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Full Title: Systematic review: interventions for abdominal pain management in Inflammatory Bowel Disease

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None

Abstract

Background

Abdominal pain is frequently reported by people with inflammatory bowel disease (IBD), including in remission. Pain is an under-treated symptom.

Aim

To systematically review evidence on interventions (**excluding disease-modifying interventions**) for abdominal pain management in IBD.

Methods

Databases (MEDLINE, EMBASE, PsycInfo, CINAHL, Scopus, Cochrane Library) were searched (February 2016). Two researchers independently screened references and extracted data.

Results

Fifteen papers were included: 13 intervention studies and two cross-sectional surveys. A variety of psychological, dietary and pharmacological interventions were reported. Four of 6 studies reported pain reduction with psychological intervention including individualised and group-based relaxation, disease anxiety-related Cognitive Behavioural Therapy and stress management. Both psychologist-led and self-directed stress management in inactive Crohn's disease reduced pain compared with controls (symptom frequency reduction index = -26.7, -11.3 and 17.2 at 6 month follow up, respectively). Two dietary interventions (alcoholic drinks with high sugar content and fermentable carbohydrate with prebiotic properties) had an effect on abdominal pain. Antibiotics (for patients with bacterial overgrowth) and transdermal nicotine patches reduced abdominal pain. Current and past cannabis users report it relieves pain. One controlled trial of cannabis reduced SF-36 and EQ-5D pain scores (1.84 and 0.7, respectively). These results must be treated with caution: data were derived from predominantly small uncontrolled studies of moderate to low quality.

Conclusions

Few interventions have been tested for IBD abdominal pain. The limited evidence suggests that relaxation and changing cognitions are promising, possibly with individualised dietary changes. There is a need to develop interventions for abdominal pain management in IBD.

Keywords: inflammatory bowel disease, Crohn's disease, ulcerative colitis, abdominal pain, pain, systematic review

Short title: Systematic review: IBD abdominal pain management

Introduction

Chronic abdominal pain is a major complaint in individuals with inflammatory bowel disease (IBD).¹ Nevertheless, it is an under-recognised and under-treated problem with a negative impact on quality of life.² There is a scarcity of research on abdominal pain in people with IBD. Management of abdominal pain has been recognised in Guidelines for IBD Management in Adults as being problematic and needing further research.³

Pain is a frequently reported symptom in active IBD, with the expectation that in the majority of patients it will resolve when the disease is controlled. However, many patients also experience pain when IBD is in remission, although there is ambiguity regarding the definition of remission and its relationship with objective markers of inflammation such as inflammatory markers or mucosal healing. A survey conducted in the United Kingdom (UK) found that up to 50% of patients with Crohn's disease (CD) and 37% of those with ulcerative colitis (UC) reported pain, irrespective of whether IBD was in relapse or in remission.⁴ Of those reporting pain, a high level of pain (pain $\geq 7/10$) was scored by 54% of patients with CD and 42% with UC.⁴ In a survey of people with IBD from 21 European countries ($n = 4990$), 62% reported daily pain and 28.5% reported regular analgesic use between flares.⁵ Only 28% reported no abdominal pain when IBD is in remission. In a large Swiss cross sectional survey ($n=2152$), general life quality was reported to be significantly lower ($p<0.0001$) in those reporting pain compared to those with no pain.⁶

In a survey of IBD outpatients, 88% reported pain in the past week.² The severity of pain was similar between genders, with slightly more women (70%) than men (65%) reporting abdominal pain. Of patients with UC in remission, over 50% have been found to have ongoing pain at least some of the time and 20% reported a moderate pain burden.⁷ Pain has been ranked by 25% of patients with UC as their most bothersome symptom.⁸ However, this is under-recognised by clinicians, many of whom report stool frequency and urgency to be most

bothersome to patients.⁹ The presence of chronic pain, as the only presenting symptom, can also at times result in unnecessary exploratory surgery or a step up in medication.¹ Pain management was in the top ten questions identified by IBD patients and clinicians to be addressed by research in a priority-setting exercise.¹⁰ It would seem that there are a considerable number of people with IBD and unmanaged pain.

Whilst the exact origins of abdominal pain which persists despite good IBD disease control remain obscure, a variety of physical and psychological factors have been identified in previous research.¹¹⁻¹⁴ The IBD inflammation-related factors may include ongoing sub-clinical inflammation, central and visceral post-inflammatory sensitisation, small intestinal bacterial overgrowth, strictures, stenosis and adhesions, food intolerances and bowel dysmotility. In animal models, there is strong evidence for central nervous system plasticity following gut inflammation, with increased neuronal excitability.¹⁵ However, low grade inflammation does not seem to fully explain altered perception of the gut pain as people with UC have less sensitivity compared to other groups, for example those with irritable bowel syndrome (IBS).¹⁶

Pain may be modulated by central factors such as psychological symptoms (e.g. stress, anxiety, depression, poor coping), sleep disturbance, medications and could arise from other medical conditions (e.g. gallstones, renal calculi, ischaemia, neoplasia).¹¹ In children and adolescents with IBD, depression often predicts abdominal pain,¹⁷ although the direction of the relationship is unclear. Studies in animals have found that intestinal inflammation induces anxiety and depression-like behaviours.¹⁸ The likely combination of factors suggest that IBD pain should be managed as a biopsychosocial problem.^{11, 18}

Abdominal pain in IBD has often been ascribed to co-existing IBS, where pain is considered a cardinal feature.^{16, 19} The overlap between IBD and IBS has proven difficult to disentangle. Some of the chronic abdominal pain in IBD has been reported to be due to IBS-type symptom patterns,²⁰ with 35% of people in remission meeting IBS diagnostic criteria, 46% in those with CD, and 44% during active disease.¹⁹ In a hospital cohort, 70% of patients with IBD have been

found to meet criteria for IBS.²¹ IBS patients have shown higher scores on the Crohn's activity disease index (CDAI) compared to CD patients, as abdominal pain and well-being are the predominant sub-scores in this measure²². However, the Rome diagnostic criteria for IBS are controversial when applied to IBD, especially as they include altered bowel habit and altered stool consistency. In UC, brain response to visceral pain during rectal distension has been found to be similar to healthy controls rather than those of IBS patients, suggesting that chronic colonic inflammation is not necessarily associated with increased afferent input and hypersensitivity.²³ Ascribing abdominal pain in IBD patients in remission to IBS does not help to relieve the pain, as interventions for IBS pain management remain largely untested in the presence of IBD.²⁴

The use of analgesics in IBD is problematic as many have the potential to exacerbate symptoms, cause gut-related side effects (e.g. paralytic ileus, slow motility) or mask a relapse.²⁴ Some patients use opioids for pain control; however they may not have substantial or lasting benefit, and patients may be faced with stigma and being labelled as 'addicted'.²⁵ The exact number of those using opioids for IBD pain management is unclear; however in CD, the proportion of opioid users for analgesia has been reported between 5% and 13%^{26, 27}. In a European cohort, 14.7% of IBD patients used opioids²⁸. In a specialised tertiary IBD centre in the United States, 28% were reported to be opioid users, with women, those with more than two surgeries and people with depression, anxiety or a history of abuse more likely to be using opioids for pain relief.²⁹ Antispasmodics may have a role in managing abdominal pain, but this has not been systematically studied in IBD²⁴ and there is also a potential risk of worsening bowel dysmotility.¹¹

A tendency to catastrophise and use emotive coping have been associated with greater pain severity and functional disability in both adolescents³⁰ and adults with IBD.²¹ These dysfunctional cognitions and negative coping strategies for pain may potentially be responsive to modification via cognitive behavioural therapy (CBT).³⁰ The possible under-recognition of the symptom of pain by clinicians, combined with patients not seeking help as they believe

that 'nothing can be done' leads to pain being under-diagnosed and not effectively managed. Additionally, inconsistencies and considerable variation in how pain is assessed in IBD may further contribute to its under-recognition and under-reporting, both in clinical practice and research.³¹

With IBD often having an onset early in life, chronic abdominal pain may have a great illness burden and a negative impact on quality of life. Recognising patient reported outcomes such as pain is integral to improving patient quality of life, which is now routinely applied as an outcome measure in IBD clinical trials.^{32 33} Systematic reviews have examined psychological interventions for the general treatment of IBD;³⁴⁻³⁶ psychological interventions for abdominal pain in children and adolescents (non-IBD population);^{37, 38} and internet delivered psychological therapies for the management of chronic pain in adults.³⁹ None of those reviews has addressed interventions for the management of pain in IBD. As there were no ongoing reviews identified on the Prospero database of prospective protocols for systematic reviews (<http://www.crd.york.ac.uk/PROSPERO>), [accessed 14.03.16], this review was prospectively registered (ID number: 24873).

Aims

To provide a comprehensive review of **non-disease modifying** interventions for abdominal pain in patients with IBD.

Methods

A series of searches were conducted with the last search on 5 February 2016 via OVID: MEDLINE (1946 to Feb 2016 week 1), EMBASE (1974 to Feb 05 2016), and PsycINFO (1806 to Feb 2016 week 1); via EBSCO: CIHAHL (05 Feb 16); and the Cochrane Library. Both medical subject heading (MeSH) and free-text search terms were used to maximise citation retrieval. The search combined two parameters: IBD (IBD, inflammatory bowel disease or ulcerative colitis or Crohn's disease) and abdominal pain. Interventional studies of any design (randomised controlled trials (RCTs), quasi-randomised controlled trials, non-randomised

controlled trials, pilot and feasibility studies) and cross sectional studies were included. The rationale for including all study designs was based on the preliminary searches indicating that only limited evidence was available. Studies were excluded if their primary aim was to modify disease activity or if pain was reported only within a composite score (such as an IBS composite score) rather than reported separately (Table 1). Our initial criteria were to include only studies where IBD participants were in remission. However, this yielded a very small and partial review, and therefore studies which included patients with active disease (or did not report disease status) were also included. Thus, studies where the primary aim was not to modify disease activity and which reported pain as a separate outcome were included, whether or not they reported disease activity and whether or not they included participants with active IBD.

The literature search process (Figure 1) followed PRISMA guidelines.⁴⁰ The retrieved references were imported to Endnote bibliographic software. After removing duplicates ($n = 921$), 5552 citations remained. All titles were screened by CN and excluded if apparently irrelevant. The remaining 32 abstracts were read and assessed against the inclusion criteria by two researchers (CN & WCD) and three were excluded. Hand searches of the reference lists of identified papers provided four additional references.

The remaining 30 papers were read in full and reviewed independently by CN & WCD. This resulted in 15 studies being excluded.⁴¹ Details of the excluded papers and reasons for exclusion are provided in an online supplementary table (Table S1). For one abstract,⁴² where the full paper was not published, an effort was made to acquire the full text electronically from the author. However, as we were unable to contact the author, the abstract was excluded.

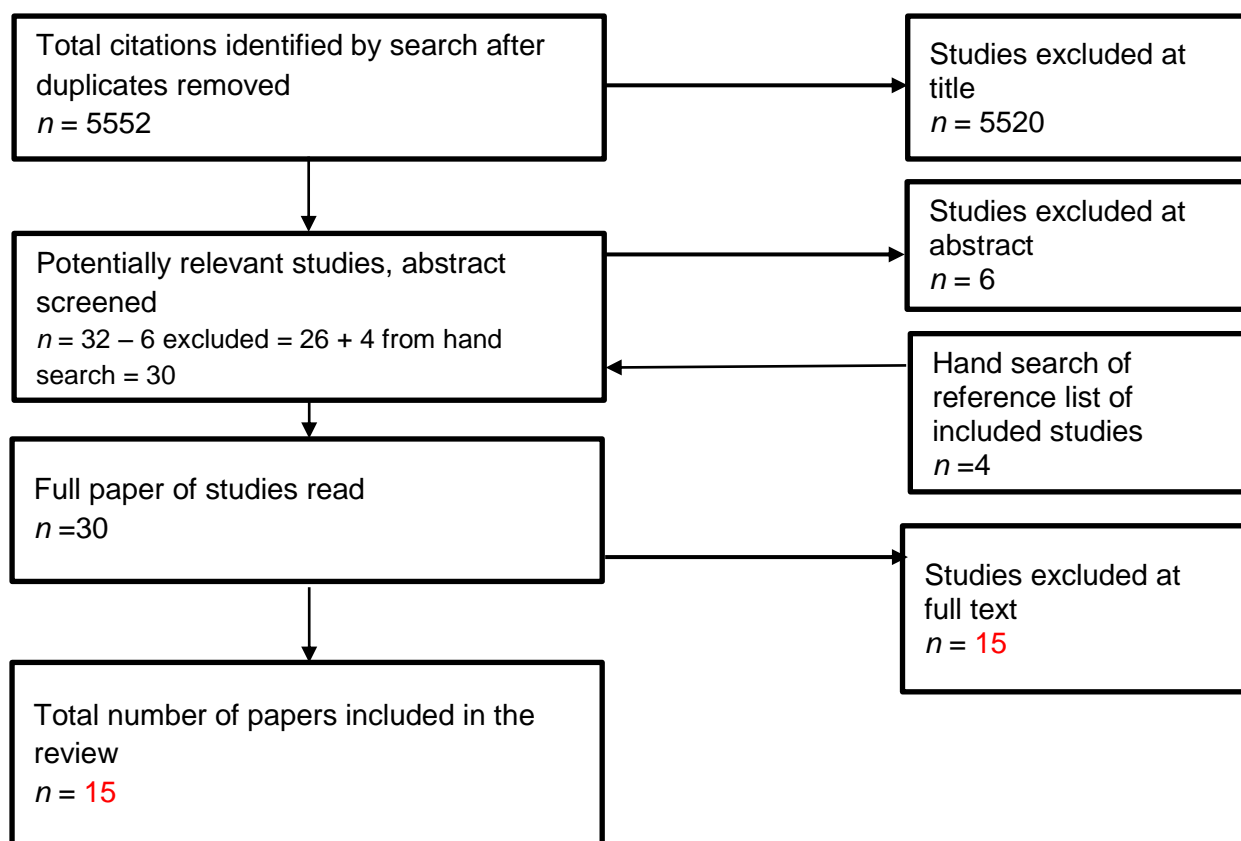


Figure 1: PRISMA flowchart of citation retrieval and selection process.

Quality appraisal

Fifteen studies were included in the review. The Critical Appraisal Skills Programme [CASP] assessment tools specific to the methodological design of each study (RCTs and cross-sectional studies) were utilised to assess the studies' quality.⁴³ Two researchers (CN and MA or LS) appraised the studies independently and then agreed the final scores. Points were deducted if: specific objectives and hypotheses were not stated; measurement tools were not validated; insufficient details were provided regarding the methodology or data analysis; evidence of selective reporting of the findings was present; or limitations were not addressed. **Two** papers were classified as high quality,^{44 45} nine as medium,⁴⁶⁻⁵⁴ and four as low quality,⁵⁵⁻⁵⁸ see Table 2. Due to the small number of retrieved citations, no studies were excluded from the review based on their quality. **Reporting of disease activity or remission status of patients was absent in eight included studies.**

Results

Of the 15 papers included in the review (Table 2), two were cross sectional surveys ($n = 555$ respondents)^{44, 52} and 13 were intervention studies ($n = 370$ total participants with IBD).^{45-51, 53-58}

Three studies had a primary focus on pain, i.e. the intervention was intended specifically to target abdominal pain,^{48, 50, 55} and the remaining studies measured abdominal pain as a secondary outcome. The sample size of controlled trials ranged from 9 to 72. Most studies involved adults only, whilst in three studies the participants were adolescents as well as one parent per adolescent.^{50, 54, 55} A range of pharmacological (metronidazole, ciprofloxacin, **transdermal nicotine**, and loperamine oxide which is a prodrug for loperamide),^{45, 46, 58} non-pharmacological (stress management, problem solving, cognitive coping skills, progressive muscle relaxation biofeedback, education on IBD),^{47, 50, 53-56} and dietary supplements (processed and unprocessed cereals, **carbohydrate supplement**, consumption of alcohol)^{48, 51, 57} interventions were tested. Three studies reported the effect of cannabis on abdominal pain among other symptoms.^{44, 49, 52} Due to the wide array of interventions being tested, different research designs, outcome measures and methods of data analysis, it was not possible to pool the results in meta-analysis. Only 2 of the 15 included studies explicitly included IBD patients in remission^{47, 58} and eight studies did not specify disease activity⁶¹⁻⁶⁶ (Table 2). These studies were included as review authors judged the study as not addressing pain linked to an acute disease flare.

The results of the review are presented grouped by type of intervention and summarised in Table 2.

Psychological interventions

Six studies used psychological approaches.

McCormick *et al*⁴⁹ used coping skills training (one day training plus 6 weeks of web-based homework and 30 minute weekly chat sessions) in a controlled intervention study. The aim

was to reduce pain and somatic symptoms in 24 adolescent girls with IBD plus a parent, allocated to intervention ($n = 13$) or waiting list control ($n = 11$). Allocation was based on availability to attend sessions. There was no significant difference in pain score between the groups after the intervention. However, the intervention group did show improvements in somatic symptoms and adaptive coping skills ($p = 0.007$). A lack of true randomisation precludes attributing improvements directly to the intervention. Disease activity was not specified. Psychosocial and disease factors associated with participation and attrition in this study were later investigated,⁵⁹ finding that higher levels of reported abdominal pain, functional disability and somatic complaints were related to lower participation. As this second paper⁵⁹ related only to attrition and not the intervention it was not included in the review.

A behavioural stress management programme in 45 patients with non-active CD measured pain as a secondary outcome in three treatment groups: therapist-led stress management, self-directed stress management or control.⁴⁷ Both intervention groups had reduced abdominal pain ($p < 0.05$) with improvement maintained up to 12 months in the therapist-led and self-directed stress management groups.

Another study used a multi-component intervention. Following a pilot phase (four participants), 23 people with IBD seeking help for stress and other symptoms including pain were randomised to 12 one-hour sessions of relaxation, biofeedback, cognitive coping strategies and education, or symptom-monitoring control.⁵⁶ Both groups improved their abdominal pain, with the symptom monitoring control group improving by significantly more than the intervention group for abdominal pain and other symptoms ($p < 0.01$). People with CD had more pain at baseline than those with UC and improved by significantly more ($p < 0.001$) than participants with UC, indicating a better response to treatment by CD patients.

Shaw and Ehlich (1987) randomised 40 UC patients with chronic pain into a group-based progressive relaxation intervention or a waiting list. Immediately following treatment and at 6-

week follow up, the treatment group reported less pain, greater pain relief, fewer words to describe pain, less distress due to pain and less frequent pain episodes.⁶⁹

Six adolescent girls and their parents (one parent per girl) participated in a 10-session skills based group intervention targeting pain, coping and functional disability.⁵⁵ Four of the six reported less pain at 6 months.

Another cohort study involving a younger sample (11-17 years),⁵⁴ examined the effects of a tailored CBT intervention targeting IBD-related concerns on anxiety and IBD symptoms. The intervention resulted in 50% of participants no longer fulfilling their principal anxiety diagnosis. Reductions were also seen for disease and pain severity, with pain reports changing from moderate to mild at post-treatment. None of these last three studies reported disease activity.

Dietary interventions

Three studies explored diet. A double-blind cross-over RCT compared processed vs. unprocessed cereals to decrease intestinal secretions in participants with short bowel syndrome; 23 of the 26 participants had IBD, but the results are not reported separately.⁵¹ Neither intervention had an effect on abdominal pain which was not reported separately for IBD participants. Disease activity was not reported.

Anecdotal reports about the exacerbation of abdominal pain and dyspepsia following consumption of alcohol were tested by Hey *et al.*⁴⁸ They tested 20 people with inactive CD and 12 healthy controls with five alcohol challenge interventions; over fifteen minutes at two week intervals. Male participants consumed 36g and females 24g of alcohol. No healthy volunteer experienced abdominal pain; pure ethanol produced the least pain in CD participants, with increased pain apparently associated with drinks with a higher sugar content (beer and alco-pop) rather than wine.⁴⁸ However, the study was small and could not be blinded.

In a cohort intervention study, 20 participants with IBD were given a fermentable polysaccharide supplement known to have positive prebiotic properties. Glucomannan hydrolysates from Konjac flour was given to participants for 14 days in an unblinded case series (3.3g/day high molecular weight carbohydrates for 14 days).⁵⁷ Reduced abdominal pain was reported at day 7 and 14 ($p = <0.001$). The supplement was well tolerated. Disease status of patients was not reported.

Pharmacological interventions

Six studies explored pharmacological interventions. One RCT compared two antibiotics in 29 participants with CD (with both active disease and in remission) and confirmed small bowel bacterial overgrowth.⁴⁶ Fifteen participants reported abdominal pain before intervention and 7/15 were improved by antibiotics, with no difference between two antibiotics. The pain score was improved significantly across both groups ($p = 0.04$).

In another RCT, 72 participants with active UC were randomised into a transdermal nicotine patch or placebo group and examined the effects on symptom improvement.⁴⁵ Over a 6 week period, participants were given patches releasing 5mg or 15mg of nicotine over 16 hours (nicotine doses were given in a stepwise manner to alleviate side effects). Abdominal pain was scored 0-2. Patients in the nicotine group reported significantly less abdominal pain compared to the placebo group ($p = .05$). Details of abdominal pain scoring were not provided.

Loperamide oxide (initial dose 2 mg and then 1 mg after each unformed stool; mean daily dose 2.7 mg) was compared to placebo for one week to treat chronic diarrhoea in 34 patients with CD.⁵⁸ The investigator assessed pain and this decreased significantly with loperamide oxide ($p = 0.02$ vs. baseline) but not with placebo. Patients did not complete a separate pain score. Although disease activity was not specified, patients had stable diarrhoea symptoms. No mention was made of blinding.

Two cross sectional surveys reported the use of marijuana for 'medicinal purposes' in people with IBD.^{44, 52} In a survey of 292 IBD patients, 36 (12.3%) were current users and 114 (39%) were past users. Among current and past users, 16.4% felt that marijuana was very useful for the relief of abdominal pain. The study took place in a US state where marijuana use was legal for CD but not UC.⁵² Disease activity status was not specified.

The second US survey of 319 IBD patients with both active and non-active disease, found that 17.6% reported that they had used marijuana for disease symptoms, with 83.9% of users reporting that it improved abdominal pain. It also had beneficial effects on abdominal cramping and joint pain. Cannabis use for more than six months at a time was a strong predictor of requiring surgery for CD patients. The authors recommended caution in the use of cannabis by CD patients until further studies explore effectiveness and safety.⁴⁴

Thirteen participants inhaled cannabis in a single-arm open-label pilot study.⁴⁹ At baseline, average Harvey Bradshaw Index (HBI) scoring for patients was 11.36, indicating active disease, and pain was reported as severe or very severe by 10 patients. After 3 months of treatment one patient reported very severe pain, 4 reported severe and the remaining eight reported mild to moderate pain severity. Average HBI score decreased from 11.36 to 5.72, with main improvements seen in the domains of abdominal pain and general well-being.

Discussion

This is the first systematic review of interventions for abdominal pain in IBD. Pain is a substantial problem for many people with IBD, but despite the high prevalence, abdominal pain in IBD has been the subject of very few intervention studies, especially when compared to other long term conditions. A recent research priority setting exercise identified that pain needs to be further explored and methods of pain management need to be identified and tested.¹⁰ It is evident from this review that the types of interventions carried out for pain in IBD vary considerably and few have been based on an explicit theoretical model of pain in IBD. In addition to this, study design and methodological quality, pain outcome measure

utilised and measurement of disease status differ between studies. Nonetheless, it appears that they can be classified into physical and psychological interventions.

Physical interventions for pain identified in this review include pharmacological treatment, dietary supplements and use of marijuana. Antibiotics for the treatment of small intestinal bacterial overgrowth⁴⁶, **transdermal nicotine patches**⁴⁵ and loperamide oxide⁵⁸ all reported reduced abdominal pain. Mixed evidence was found for the effects of dietary intervention; **a fermentable carbohydrate supplement (Glucomannan hydrolysates)** reduced abdominal pain after a 7-day period⁵⁷ and alcoholic drinks with higher sugar content were associated with greater pain.⁴⁸ However, an intervention investigating processed cereals and intestinal secretions found no effects on abdominal pain.⁵¹ One excluded study (pain outcomes were not reported separately) was a double-blind cross-over RCT of an Immunoglobulin G exclusion diet in 40 patients with active or inactive CD.⁶⁰ There was no difference in a composite pain, general wellbeing and stool frequency score and a high drop-out rate; however the authors report in their abstract that abdominal pain reduced. Dietary approaches similar to those used for IBS are reported anecdotally to help abdominal discomfort in IBD.⁶¹ Use of marijuana is reported by people with IBD as effective for abdominal pain^{44, 52} but users are undoubtedly self-selected and may have motivation for reporting medicinal benefit, even where surveys are anonymised. This warrants further evaluation.

There is some previous research on cognitive, emotional and behavioural factors associated with pain severity in IBD.^{21, 30} This review found a number of psychological interventions: both self-directed and therapist-led stress management interventions resulted in reduced abdominal pain⁴⁷ and a 10-week manualised programme examining cognitions, emotions, stress and behaviours led to less reported pain in 4 out of 6 adolescent girls.⁵⁵ Integrating disease-specific concerns into CBT treatment also had beneficial effects in reducing pain as well as anxiety in a sample of children and adolescents with IBD.⁵⁴ Results for a coping skills training intervention⁵⁰ and another multi-component behavioural treatment package

(including biofeedback, relaxation and cognitive coping) ⁵⁶ were less promising, although McCormick *et al.*⁵⁰ did find improved coping skills and fewer somatic symptoms. Schwarz and Blanchard ⁵⁶ found that the control group intervention of symptom monitoring reported a greater reduction in pain than in the intervention group.

Social learning has been suggested as a basis for treating IBD pain, incorporating elements of CBT, social learning and relaxation in a multi-modal intervention,⁶² but this approach does not so far seem to have been used in studies.

Two studies considered for inclusion but excluded at the full paper stage focused on people with IBD with concomitant symptoms of IBS.^{63, 64} Both studies were excluded as no separate measure of pain was included, only a composite IBS score. However, these are noteworthy as pain is a substantial element of IBS scores. In Berrill *et al.*'s study of mindfulness therapy, no difference in IBS score at follow-up was found between 38 intervention and control participants who had IBS at baseline. ⁶³ Piche *et al.* compared use of osteopathy with no intervention in 38 patients with CD who were also on 8-weekly infliximab. Severity of IBS symptoms was significantly improved up to day 60 in the intervention group.⁶⁴ These are mentioned here as it would be interesting to explore interventions for IBS symptoms in IBD patients and measure pain directly.

Lastly, three relevant studies were published after the database search had been carried out. ^{64, 6, 65} Volz *et al.*'s RCT study investigated the effects of transcranial stimulation on reducing abdominal pain in IBD patients and significant reductions in abdominal pain, pain catastrophising and IBS symptom scores were found in a sample of 20 patients.⁶⁵ Two retrospective studies of a low fermentable carbohydrate (FODMAP) diet have also reported pain benefits. Maagaard had responses from 40 of 109 IBD patients put on a low FODMAP diet a mean of 16 months previously. 63% reported that abdominal pain responded to the diet, but long term adherence was poor. ⁶⁶ Prince *et al.* conducted a chart review of symptoms in 88 IBD patients referred for low FODMAP diet, a minimum of 6 weeks after

referral. The proportion reporting moderate or severe abdominal pain fell from 43% to 18% ($p < 0.001$).⁶⁷

There are limitations of both the included studies and of the review. Firstly, most included studies were of low to medium quality, reducing the strength of evidence within this review. In particular, studies' methodological limitations included small samples, high attrition rates and non-validated pain measures. Most studies did not specify disease status, despite most implying that patients were not in acute flare. This, along with the varied study design and intervention type, made comparability between studies' findings difficult. Additionally, some studies assessed overall pain rather than abdominal pain specifically. On the other hand, strengths of the review lie in the transparent process of data extraction and paper screening, with independent researchers carrying out quality appraisal processes.

Recommendations for clinical practice

It is important that pain in IBD is acknowledged and assessed. While the first step is undoubtedly IBD disease control, clinicians should recognise that good disease control does not always mean that pain resolves. Proactively asking about this symptom in remission and then taking it seriously is important. At present, there is limited evidence to guide management, but referral to a dietitian or for psychological support might be considered, depending on patient preference and local availability.

Recommendations for future research

In an attempt to gain a better understanding of pain in IBD and effective treatment approaches, a number of recommendations for future research are presented. The use of better powered studies, more rigorous methodological techniques in Randomised Controlled Trials and the use of validated pain measures is required to strengthen evidence in this area. Future studies should specify pain site (e.g. abdominal, joint or other pain) and indicate disease status of participants. In particular, pain outcome measures should strive to address levels of emotional well-being, physical and social interaction, work status and overall pain

experience when assessing pain. Further research would be informed by research on pain in other chronic conditions such as inflammatory and relapsing-remitting diseases. Exploring the similarities and differences between abdominal pain in IBS and IBD in remission is important in determining whether IBS-pain interventions may be suitable for IBD. A number of psychotherapeutic interventions have been carried out in paediatric IBD research on reducing depression and disease-related outcomes which could also be informative for adult populations.⁶⁸⁻⁷⁰ Finally, a better understanding of the range of contributing factors to pain is required, to enable interventions to be designed based on sound theoretical principles. For example a recent paper has explored the interacting effect between pain and fatigue.⁷¹ The interventions considered in the included studies did not fully consider the interplay of factors causing pain. It is likely that a range of pharmacological, non-pharmacological and dietary manipulation will provide the best effects for patients, yet the interrelationship between these groups of factors is not well understood and needs further investigation.

Conclusions

Despite IBD patients' frequent reports of chronic abdominal pain, only a few interventions have been tested in this population to alleviate the symptom or to improve pain perception and management. The current limited evidence suggests that learning to manage pain through relaxation or cognitive techniques may be the most promising approaches, possibly with some individualised dietary changes. Pharmacological treatment and marijuana use show some short-term benefits. This scarcity of evidence warrants further research into the development and testing of interventions for abdominal pain management in IBD.

Declaration of interests: None of the authors has a conflict of interest to declare.

Authorship Statement

- (i) **Guarantor of the article:** Christine Norton
- (ii) **Specific author contributions:** CN and WCD designed the study and drafted the protocol; CN and WCD conducted the searches; CN, WCD, MA and LS extracted data; CN, MA and LS conducted quality appraisal of included studies. All authors contributed to manuscript preparation.
- (iii) All authors approved the final version of the manuscript.

Figure legend

Figure 1: PRISMA flowchart of citation retrieval and selection process

Table 1 Inclusion and exclusion criteria for studies in the review

Facet	Inclusion	Exclusion
Population	Individuals with IBD At least some participants reporting symptom of abdominal pain Any age	We had intended originally to exclude participants with active IBD. However, it was not possible to apply this as most studies did not included a measure of disease activity. Individuals with IBD pain only in other locations (e.g. joint pain)
Intervention	Any interventional or observational studies seeking to improve pain or reporting approaches which might induce or provoke pain. Interventions may be Health Care Profession or patient-led.	Medication or other intervention intended to induce or maintain IBD remission or reduce IBD inflammation
Control / Comparison	No comparison or any alternative intervention	
Outcomes	Pain score, questionnaire, or participant evaluation of pain as a primary or secondary outcome measure	No pain outcome reported, or not reported separately from other composite scores or outcome measures
Study Design	Any	Reviews, editorials, letters or conference abstracts (unless providing sufficient data to be included in the review)

Key: IBD - inflammatory bowel disease

Table 2. Summary of included studies

Author, design, reference	Population	Intervention	Pain measure and outcomes	Comment
Castiglione, RCT, ⁶²	29 CD with positive breath test for small bowel bacterial overgrowth; 13 active CD, 16 in remission; 15 with baseline abdominal pain	Oral Metronidazole 250mg tds vs oral Ciprofloxacin 500mg bd both for 10 days	Pain on 0-3 scale at one week later: no difference between groups	Medium quality study
Garcia-Vega, RCT, ⁶³	45 CD in remission	A: psychologist stress management (relaxation, problem solving and coping) B: self-directed stress management (written guide + relaxation tape) C: control	Pain scored for frequency and intensity. A & B: reduction of abdominal pain (both $p < 0.05$). C: no significant change Maintained at 12 months	Medium quality study. Non-validated pain score
Hayutin, cohort intervention, ⁶³	2 UC, 4 CD. Disease activity not reported.	10 weekly session manualised programme - cognitions, emotions, stress and behaviours	abdominal pain index post treatment: 4/6 reported less pain. Mean pain score reduced. 6 months: 4/6 reported less pain.	Low quality study
Hey, crossover study, ⁶⁴	20 CD in remission throughout the study period, 12 healthy controls.	Alcohol consumption - 2 week intervals investigating effect of red wine, white wine, Smirnoff Ice, Elephant Beer and ethanol.	Self-reported pain (scored 0-3). Smirnoff Ice and Elephant beer resulted in more pain in CD ($p < 0.05$).	Medium quality study
Lahat, open-label pilot study, ⁶⁵	2 UC, 11 CD. Average Harvey Bradshaw Index score 11.36 (active disease)	Inhaled cannabis treatment over 3 months	SF-36, EQ-5D & Harvey Bradshaw Index (pain subscales).- After 3 months treatment very severe pain reported by 1 patient, severe by 4 and mild to moderate by the rest.	Medium quality study. No controls, unblinded
McCormick, RCT, ⁶⁶	13 CD, 8 UC, 3 IC. Disease activity not reported.	Coping skills training, one day manualised cognitive behavioural intervention (6 hours), 6-week web-based component homework & weekly 30-minute online chat.	Abdominal pain index: no significant differences between groups on pain or somatic symptoms.	Medium quality study
Pagoldh, RCT, ⁶⁷	26 short bowel syndrome – of which 23 IBD: 11 UC, 12 CD. Disease activity not reported.	Group A: diet supplement of processed cereals vs. Group B: unprocessed cereals 1g/kg body weight in 24 hours, 3 daily doses.	Self-evaluated descriptive survey - No difference in pain scores between groups	Medium quality study.
Pullan, RCT, ⁴⁵	72 UC, active disease (global clinical score (0-3) nicotine group = 1.5, placebo = 1.4)	Transdermal nicotine patches (releasing 5 or 15mg of nicotine over a 16 hour period) vs placebo. Doses increased over intervention period for experimental group in stepwise manner.	The patients in the nicotine group had less abdominal pain ($p = .05$). At 6 weeks abdominal pain (scored 0-2) for nicotine group = 0.3 and placebo group = 0.6	High quality study.

Ravikoff Alegretti, cross-sectional, ⁶⁸	102 UC, 177 CD, 13 IC. Disease activity not reported.	Self-initiated marijuana use.	Self-rating of pain relief - Of past and current users, 32/48 reported it was very helpful or gave complete relief for abdominal pain; 11/48 reported it as ineffective, or slightly or moderately helpful	Medium quality study. Uncontrolled, self-selected population. No data on dose
Reigada, cohort study, ⁷⁰	9 IBD – 8 CD. Disease activity not reported.	12 weekly individualised Cognitive Behavioural Therapy and IBD-specific anxiety including relaxation, cognitive restructuring and exposure exercises.	VAS (0-8) - Reduction in pain symptoms was reported from moderate to mild pain symptoms from pre-treatment to post-treatment.	Medium quality study
Schwarz & Blanchard, RCT, ⁷²	21 IBD – 10 CD, 10 UC, 1 IC. Disease activity not reported.	12 one-hour sessions; progressive muscle relaxation, thermal biofeedback, training in cognitive coping and education.	Daily 8-symptom rating diary including abdominal pain on 5 point scale - Both groups reduced abdominal pain, but symptom monitoring control group reduced by more than intervention group.	Low quality study. 2 dropped out of control in RCT. Wait list then crossed over to intervention and symptoms worsened
Shaw & Ehrlich, RCT, ⁶⁹	40 UC with chronic pain for at least 6 months. Disease activity not reported.	6 weekly 75 minute training sessions; progressive relaxation in groups of 5-8, with home audio tapes to practice at home daily.	McGill Pain Questionnaire - Post treatment and following 6 weeks, treatment group showed less intense pain rating, greater pain relief, fewer words to describe pain, less distress due to pain and less frequent pain episodes.	Medium quality study. Method of randomisation unclear. Not blinded
Storr, cross-sectional, ⁶¹	189 CD, 53 UC, 21 IC. Both active and inactive disease. Severe disease activity in users/non-users = 31.1%/22.1%.	Self-initiated cannabis use.	5 point pain score: 0 = none 4 = severe and preventing daily activities. 47/56 users (83.9%) reported cannabis helps abdominal pain.	High quality study
Suwannaporn, cohort intervention, ⁷³	34 IBD. Disease activity not reported.	Glucomannan hydrolysates from konjac flour 3.3g in 150 mls water daily for 14 days (soluble fibre and prebiotic properties).	5 point pain score: 0 = none 4 = severe and preventing daily activities. Pain improved at day 14.	Low quality study. Non-validated pain score used
Van Outryve & Touissant, RCT, ⁷⁴	34 CD with stabilised non-diarrhoeal symptoms. Disease activity not reported.	Initial 2mg loperamide oxide and then 1 week loperamide oxide 1mg after each unformed stool, up to 8mg/day max.	Investigator rating 0-3. Investigator rated abdominal pain improved compared to baseline.	Low quality study. No patient rating of outcomes.

Abbreviations: bd – twice a day; CD – Crohn’s disease; EQ-5D – EuroQool; IBD – inflammatory bowel disease; IC – indeterminate colitis; tds –three times a day; RCT – randomised controlled trial; SF-36 – short form 36; UC – ulcerative colitis; VAS – visual analogue scale, NA – information not available.

Prisma checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8, Table 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	N/A

Section/topic	#	Reported on page #	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8 & 10, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097³⁴

For more information, visit: www.prisma-statement.org.

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