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Interventions for the management of abdominal pain in Crohn's disease (Protocol)

Iheozor-Ejiofor Z, Gordon M, Akobeng AK

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[Intervention Protocol]

Interventions for the management of abdominal pain in Crohn's disease

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the efficacy and safety of interventions for managing abdominal pain in people with Crohn's disease.

BACKGROUND

Description of the condition

Crohn's is a remitting and relapsing disease of the gastrointestinal tract. It affects over 3.5 million young people and adults in the USA and Europe (Kaplan 2015). Active Crohn's disease presents as abdominal pain, fatigue, weight loss and diarrhea. It has no known cure, but can be managed, therefore, places a huge financial burden on healthcare systems. The annual care costs of irritable bowel disease (IBD) to the National Health Service (NHS) was estimated at over GBP 1 billion in 2010 (RCP 2012). For Crohn's disease alone, this amounts to over GBP 6000 per patient annually (Ghosh 2015). Treatment of the disease may involve surgical intervention or immunosuppression using thiopurines and anti-tumor necrosis factor (anti-TNF) metabolites (Gjuladin-Hellon 2019). These interventions aim to induce remission, maintain remission and manage the symptoms (Greenley 2013).

Abdominal pain is a common and debilitating symptom of Crohn's and other IBDs that is multifaceted. It could be a symptom of relapse of the disease, due to adverse effects of medication, surgical complications and strictures or adhesions secondary to IBD (Srinath 2012). In the absence of the aforementioned factors, around 20% to 50% of people with Crohn's in remission still experience pain (Bielefeldt 2009). This has been attributed to functional abdominal pain disorders (FAPD) such as irritable bowel syndrome (IBS), functional abdominal pain, abdominal migraine and functional dyspepsia (Odes 2017), although the definition of such disorders involves the explicit exclusion of pathology such as IBD. There is a lack of evidence to indicate whether there is a specific variant of functional pain coexisting within people with IBD or a separate pain disorder that can be attributed to IBD pathologic mechanisms. The etiology and management of abdominal pain in Crohn's disease, therefore, may vary in ways that cannot be fully explained. It may also vary in adults and children. Finally, it may also be influenced by disease activity.

Description of the intervention

Pharmacological interventions

Medication for Crohn's disease 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, non-steroidal anti-inflammatory drugs (NSAIDs), laxatives, antidepressants, antiemetic agents, cyclo-oxygenase-2 inhibitors (COX-2), and psychoactive drugs such as cannabis and opioids (Srinath 2012). Due to potential adverse effects of some of these drugs, short-term use is advised.

Non-pharmacological interventions

Non-pharmacological interventions used in managing pain may include dietary, psychological, lifestyle advice and alternative medicine. These interventions are generally considered less invasive and may be used as adjuvant treatment. Cognitive behavioral 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 and as such it is key to consider the specific evidence and conceptual alignment of the approach delivered to understand 'what' the therapy was, as

well as 'whether' it was effective. Alternative treatments such as acupuncture and TENS, which have been used with other conditions such as IBS, are becoming more commonly used in people with IBD albeit with limited evidence (Srinath 2012). Dietary interventions studied include FODMAP (Fermentable Oligo-, Di-, Monosaccharides And Polyols) and supplements with prebiotic properties; however, there seems to be weak conflicting evidence on their effectiveness (Norton 2017).

How the intervention might work

The mechanism of action of different interventions depends on the nature or cause of the abdominal pain. Antispasmodics suppress intestinal spasms which cause pain from inflammation or obstruction (Srinath 2012). Pain caused by strictures can be eliminated by the introduction of foods which can pass through with ease thereby preventing intestinal pain (Srinath 2012). Psychological techniques such as cognitive behavioral therapy tend to help people with Crohn's disease change negative behaviors and provide coping mechanisms which might be worsening their pain (Norton 2017). There are concerns around the safety of these interventions. In addition to offering short-term relief, there seems to be concerns among people with IBD about the stigma of addiction associated with the use of opioids. The use of opioids in chronic pain can also lead to people exhibiting withdrawal symptoms which are similar to Crohn's disease symptoms (Pauly 2017). This may complicate further treatment. While some interventions such as neurochemicals and acupuncture have only been used in conditions such as IBS, others such as COX-2 inhibitors have been associated with little to no effect.

Why it is important to do this review

Abdominal pain in people with Crohn's disease can lead to depressive symptoms, a decline quality of life and an increase the use of healthcare facilities (Srinath 2012); therefore, effective pain management is 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). While several non-Cochrane systematic reviews have assessed interventions for pain management in IBD, currently none has assessed the efficacy and safety of these interventions in Crohn's disease. Even though this review covers interventions that have been previously assessed in published Cochrane systematic reviews in the group portfolio (Iheozor-Ejiofor 2019; Kafil 2018; Limketkai 2019; Timmer 2011), the focus is only on studies that have been conducted for the purpose of providing relief for abdominal pain.

OBJECTIVES

To assess the efficacy and safety of interventions for managing abdominal pain in people with Crohn's disease.

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

with other active interventions or standard therapy, placebo or no therapy. We will exclude studies that do not report on any abdominal pain outcomes.

Types of participants

People with Crohn's disease who are experiencing abdominal pain.

Types of interventions

- Pain-relieving drugs such as antispasmodics, antidepressants, laxatives, antidiarrheal agents, antibiotics, analgesics, antireflux agents, antiemetic agents, antimigraine agents, antihistaminic agents, serotonergic agents and psychoactive drugs.
- Behavior therapy, for example, cognitive behavioral therapy, hypnotherapy.
- Lifestyle advice, for example, advice on physical activity including exercise.
- Dietary interventions such as FODMAP; additional fiber intake; decrease in gas-producing foods; extra fluid intake; lactulose-, gluten-, histamine-free diet.
- Pre- and probiotics.
- Alternative medicines, for example, acupuncture, homeopathy, body-oriented therapy, musculoskeletal therapy (osteopathy/chiropractic), yoga.

Types of outcome measures

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 to adverse events.

Secondary outcomes

- Anxiety/depression.
- Adverse events (total of number of participants with any event)
- Serious adverse events (as defined by good clinical practice reporting within the primary study)

Timing of outcome measurement

Where outcomes are measured at multiple time points, we will subgroup them into three time periods: short-term (within one month of the intervention), medium-term (more than one month to six months) and long-term (more than six months).

Search methods for identification of studies

Electronic searches

We will search the following sources from the inception of each database to the date of search and will place 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;
- CINAHL via EBSCO (Cumulative Index to Nursing and Allied Health Literature);

- AMED (Allied and Complementary Medicine database) via Ovid;
- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization 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 will carefully check relevant systematic reviews for studies for potential inclusion in our review. In addition, we will scrutinize the references of included studies in our review. We will seek unpublished trials by contacting experts in the field and we will scan 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 will attempt to obtain translations of papers when necessary.

Data collection and analysis

We will carry out data collection and analysis according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Selection of studies

Two review authors will independently screen the titles and abstracts identified from the literature search. We will discard studies which do not meet the inclusion criteria. We will then obtain the full report of studies that appear to meet our inclusion criteria or for which there is insufficient information to make a final decision. Two review authors will independently assess these articles to establish whether the studies meet the inclusion criteria. We will resolve disagreements by discussion, with a third review author consulted if resolution is not possible. We will enter studies rejected at this or subsequent stages in the 'Characteristics of excluded studies' tables and record the main reason for exclusion.

Where studies have multiple publications, we will collate the reports of the same study so that each study, rather than each report, is the unit of interest for the review, and such studies have a single identifier with multiple references.

Data extraction and management

Two review authors will independently carry out data extraction using piloted data extraction forms. We will extract the following data from full-text articles that meet the inclusion criteria:

- trial setting: country and number of trial centers;
- methods: study design, total study duration and date;
- participant characteristics: age, sociodemographics, ethnicity, diagnostic criteria, pain location and total number of participants;
- 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 and sample size;
- funding source.

We will list all treatment arms in the 'Characteristics of included studies' table.

Assessment of risk of bias in included studies

Two review authors will independently assess all studies meeting the inclusion criteria for their risk of bias using criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The domains will be:

- 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 bias such as imbalance in participants' baseline characteristics.

We will judge the studies to be at low, high or unclear risk of bias for each domain assessed, based on the guidance in *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

After data extraction, the two review authors will compare the extracted data and discuss and resolve discrepancies before the data are transferred into the 'Characteristics of included studies' table. For cluster RCTs, we intend to judge risk of bias as prescribed in Section 16.3.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Measures of treatment effect

For the dichotomous outcomes, we will express treatment effect as risk ratios (RR) with corresponding 95% confidence intervals (CI). For continuous outcomes, we will express the treatment effect as mean difference (MD) with 95% CI. Where endpoint and change score are both reported, we will use endpoint scores for data analysis. However, if the studies assess the same continuous outcome in different ways, we will estimate the treatment effect using the standardized mean difference (SMD). We will present SMDs as standard deviations and interpret them as follows: 0.2 represents a small effect, 0.5 a moderate effect and 0.8 a large effect (Cohen 1988).

Unit of analysis issues

The participant will be the unit of analysis. For studies comparing more than two intervention groups, we will make multiple pairwise comparisons between all possible pairs of intervention groups. To avoid double counting, we intend to divide out shared intervention groups evenly among the comparisons. For dichotomous outcomes, we plan to divide up both the number of events and the total number of participants. For continuous outcomes, we will only divide up the total number of participants and leave the means and standard deviations unchanged. Cross-over studies will only be included if data are separately reported before and after cross-over and will use only pre-cross-over data. We do not anticipate finding any cluster RCTs; however, study data will only be used if the authors have used appropriate statistical methods in taking clustering effect into account. We will also exclude cluster RCTs in a sensitivity analysis to assess their impact on the results.

Dealing with missing data

We aim to contact authors where there are missing data or studies have not reported data in sufficient detail. We will attempt to estimate missing standard deviations using relevant statistical tools and calculators available in Review Manager 5 if studies report standard errors (Review Manager 2014). Studies that fail to report measures of variance will be judged at high risk of selective reporting bias.

Assessment of heterogeneity

We will scrutinize studies to ensure that they are clinically homogeneous in terms of participants, intervention, comparator and outcome. To test for statistical heterogeneity, we will use a Chi^2 test using a P value of less than 0.1 to give an indication of the presence of heterogeneity. Inconsistency will be quantified and represented by the I^2 statistic. The thresholds will be interpreted as follows (Higgins 2011):

- 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 will be minimized by using an inclusive search strategy. We will investigate publication bias using a funnel plot if there are 10 or more studies. The magnitude of publication bias will be determined by visual inspection of the asymmetry of the funnel plot. In addition, we will test funnel plot asymmetry by performing a linear regression of intervention effect estimate against its standard error, weighted by the inverse of the variance of the intervention effect estimate (Egger 1997).

Data synthesis

To summarize the study characteristics, we will conduct a narrative synthesis of all the included studies. We will then carry out a meta-analysis if we have two or more studies that have assessed similar populations, interventions and outcomes. We will analyze studies of children, adults and different subintervention types separately. We will use Review Manager 5 (Review Manager 2014). Study data will be synthesized using the random-effects model if there is statistical heterogeneity (I^2 greater than 0%), otherwise we will use the fixed-effect model. We will combine effect estimates of studies which report data in a similar way in the meta-analysis. We will pool RRs for dichotomous outcomes and MDs or SMDs for continuous outcomes alongside 95% CIs. Where we are unable to carry out a meta-analysis (e.g. due to lack of uniformity in data reporting), we will present a narrative summary of the included studies.

Subgroup analysis and investigation of heterogeneity

If there is heterogeneity, we will investigate possible causes and address them using methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will undertake subgroup analyses of potential effect modifiers if there are 10 or more studies. We have identified several potential modifiers of effect:

- disease activity (active versus inactive disease);
- pain location;

- disease location.

It is recognized that the nature of the studies likely to be included in this review may be heterogeneous in a number of key clinical and methodologic ways that cannot be fully predicted. If we identify such factors and they become relevant to ensure integrity of the analysis, we may modify this list and report them fully.

Sensitivity analysis

Where possible, we will undertake a sensitivity analysis on the primary outcome of 'treatment success', to assess whether the findings of the review are robust to the decisions made during the review process. In particular, we will exclude studies at high or unclear risk of selection bias due to allocation bias and performance bias, from analyses that have a mix of studies with different risk of bias judgments. Where data analyses include studies with reported and estimated standard deviations, we will exclude those with estimated standard deviations to assess whether this affects the findings of the review. We will investigate whether the choice of model (fixed versus random) may have affected the results.

GRADE and 'Summary of findings' table

We will present the main results in a 'Summary of findings' table. Each comparison and primary outcome will be exported to GRADEprofiler software (developed by the GRADE Working Group) for quality assessment (GRADEpro GDT). Data permitting, we intend to present four 'Summary of findings' tables in the following hierarchy: comparisons involving pain-relieving drugs, behavioral therapy, lifestyle advice, dietary interventions, and pre- and probiotics. Other comparisons will be graded and presented in

additional tables. Based on risk of bias, inconsistency, imprecision, indirectness and publication bias, we will grade 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 will justify all decisions to downgrade the quality of studies using footnotes and we will make comments to aid reader's understanding of the review where necessary.

We plan on including all 4 primary outcomes within the tables

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Maria-Inti Metzendorf, the Information Specialist of the Cochrane Metabolic and Endocrine Disorders Group, developed the search strategies, which will be run by Yuhong Yuan (Information Specialist, Cochrane Upper GI and Pancreatic Diseases Group).

REFERENCES

Additional references

Bielefeldt 2009

Bielefeldt K, Davis B, Binion DG. Pain and inflammatory bowel disease. *Inflammatory Bowel Diseases* 2009;**15**(5):778-88. [DOI: [10.1002/ibd.20848](https://doi.org/10.1002/ibd.20848)]

Cohen 1988

Cohen J. *Statistical Power Analysis in the Behavioral Sciences*. 2nd Edition. Hillsdale (NJ): Lawrence Erlbaum Associates, Inc, 1988.

ECCO 2010

Dignass A, Van Assche G, Lindsay JO, Lemman M, Söderholm J, Colombel JF, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. *Journal of Crohn's and Colitis* 2010;**4**(1):28-62. [DOI: [10.1016/j.crohns.2009.12.002](https://doi.org/10.1016/j.crohns.2009.12.002)]

Egger 1997

Egger M, Smith GD, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629. [DOI: [10.1136/bmj.315.7109.629](https://doi.org/10.1136/bmj.315.7109.629)]

Ghosh 2015

Ghosh N, Premchand P. A UK cost of care model for inflammatory bowel disease. *Frontline Gastroenterology* 2015;**6**(3):169-74. [DOI: [10.1136/flgastro-2014-100514](https://doi.org/10.1136/flgastro-2014-100514)]

Gjuladin-Hellon 2019

Gjuladin-Hellon T, Gordon M, Iheozor-Ejiofor Z, Akobeng AK. Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2019, Issue 6. [DOI: [10.1002/14651858.CD008414.pub3](https://doi.org/10.1002/14651858.CD008414.pub3)]

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Greenley 2013

Greenley RN, Kunz JH, Schurman JV, Swanson E. Abdominal pain and health related quality of life in pediatric inflammatory bowel disease. *Journal of Pediatric Psychology* 2013;**38**(1):63-71. [DOI: [10.1093/jpepsy/jss097](https://doi.org/10.1093/jpepsy/jss097)]

Higgins 2011

Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. Available from www.handbook.cochrane.org: The Cochrane Collaboration, 2011.

Iheozor-Ejiofor 2019

Iheozor-Ejiofor Z, Gordon M, Clegg A, Freeman SC, Gjuladin-Hellon T, MacDonald JK, et al. Interventions for maintenance of surgically induced remission in Crohn's disease: a network

meta-analysis. *Cochrane Database of Systematic Reviews* 2019, Issue 9. [DOI: [10.1002/14651858.CD013210.pub2](https://doi.org/10.1002/14651858.CD013210.pub2)]

Kafil 2018

Kafil TS, Nguyen TM, MacDonald JK, Chande N. Cannabis for the treatment of Crohn's disease. *Cochrane Database of Systematic Reviews* 2018, Issue 11. [DOI: [10.1002/14651858.CD012853.pub2](https://doi.org/10.1002/14651858.CD012853.pub2)]

Kaplan 2015

Kaplan G. The global burden of IBD: from 2015 to 2025. *Nature Reviews. Gastroenterology & Hepatology* 2015;**12**:720-7.

Limketkai 2019

Limketkai BN, Iheozor-Ejiofor Z, Gjuladin-Hellon T, Parian A, Matarese LE, Bracewell K, et al. Dietary interventions for induction and maintenance of remission in inflammatory bowel disease. *Cochrane Database of Systematic Reviews* 2019, Issue 2. [DOI: [10.1002/14651858.CD012839.pub2](https://doi.org/10.1002/14651858.CD012839.pub2)]

NICE 2019

National Institute for Health and Care Excellence. Crohn's disease: management. www.nice.org.uk/guidance/ng129 (accessed 1 July 2019).

Norton 2017

Norton C, Czuber-Dochan W, Artom M, Sweeney L, Hart A. Systematic review: interventions for abdominal pain management in inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics* 2017;**46**:115-25.

Odes 2017

Odes S, Friger M, Sergienko R, Schwartz D, Sarid O, Slonim-Nevo V, et al. Simple pain measures reveal psycho-social pathology in patients with Crohn's disease. *World Journal of Gastroenterology* 2017;**23**(6):1076-89. [dx.doi.org/10.3748/wjg.v23.i6.1076]

Pauly 2017

Pauly NJ, Michailidis L, Kindred MG, Flomenhoft D, Lofwall MR, Walsh SL, et al. Predictors of chronic opioid use in newly diagnosed Crohn's disease. *Inflammatory Bowel Diseases* 2017;**23**(6):1004-10. [DOI: [10.1097/MIB.0000000000001087](https://doi.org/10.1097/MIB.0000000000001087)]

RCP 2012

Royal College of Physicians. Report of the results for the national clinical audit of adult inflammatory bowel disease inpatient care in the UK. UK IBD Audit; London: RCP 2012.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Srinath 2012

Srinath AI, Walter C, Newara MC, Szigethy EM. Pain management in patients with inflammatory bowel disease: insights for the clinician. *Therapeutic Advances in Gastroenterology* 2012;**5**(5):339-57. [DOI: [10.1177/1756283X12446158](https://doi.org/10.1177/1756283X12446158)]

Timmer 2011

Timmer A, Preiss JC, Motschall E, Rucker G, Jantschek G, Moser G. Psychological interventions for treatment of

inflammatory bowel disease. *Cochrane Database of Systematic Reviews* 2011, Issue 2. [DOI: [10.1002/14651858.CD006913.pub2](https://doi.org/10.1002/14651858.CD006913.pub2)]

APPENDICES**Appendix 1. Search strategies**

Cochrane Central Register of Controlled Trials (Ovid EBMR)

1. exp Pain/
2. (pain* or headache* or migraine* or fibromyalgia* or neuralgia* or colic*).tw.
3. (discomfort* or ache or aching or aches).tw.
4. or/1-3
5. Crohn Disease/
6. Inflammatory Bowel Diseases/
7. ((Crohn or Crohn*).tw.
8. (inflammatory bowel disease*).tw.
9. (enteritis or ileitis or ileocolitis or colitis).tw.
10. or/5-9
11. 4 and 10

MEDLINE (Ovid)

1. exp Pain/
 2. (pain* or headache* or migraine* or fibromyalgia* or neuralgia* or colic*).tw.
 3. (discomfort* or ache or aching or aches).tw.
 4. or/1-3
 5. Crohn Disease/
 6. Inflammatory Bowel Diseases/
 7. (Crohn or Crohn*).tw.
 8. (inflammatory bowel disease*).tw.
 9. (regional enteritis or regional ileitis or terminal ileitis or granulomatous enteritis or ileocolitis or granulomatous colitis).tw.
 10. or/5-9
 11. 4 and 10
- [Cochrane Handbook RCT filter - sensitivity max version]
12. randomized controlled trial.pt.
 13. controlled clinical trial.pt.
 14. randomi?ed.ab.

(Continued)

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

[Wong 2006 – systematic reviews filter – sensitivity and specificity best balance version]

24. meta analysis.mp,pt. or review.pt. or search*.tw.
25. 11 and 24
26. 23 or 25

PsycINFO (OvidSP)

1. exp Pain/
2. Pain Measurement/
3. Pain Perception/
4. Pain Management/
5. (pain* or headache* or migraine* or fibromyalgia* or neuralgia* or colic*).tw.
6. (discomfort* or ache or aching or aches).tw.
7. or/1-6
8. Crohn Disease/
9. (Crohn or Crohn*).tw.
10. (inflammatory bowel disease*).tw.
11. (regional enteritis or regional ileitis or terminal ileitis or granulomatous enteritis or ileocolitis or granulomatous colitis).tw.
12. or/8-11
13. 7 and 12

[Eady 2008 "PsycInfo search strategies" filter – best sensitivity version]

14. control*.tw. OR random*.tw. OR exp Treatment/
15. 13 and 14

AMED (Ovid)

1. (pain* or headache* or migraine* or fibromyalgia* or neuralgia* or colic*).tw.
2. (discomfort* or ache or aching or aches).tw.

(Continued)

3. or/1-2

4. (Crohn or Crohn*).tw.

5. (inflammatory bowel disease*).tw.

6. (enteritis or ileitis or ileocolitis or colitis).tw.

7. or/4-6

8. 3 and 7

CINAHL (EBSCO)

S1. MH "Pain+"

S2. TI (pain* OR headache* OR migraine* OR fibromyalgia* OR neuralgia* OR colic*)

S3. AB (pain* OR headache* OR migraine* OR fibromyalgia* OR neuralgia* OR colic*)

S4. TI (discomfort* OR ache OR aching OR aches)

S5. AB (discomfort* OR ache OR aching OR aches)

S6. S1 OR S2 OR S3 OR S4 OR S5

S7. MH "Crohn Disease"

S8. TI (Crohn or Crohn*)

S9. AB (Crohn or Crohn*)

S10. TI (inflammatory bowel disease*)

S11. AB (inflammatory bowel disease*)

S12. TI ("regional enteritis" OR "regional ileitis" OR "terminal ileitis" OR "granulomatous enteritis" OR ileocolitis OR "granulomatous colitis")

S13. AB ("regional enteritis" OR "regional ileitis" OR "terminal ileitis" OR "granulomatous enteritis" OR ileocolitis OR "granulomatous colitis")

S14. S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13

S15. S6 AND S14

[Wong 2006 "CINAHL therapy studies" filter – best sensitivity version]

S16. MH "prognosis+" OR MH "study design+" OR random*

S17. S15 AND S16

WHO ICTRP Search Portal (Standard search)

pain* AND Crohn* OR

headache* AND Crohn* OR

migraine* AND Crohn* OR

colic* AND Crohn* OR

pain* AND inflammatory AND bowel AND disease OR

headache* AND Inflammatory AND bowel AND disease OR

(Continued)

migraine* AND Inflammatory AND bowel AND disease OR

colic* AND Inflammatory AND bowel AND disease OR

pain* AND enteritis* OR

headache* AND enteritis* OR

migraine* AND enteritis* OR

colic* AND enteritis* OR

pain* AND ileitis* OR

headache* AND ileitis* OR

migraine* AND ileitis* OR

colic* AND ileitis* OR

pain* AND ileocolitis* OR

headache* AND ileocolitis* OR

migraine* AND ileocolitis* OR

colic* AND ileocolitis*

ClinicalTrials.gov (Advanced search)

Condition/ Disease: (Crohn OR Crohns OR Crohn ´s OR “inflammatory bowel disease” OR “regional enteritis” OR “regional ileitis” OR “terminal ileitis” OR “granulomatous enteritis” OR ileocolitis OR “granulomatous colitis”)

Other terms: (pain OR pains OR painful OR headache OR headaches OR migraine OR migraines OR fibromyalgia OR neuralgia OR colic OR colics)

Study Type: Interventional Studies

CONTRIBUTIONS OF AUTHORS

ZIE: developed; co-ordinated the development; produced the first draft; contributed to writing and editing; made an intellectual contribution to; approved the final version prior to submission; and is a guarantor of the protocol.

MG: conceived the review question; secured funding; and developed, contributed to writing and editing, made an intellectual contribution to, advised on, approved the final version prior to submission, and is a guarantor of the protocol.

AKA: developed; made an intellectual contribution to; advised on; and approved the final version of the protocol prior to submission.

DECLARATIONS OF INTEREST

ZIE: none.

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 for them, as confirmed below. From these 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.

AKA: none.