome 2: Pain frequency (6 weeks after end of intervention)

	Relaxation training			Wait-list			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Shaw 1987	6.7	3.07	20	3.4	2.23	20	3.30 [1.64 , 4.96]	



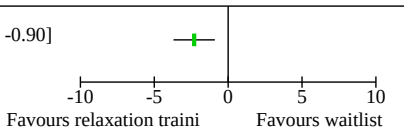
Analysis 2.3. Comparison 2: Relaxation training vs wait-list, Outcome 3: Pain intensity (end of intervention)

	Relaxation training			Wait-list			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Shaw 1987	5.4	1.84	20	7.1	2.08	20	-1.70 [-2.92 , -0.48]	



Analysis 2.4. Comparison 2: Relaxation training vs wait-list, Outcome 4: Pain intensity (6 weeks after end of intervention)

Study or Subgroup	Relaxation training Mean	SD	Total	Wait-list Mean	SD	Total	Mean Difference IV, Random, 95% CI
Shaw 1987	4.5	2.01	20	6.8	2.48	20	-2.30 [-3.70 , -0.90]

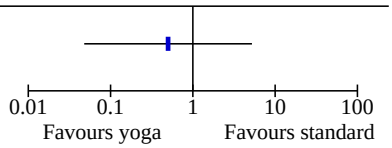


Comparison 3. Yoga vs no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.2 State anxiety	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.3 Trait anxiety	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

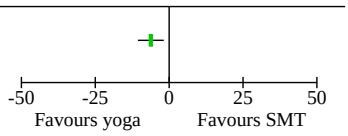
Analysis 3.1. Comparison 3: Yoga vs no intervention, Outcome 1: Withdrawal due to adverse events

Study or Subgroup	Yoga Events	Total	No intervention Events	Total	Risk Ratio M-H, Random, 95% CI
Sharma 2015	1	30	2	30	0.50 [0.05 , 5.22]



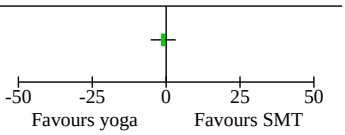
Analysis 3.2. Comparison 3: Yoga vs no intervention, Outcome 2: State anxiety

Study or Subgroup	Yoga Mean	SD	Total	No intervention Mean	SD	Total	Mean Difference IV, Random, 95% CI
Sharma 2015	32.8	8.21	30	39	9.05	30	-6.20 [-10.57 , -1.83]



Analysis 3.3. Comparison 3: Yoga vs no intervention, Outcome 3: Trait anxiety

Study or Subgroup	Yoga Mean	Yoga SD	Yoga Total	No intervention Mean	No intervention SD	No intervention Total	Mean Difference IV, Random, 95% CI
Sharma 2015	41.24	8.22	30	42.26	8.49	30	-1.02 [-5.25 , 3.21]

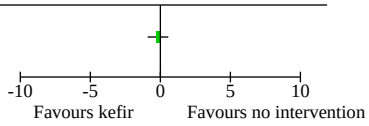


Comparison 4. Kefir vs no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Pain intensity	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: Kefir vs no intervention, Outcome 1: Pain intensity

Study or Subgroup	Kefir Mean	Kefir SD	Kefir Total	No intervention Mean	No intervention SD	No intervention Total	Mean Difference IV, Random, 95% CI
Yilmaz 2019	0.33	0.61	15	0.5	1.08	10	-0.17 [-0.91 , 0.57]



ADDITIONAL TABLES

Table 1. Primary outcome details

Comparison	Study ID	Disease type	Disease activity	Length of intervention	Measurement of pain	Number of randomised participants
Low FODMAPs diet vs. sham diet	Cox 2020	IBD	inactive	4 weeks	Pain frequency and intensity: IBS-SSS for pain rating scale 0 - 100, GSRS rating scale 0-3	52 (IG:27; CG: 25)
Yoga intervention vs. no intervention	Sharma 2015	UC/IBD	inactive	8 weeks	presence or absence of pain	100 (IG:50; CG: 50)
Relaxation training vs. wait-list	Shaw 1987	UC	unclear	6 weeks	Pain frequency: Hours between pain episodes Pain intensity: Scale 0 - 10	40 (IG:20; CG: 20)

Table 1. Primary outcome details *(Continued)*

Kefir diet (Lactobacillus bacteria) vs. no intervention	Yilmaz 2019	IBD	inactive to moderate	4 weeks	Pain intensity: rating scale 0 - 3	48 (IG:28; CG: 20)
Stellate ganglion block vs. sulfasalazine	Zhao 2017	UC	unclear	30 days	"Stomachache" (result values provided without explanation)	120 (IG:90; CG: 30)

IBD: irritable bowel disease; UC: ulcerative colitis

Table 2. Primary outcome data

Comparison	Study ID	Treatment success end of study data IG/CG	Pain frequency data IG/CG	Pain intensity data IG/CG	Withdrawals due to adverse events IG/CG
Low FODMAPs diet vs. sham diet	Cox 2020	NR	mean(SD) end of study IG=31(21.6) CG=35(21.6)	mean(SD) end of study IG=20(14.4) CG=29(14.4)	IG=2 CG=1
Yoga intervention vs. no intervention	Sharma 2015	NR	NR	NR	IG=1 CG=2
Relaxation training vs. wait-list	Shaw 1987	NR	mean(SD) end of study IG=5.6(2.64) CG=3(2.05) mean(SD) 6-week follow-up IG=6.7(3.07) CG=3.4(2.23)	mean(SD) end of study IG=5.4(1.84) CG=7.1(2.08) mean(SD) 6-week follow-up IG=4.5(2.01) CG=6.8(2.48)	NR
Kefir diet (Lactobacillus bacteria) vs. no intervention	Yilmaz 2019	NR	NR	mean(SD) end of study IG=0.33(0.61) CG=0.5(1.08)	IG=0 CG=0
Stellate ganglion block vs. sulfasalazine	Zhao 2017	NR	NR	NR	NR

APPENDICES

Appendix 1. Search strategies

Cochrane CCTR, CDSR search strategy (via Ovid)

1. exp Pain/
2. pain*.tw,kw.
3. ((abdominal or abdomen) and (discomfort* or ache* or aching or migraine* or fibromyalgia* or neuralgia* or colic*)).tw,kw.
4. or/1-3
5. exp Colitis, Ulcerative/
6. Inflammatory Bowel Diseases/
7. (ulcer* adj5 colitis).tw,kw.
8. inflammatory bowel disease*.tw,kw.
9. (colitis gravis or proctocolitis or procto colitis or mucosal colitis or colorectitis or UC).tw,kw.
10. or/5-9
11. 4 and 10

2 MEDLINE search strategy (via Ovid)

1. exp Pain/
2. pain*.tw,kw.
3. ((abdominal or abdomen) and (discomfort* or ache* or aching or migraine* or fibromyalgia* or neuralgia* or colic*)).tw,kw.
4. or/1-3
5. exp Colitis, Ulcerative/
6. Inflammatory Bowel Diseases/
7. (ulcer* adj5 colitis).tw,kw.
8. inflammatory bowel disease*.tw,kw.
9. (colitis gravis or proctocolitis or procto colitis or mucosal colitis or colorectitis or UC).tw,kw.
10. or/5-9
11. 4 and 10
12. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. randomi?ed.ab.
15. placebo.ab.
16. drug therapy.fs.
17. randomly.ab.
18. trial.ab.
19. groups.ab.
20. or/12-19
21. exp animals/ not humans/
22. 20 not 21
23. 11 and 22
24. cochrane database of systematic reviews.jn. or search*.tw. or meta analysis.pt. or medline.tw. or systematic review.tw.
25. 11 and 24
26. 23 or 25

(lines 12-22: *[Cochrane Handbook RCT filter - sensitivity max version]*

line 24:*[Wong 2006 – systematic reviews filter – specificity maximizing version])*

3 PsycINFO search strategy (via Ovid)

1. exp Pain/
2. Pain Measurement/
3. Pain Perception/
4. Pain Management/

5. pain*.tw.
6. ((abdominal or abdomen) and (discomfort* or ache* or aching or migraine* or fibromyalgia* or neuralgia* or colic*)).tw.
7. or/1-6
8. exp Ulcerative Colitis/
9. (ulcer* adj5 colitis).tw.
10. inflammatory bowel disease*.tw.
11. (colitis gravis or proctocolitis or procto colitis or mucosal colitis or colorectitis or UC).tw.
12. or/8-11
13. 7 and 12
14. (control* or random*).tw. or exp Treatment/
15. 13 and 14

4 CINAHL search strategy (EBSCO)

S1. MH "Pain+"
S2. TI pain* OR AB pain*
S3. TI ((abdominal or abdomen) and (discomfort* or ache* or aching or migraine* or fibromyalgia* or neuralgia* or colic*)) OR AB ((abdominal or abdomen) and (discomfort* or ache* or aching or migraine* or fibromyalgia* or neuralgia* or colic*))
S4. S1 OR S2 OR S3
S5. (MH "Colitis, Ulcerative")
S6. TI (ulcer* and colitis) OR AB (ulcer* and colitis)
S7. TI inflammatory bowel disease* OR AB inflammatory bowel disease*
S8. TI (colitis gravis or proctocolitis or procto colitis or mucosal colitis or colorectitis or UC) OR AB (colitis gravis or proctocolitis or procto colitis or mucosal colitis or colorectitis or UC)
S9. S5 OR S6 OR S7 OR S8
S10. S4 AND S9
S11. MH "prognosis+" OR MH "study design+" OR random*
S12. S10 AND S11

(Line S11: [Wong 2006 "CINAHL therapy studies" filter – best sensitivity version])

5 AMED search strategy (via Ovid)

1. pain*.tw.
2. ((abdominal or abdomen) and (discomfort* or ache* or aching or migraine* or fibromyalgia* or neuralgia* or colic*)).tw.
3. or/1-2
4. (ulcer* adj5 colitis).tw.
5. inflammatory bowel disease*.tw.
6. (colitis gravis or proctocolitis or procto colitis or mucosal colitis or colorectitis or UC).tw.
7. or/4-6
8. 3 and 7

6 ClinicalTrials.gov search strategy (Advanced Search)

Condition/ Disease: (ulcerative colitis OR inflammatory bowel disease OR colitis gravis OR proctocolitis OR procto colitis OR mucosal colitis OR colorectitis)
Other terms: (pain OR pains OR ache* OR aching OR fibromyalgia* OR neuralgia* OR colic*)
Study Type: Interventional Studies

7 WHO ICTRP Search Portal search strategy (Standard search)

pain* AND ulcerative colitis OR
ache* AND ulcerative colitis OR
aching AND ulcerative colitis OR
colic* AND ulcerative colitis OR
pain* AND inflammatory bowel disease OR
ache* AND inflammatory bowel disease OR
aching AND inflammatory bowel disease OR
colic* AND inflammatory bowel disease OR
pain* AND proctocolitis OR
ache* AND proctocolitis OR
aching AND proctocolitis OR

colic* AND proctocolitis OR
pain* AND colorectitis OR
ache* AND colorectitis OR
aching AND colorectitis OR
colic* AND colorectitis

HISTORY

Protocol first published: Issue 4, 2020

CONTRIBUTIONS OF AUTHORS

Morris Gordon: conceived the review question; developed the review; secured funding; contributed to writing and editing the review; contributed to screening and data extraction; made an intellectual contribution to the review; approved the final version prior to submission; and is the review guarantor.

Vassiliki Sinopoulou: contributed to writing and editing the review; contributed to screening and data extraction; led the write-up of the results, approved the final version prior to submission.

Terence Dovey: contributed to screening, data extraction; approved the final version prior to submission.

Anthony K Akobeng: developed the review; made an intellectual contribution to the review; advised on the review; approved the final version prior to submission.

DECLARATIONS OF INTEREST

MG: "Since August 2016, I have received travel fees to attend international scientific and training meetings from Pharma companies. These grants included no honoraria, inducement, advisory role or any other relationship and were restricted to the travel and meeting related costs of attending such meetings. These include: DDW May 2017, World Congress of Gastroenterology October 2017, DDW May 2018, Advances in IBD December 2018, DDW May 2019.
The companies include: Biogaia (2017-19), Ferring (2018), Allergan (2017), synergy (bankrupt - 2018) and Tillots (2017-19). None of these companies have had any involvement in any works completed by me and I have never had any payments for any other activities from them. From this date onwards, I have made a personal undertaking to take no further funds from any pharmaceutical or formula company in any form for travel or other related activities. This is to lift the limitations such funding has on my ability to act as a first and corresponding author on reviews, in line with the Cochrane policies on such matters and is reported in line with these policies. These current declarations will expire over the next 3 years and this statement updated regularly to reflect this".

VS: none.

TD: none.

AKA: none.

SOURCES OF SUPPORT

Internal sources

- NIHR, UK

  This review was supported by an NIHR Evidence Synthesis grant

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Initially we had planned to include RCTs that included UC participants as part of IBD cohorts. However, we found that many of them did not provide separate data for their CD and UC participants. For this reason, they were excluded from this review and only included in our companion review on Crohn's Disease.

As this review includes very few RCTs, we found no studies comparing more than two interventions, no cross-over trials and no cluster-trials. The parts of the protocol methods about how we would tackle these topics were condensed. The same applies to the subgroup and sensitivity analyses section, as we did not carry out any, due to the low number of studies and the fact that each intervention was represented by only one RCT.

Also, in line with the companion review on Crohn's disease, quality of life has not been included as an outcome, as in the original protocol. This was due to concerns about this being a surrogate for the question of pain, as it is impacted by so many other aspects of UC.