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Title	Interventions for fatigue in inflammatory bowel disease (Protocol)
Authors	Farrell, Dawn;Savage, Eileen;Jelsness-Jørgensen, Lars P.;Czuber-Dochan, Wladyslawa;Artom, Micol
Publication date	2015-12-23
Original Citation	Farrell, D., Savage, E., Norton, C., Jelsness-Jørgensen, L. P., Czuber-Dochan, W. and Artom, M. (2015) 'Interventions for fatigue in inflammatory bowel disease', Cochrane Database of Systematic Reviews, CD012005 (12pp). doi:10.1002/14651858.CD012005
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1002/14651858.CD012005
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Download date	2026-11-06 18:49:05
Item downloaded from	https://hdl.handle.net/10468/5281



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Interventions for fatigue in inflammatory bowel disease.
Cochrane Database of Systematic Reviews 2015, Issue 12. Art. No.: CD012005.
DOI: 10.1002/14651858.CD012005.

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[Intervention Protocol]

Interventions for fatigue in inflammatory bowel disease

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Editorial group: Cochrane IBD Group.
Publication status and date: New, published in Issue 12, 2015.

Citation: Farrell D, Savage E, Norton C, Jelsness-Jørgensen LP, Czuber-Dochan W, Artom M. Interventions for fatigue in inflammatory bowel disease. *Cochrane Database of Systematic Reviews* 2015, Issue 12. Art. No.: CD012005. DOI: 10.1002/14651858.CD012005.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The aim of this review is to assess the efficacy and safety of interventions for fatigue in IBD.

BACKGROUND

Description of the condition

Inflammatory bowel disease (IBD) represents a group of chronic, progressive, complex inflammatory disorders of the digestive tract, and approximately five million people have a diagnosis of IBD worldwide (Wilson 2012). Crohn's disease (CD) and ulcerative colitis (UC) are the two most common forms of IBD. Both diseases are characterised by periods of relapse and remission, and they have overlapping and distinct pathological and clinical features (Bernstein 2010). Individuals with CD or UC experience a wide range of symptoms including diarrhoea, abdominal pain, fatigue, weight loss and rectal bleeding (Cronin 2005).

Fatigue has been identified as one of the most burdensome symptoms experienced by individuals with IBD (Farrell 2013). This symptom is particularly problematic during active disease with prevalence rates reported as high as 86% (Minderhoud 2007). A number of studies report that between 40% to 83% of patients continue to experience high rates of fatigue during remission (Minderhoud 2003; Romberg-Camps 2010; Van Langenberg 2010; Wilson 2012; Vogelaar 2014). These high rates of fatigue are comparable with rates experienced by oncology patients (Stone 2008). Furthermore, a study by Jelsness-Jørgensen 2011a found that chronic fatigue, defined as substantial fatigue with duration of more than six months, was significantly more common in patients with UC and CD than healthy controls. In addition, patients with IBD experiencing chronic fatigue have significantly higher levels of disease-related worries and concerns (Jelsness-Jørgensen 2012). Reduced energy level is a leading and consistent concern among individuals with IBD (Drossman 1989; Casati 2000; Casellas 2001; De Rooy 2001; Jelsness-Jørgensen 2011b). In addition, IBD-related fatigue negatively impacts on health-related quality of life and activities of daily living (Minderhoud 2003; Jelsness-Jørgensen 2011c; Graff 2011; Czuber-Dochan 2013a; Czuber-Dochan 2013b; Opheim 2014). Despite the high prevalence of chronic fatigue in IBD, this subjective complaint remains largely ignored in the IBD literature, particularly regarding the investigation of underlying mechanisms and treatment strategies for fatigue.

Fatigue has been difficult to delineate due to the subjective nature of the symptom. In chronic diseases, with consideration given

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in the context of IBD, fatigue has been defined as a 'persistent, overwhelming sense of tiredness, weakness or exhaustion resulting in a decreased capacity for physical and mental work' (Lai 2003; Dittner 2004). Although some studies have continued to measure fatigue in IBD from a uni-dimensional perspective, for example in terms of prevalence (Minderhoud 2003), or severity (Opheim 2014) only, it is now generally accepted that fatigue is a multidimensional phenomenon, characterised by diminished perceived physical energy, mental capacity and psychological status (Van Langenberg 2010). These physical, cognitive and affective dimensions of fatigue form the components of generic fatigue measures such as the Multidimensional Fatigue Inventory. More recent studies have assessed fatigue using multiple dimensions, such as severity/intensity, frequency, duration, distress and impact (Bager 2012). Furthermore, the characteristics of fatigue are captured to varying degrees by the diverse range of symptom and quality of life measures available, including both generic and disease specific indices (Hjollund 2007). It is known that IBD-related fatigue is associated with a number of physical, psychological and situational factors, with increased disease activity, depression, anxiety and stress found to be consistently associated with greater levels of fatigue (Czuber-Dochan 2013a). As a result, the non-specific, subjective, complex nature of fatigue can often hamper the management of this burdensome symptom. Although healthcare professionals perceive fatigue as an important and problematic symptom in patients with IBD, the management of fatigue remains poorly understood (Czuber-Dochan 2014a). Healthcare professionals have identified the need for more information and education to facilitate the management of fatigue in clinical practice (Czuber-Dochan 2014b). However, the effectiveness of interventions for fatigue in IBD has not been systematically reviewed.

Description of the intervention

Given the multidimensional nature of fatigue involving biological, psychosocial, and behavioural processes (Opheim 2014), pharmacological and non-pharmacological interventions either alone or in combination may help to improve or alleviate fatigue. Pharmacological interventions involve the administration of drugs through any route. Non-pharmacological interventions may include any type of physical, psychological, psychosocial, behavioural or educational interventions. Interventions have been developed to address the problem of IBD-related fatigue either directly or indirectly. For example, directly in terms of an intervention specifically aimed at improving or alleviating fatigue (Vogelaar 2014), or indirectly in terms of an intervention aimed at the overall management of IBD which assesses fatigue as an outcome (Garcia-Vega 2004). However, there is uncertainty regarding the effectiveness of these interventions in alleviating fatigue, particularly in the long term.

How the intervention might work

Interventions may address the physical, psychological or situational factors contributing to fatigue. It is important that these contributory factors are clearly understood in order to target interventions effectively. For example, where fatigue is related to a physical problem such as anaemia, iron supplements or intravenous iron therapy may be beneficial. Alternatively, if the physical issue is inflammation due to a disease flare, a pharmacological intervention such as biological therapy may be valuable. If altered mood is a factor contributing to fatigue, psychosocial behavioural interventions may be valuable. Often fatigue is influenced by a number of factors, therefore a multi-component intervention may be an effective approach.

Why it is important to do this review

The incidence of IBD has been increasing over time (Molodecky 2012). Fatigue has been identified as the most burdensome symptom experienced by individuals with IBD that impacts negatively on all aspects of daily life (Wilson 2012; Farrell 2013). Due to the increasing prevalence, debilitating character and unknown etiology, interventions for IBD-related fatigue have received increased attention. Recently, in other chronic conditions which are associated with fatigue there has been an increase in the number of Cochrane reviews on interventions for fatigue. For example for cancer-related fatigue there are reviews assessing the effect of pharmaceutical interventions (Minton 2010), blood transfusions (Preston 2012), exercise (Cramp 2012), education (Bennett 2009), and psychosocial interventions (Goedendorp 2009). However, unlike cancer and other chronic conditions such as multiple sclerosis (Heine 2015), peripheral neuropathy (White 2014) and rheumatoid arthritis (Cramp 2013), no systematic review has been undertaken to assess the effects of interventions for fatigue in IBD. It is therefore proposed to systematically review and synthesise existing evidence on the effects of interventions for fatigue in individuals with IBD.

OBJECTIVES

The aim of this review is to assess the efficacy and safety of interventions for fatigue in IBD.

METHODS

Criteria for considering studies for this review

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Types of studies

All types of randomised controlled trials (RCTs) will be considered for inclusion.

Types of participants

Children, adolescents and adults of all ages with a clinical diagnosis of Crohn's disease, ulcerative colitis (with or without a total colectomy), or any other form of IBD (e.g. indeterminate colitis or IBD unclassified) will be considered for inclusion. Participants will be included regardless of whether disease status is active or in remission.

Types of interventions

Any pharmacological and non-pharmacological interventions designed to help alleviate fatigue in individuals with IBD will be included. To be eligible for inclusion, an intervention must have a focus on fatigue explicitly stated in its aims, content, or as a primary or secondary outcome measure.

The following comparisons will be considered:

1. Pharmacological versus non-pharmacological;
2. Pharmacological versus pharmacological (different drugs or same drugs with different doses and time intervals);
3. Pharmacological versus usual or standard care;
4. Non-pharmacological versus usual or standard care;
5. Non-pharmacological versus non-pharmacological (different non-pharmacological interventions or same non-pharmacological intervention with different formats); or
6. Any of the above versus placebo.

Interventions may be delivered in any form, for example but not limited to, face to face, telephone, the internet, or technology in the case of non-pharmacological interventions. Interventions may be delivered individually or be group focused and occur in different settings such as a clinic or home environment.

Types of outcome measures

Primary outcomes

The primary outcome for this review will be fatigue. Therefore, eligible studies for inclusion must have fatigue or loss of energy measured as a primary or secondary outcome. Measures of fatigue will be self-reported as it is a subjective phenomenon and these instruments may be generic or disease specific. Examples of generic self-reported measures include but are not limited to: the Fatigue Severity Scale (Krupp 1989), Chalder Fatigue Scale (Chalder 1993), Fatigue Impact Scale (Fisk 1994; Fisk 2002), Visual Analogue Scale of Fatigue (Lee 1991), Piper Fatigue Scale (Piper 1998), Functional Assessment of Chronic Illness Therapy - Fatigue (Yellen 1997), Multidimensional Fatigue Inventory (Smets 1996), and the Multidimensional Assessment of Fatigue (Tack 1991). An example of a disease specific measure includes the Inflammatory Bowel Disease fatigue scale (Czuber-Dochan 2014c). In addition, studies that report data on fatigue, loss of energy, vigour and vitality which was assessed as a single question or as a subscale of a questionnaire (e.g. the vitality subscale of the SF-36 or Inflammatory Bowel Disease Questionnaire (IBDQ) (Ware 1992; Irvine 1999)) will be included. Multidimensional characteristics of fatigue symptoms may be measured. For example, these characteristics may include intensity, severity, frequency, duration, distress or dimensions including physical fatigue, mental fatigue or general fatigue.

Secondary outcomes

Secondary outcomes will include:

1. Any measure of quality of life (e.g. SF-36 or IBDQ); and
2. Adverse events.

Adverse events will include:

1. The proportion of participants who experience any adverse event (i.e. an unfavourable outcome occurring during, but not necessarily caused by the intervention);
2. Serious adverse events (i.e. an adverse event that results in death, requires hospitalisation or a life-threatening event, resulting in a persistent or significant disability); and
3. Withdrawal due to an adverse event.

Search methods for identification of studies

Electronic searches

We will search MEDLINE, CINAHL, EMBASE and PsycINFO from inception to date. We will also search the Cochrane IBD Group Specialized Register and the Cochrane Central Register of Controlled trials (CENTRAL) for applicable RCTs. The search strategies will be modified for each database. Search limits will include humans and English only. The search strategies will use the relevant database filters or the recommended Cochrane search string for the identification of RCTs (Lefebvre 2011). The search strategies for each database are reported in Appendix 1, Appendix 2, Appendix 3, Appendix 4, Appendix 5 and Appendix 6. One author (DF) will liaise with the Cochrane IBD Group Trials Search Coordinator for the identification of potentially eligible studies.

Searching other resources

To identify other relevant published, unpublished and ongoing trials we will:

1. Examine the reference lists of included studies and review articles for additional citations;

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2. Search ongoing trials and research registers including the Current Controlled Trials register (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/), using the search terms 'fatigue' and 'inflammatory bowel disease' or 'ulcerative colitis' or 'Crohn's disease';

3. Contact trial authors, known specialists in the field and pharmaceutical companies to identify further published and unpublished trials and ask if they are willing to disclose their unpublished data; and

4. Search published abstracts from conference proceedings, including the European Crohn's and Colitis Organisation Congress, Digestive Disease Week and Advances in Inflammatory Bowel Diseases.

Data collection and analysis

Selection of studies

Initially, two review authors (DF, MA) will independently screen titles and abstracts identified by the search and exclude those studies that are obviously not relevant to the review. The remaining titles and abstracts will be independently examined for eligibility by two review authors (DF, ES) based on the predetermined inclusion criteria described above. Full text papers will be retrieved for all studies appearing to meet the inclusion criteria and will be read independently by two review authors (DF, ES). We will only include trials with a heterogeneous sample of disorders,if relevant data from participants with IBD can be extracted. We will contact study authors where information is unclear or missing in order to reach a decision about inclusion. Disagreement about the selection of a study will be resolved by consensus. In the event a consensus cannot reached, arbitration will be sought from a third author (CN).

Data extraction and management

For each included study, two review authors will independently extract and document the relevant data using standardised data extraction forms. The lead author (DF) will extract data for all included trials. Second independent extraction of data from included trials will be shared between three review authors (WCD or LPJJ or MA). If necessary, study authors will be contacted to provide additional (unpublished) relevant information. We will resolve any disagreements by consensus including discussion with two additional authors (ES and CN). We will gather data on the following and document in both data extraction forms and Review Manager 5:

Study

- Study aim

Participant characteristics

- Number of participants
- Setting of study
- Country of origin
- Demographic characteristics such as age and gender
- Disease characteristics such as disease type, disease status and treatment type
- Inclusion and exclusion criteria for participation in the study

Intervention characteristics

For each arm:·

- Assignment to groups·
- The aim, type, mode and content of the intervention·
- Time points of delivery ·
- Duration of the intervention, number and duration of sessions/dose
- Providers of the intervention
- Comparison intervention/s
- Setting of the intervention
- Participant adherence

Outcomes

- Time, frequency and duration at which outcomes are measured
- Instruments used for key primary and secondary outcomes
- Adverse events

Others

- Funding
- Declaration of interest
- Sample size and evidence of power calculation statistical analysis.
- Follow up - withdrawal/dropout

Assessment of risk of bias in included studies

For each study, the authors who extracted the data from the included studies will also independently assess methodological quality using the Cochrane risk of bias tool (Higgins 2011a). We will assess trials for random sequence generation, allocation concealment, blinding (participants, personnel and outcome assessors), incomplete outcome data, outcome misclassification, selective outcome reporting and other potential sources of bias. We will then make a judgment on each of these criteria relating to the risk of bias, of 'low risk of bias', 'high risk of bias' or 'unclear risk of bias'.

We will use the GRADE criteria (risk of bias, inconsistency, imprecision, indirectness and publication bias) to assess the overall quality of evidence for the prespecified primary and secondary outcomes (Schünemann 2011a; Schünemann 2011b). All decisions to downgrade or upgrade the quality of the evidence will be explained using footnotes.

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If agreement cannot be achieved by the two review authors (DF and WCD or LPJJ or MA) through discussion, another two other review authors (ES and CN) will provide consensus assessment.
Using the GRADEpro software, we will create a 'Summary of findings' table for the following outcomes:

- Fatigue;
- Quality of life; and
- Adverse events.

Measures of treatment effect

We will use the Cochrane Collaboration's Review Manager Software, RevMan 5, for all analyses. Outcomes will be recorded both at the end of the intervention period and at the end of the follow-up for the purpose of comparison between the intervention and control groups. We will calculate the mean difference (MD) and the corresponding 95% confidence interval (CI) for continuous outcomes. We will calculate the risk ratio (RR) and 95% CI for dichotomous outcomes (e.g. fatigue or no fatigue). We will calculate the number needed to treat for an additional beneficial outcome (NNTB) where appropriate.

Unit of analysis issues

The level at which randomisation occurs will be accounted for in the data analysis. We expect that participants will be individually randomised to one of two groups, where the unit of analysis will be the individual.
Where groups of individuals are randomised together to the same intervention (i.e. cluster-randomised trials), the group will be the unit of analysis. Group level interventions are often analysed and reported at an individual rather than a group level, or without adjusting for group effect. Authors will be contacted for further information if these group data are not reported.
Where individuals undergo more than one intervention during the period of the study (i.e. in a cross-over trial), an assessment of the suitability of this method for the condition and intervention in question and the likelihood of serious carry-over will be addressed. If neither carry-over nor period effects are an issue, we will follow the methods of analysis for cross-over trials as recommended in Chapter 16 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011b).
We will follow the recommendations outlined in Chapter 16 of the Cochrane Handbook for Systematic Reviews of Interventions for studies where events may reoccur, studies where there are multiple treatment attempts, and studies where there are multiple intervention groups or repeated observations on participants (Higgins 2011b).

Dealing with missing data

Where data are missing, we will contact the trial authors and request the missing data. If this information is unattainable, an available case analysis will be undertaken by analysing only the available data (i.e. ignoring the missing data). If change scores are not available and the mean change can be calculated, standard deviations will be imputed from baseline data using methods recommended in Chapter 16 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011b). If the number of patients randomised to each group and the number of drop outs are known, a worst case intention-to-treat (ITT) analysis, whereby all drop outs are assumed to be treatment failures, will be calculated.

Assessment of heterogeneity

The studies will be assessed for clinical homogeneity with regards to participants, interventions, and outcomes. A meta-analysis would not be appropriate for studies judged to be clinically heterogeneous. We plan to assess heterogeneity as follows.

1. We will review the results of the Chi^2 test to determine if the heterogeneity is statistically significant. A P value of 0.10 will be considered statistically significant.
2. If the Chi^2 test indicates statistically significant heterogeneity, we will quantify the heterogeneity across studies by reporting the I^2 results. An I^2 value of 25% represents low heterogeneity, 50% represents moderate heterogeneity and 75% represents high heterogeneity.
3. If there is significant heterogeneity, the forest plot will be visually inspected and a sensitivity analysis performed, excluding any obvious outliers, to assess if this explains the heterogeneity. For example, if the original pooled analysis had an I^2 value of 68% and after the outlier study (or studies) was excluded the I^2 value changed to 22%. If the sensitivity analysis appears to explain the heterogeneity, the outlier study (or studies) will be examined to determine if it differs from the other studies in the pooled analysis, in a way that could explain the heterogeneity. For example, the outlier study may include participants with both active and quiescent disease, while the other studies in the pooled analysis enrolled patients with quiescent disease only.
4. Finally if heterogeneity is suspected, the possibility of utilising a random-effects model of meta-analysis will be considered as recommended in Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2011).

Assessment of reporting biases

All studies will be assessed for reporting bias. If reporting bias is suspected, we will attempt to contact trial authors and request missing outcome data. For example, results for pre-specified outcomes that were not reported in the paper. Alternatively, if this information is unattainable and there are an appropriate number of studies in the pooled analysis (i.e. > 10 studies), we will explore

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potential publication bias by testing for funnel plot asymmetry (Sterne 2011).

Data synthesis

Where appropriate, the data from included studies will be combined in a meta-analysis. Data will be pooled when patients, interventions and outcomes are sufficiently similar, which will be determined by consensus. We will pool statistically homogeneous studies (I^2 < 50%) using a fixed-effect model. We will pool statistically heterogeneous ($I^2 \geq$ 50%) studies using a random-effects model. Data will not be pooled if there is a high degree of statistical heterogeneity (I^2 > 75%). For continuous outcomes, we will calculate the pooled mean difference (MD) and corresponding 95% confidence interval (CI). Where different scales are used to measure the same underlying construct, we will calculate the standardised mean difference (SMD) and corresponding 95% CI. Continuous data will be combined only where (i) means and standard deviations are available or calculable and (ii) there is no clear evidence of a skewed distribution (Deeks 2011). For dichotomous outcomes, we will calculate the pooled RR and corresponding 95% CI. According to Cohen 1977, we will classify effect sizes into small (< 0.2), medium (0.2 to 0.8) and large (> 0.8).

Subgroup analysis and investigation of heterogeneity

If sufficient power and data are available, subgroup analysis will be performed for the following subsets: disease type (Crohn's disease, ulcerative colitis); disease activity (active disease, inactive disease), sex (male, female); age groups (child, adolescents, adults, elderly), co-morbidities, and intervention type (pharmacological non-pharmacological). All review authors will be involved in interpreting the analyses. We will restrict subgroup analyses to looking at effects of subgroups on the primary outcome.

Sensitivity analysis

Sensitivity analysis will be performed, where appropriate, to explore the effects of risk of bias. Studies identified as high risk of bias will be excluded from the pooled analysis to see if the effect estimate changes in a substantive way. If no substantive difference exists, the studies with a high risk of bias will be included in the main analysis. For allocation concealment, we intend to re-analyse the data including only those trials with adequate concealment of allocation. Finally for blinding of outcome assessment, trials with double blinding of outcome assessment will be included in a re-analysis, due to the subjective nature of fatigue. Sensitivity analysis will be conducted for the primary outcome only. We will also compare the results of any 'available case' analysis with a worst case ITT analysis to see if the effect estimate changes.

ACKNOWLEDGEMENTS

Funding for the IBD/FBD Review Group (September 1, 2010 - August 31, 2015) has been provided by the Canadian Institutes of Health Research (CIHR) Knowledge Translation Branch (CON - 105529) and the CIHR Institutes of Nutrition, Metabolism and Diabetes (INMD); and Infection and Immunity (III) and the Ontario Ministry of Health and Long Term Care (HLTC3968FL-2010-2235).

Miss Ila Stewart has provided support for the IBD/FBD Review Group through the Olive Stewart Fund.

The Health Research Board, Ireland has provided support to the primary author through a Cochrane Fellowship

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. EMBASE search strategy

1. exp Crohn disease/ or crohn*.mp.
2. (colitis and ulcerat*).mp. or exp ulcerative colitis/
3. (inflammatory bowel disease* or IBD).mp.
4. 1 or 2 or 3
5. random$.mp.
6. factorial$.mp.
7. (crossover$ or cross over$ or cross-over$).mp.
8. placebo$.mp.
9. single blind.mp.
10. double blind.mp.
11. triple blind.mp.
12. (singl$ adj blind$).mp.

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13. (double$ adj blind$).mp.
14. (tripl$ adj blind$).mp.
15. assign$.mp.
16. allocat$.mp.
17. crossover procedure/
18. double blind procedure/
19. single blind procedure/
20. triple blind procedure/
21. randomized controlled trial/
22. or/1-17
23. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
24. 18 not 19
25. exp fatigue/
26. exp chronic fatigue syndrome/
27. (physical fatigue OR mental fatigue OR muscle fatigue).mp.
28. (energy OR tired* OR sleep* OR drows* OR letharg* OR lassitude OR weari*).mp.
29. (exhaust* OR listless* OR apath* OR malaise).mp.
30. ((asthenia OR asthenic) adj3 syndrome).tw.
31. ((lack OR loss OR lost) adj3 (energy OR vigo* OR vitality).tw.
32. 25 or 26 or 27 or 28 or 29 or 30 or 31
33. 4 AND 24 AND 32

Appendix 2. MEDLINE search strategy

1. exp Crohn disease/ or crohn*.mp.
2. (colitis and ulcerat*).mp. or exp ulcerative colitis/
3. (inflammatory bowel disease* or IBD).mp.
4. 1 or 2 or 3
5. random$.mp.
6. factorial$.mp.
7. (crossover$ or cross over$ or cross-over$).mp.
8. placebo$.mp.
9. single blind.mp.
10. double blind.mp.
11. triple blind.mp.
12. (singl$ adj blind$).mp.
13. (double$ adj blind$).mp.
14. (tripl$ adj blind$).mp.
15. assign$.mp.
16. allocat$.mp.
17. crossover procedure/
18. double blind procedure/
19. single blind procedure/
20. triple blind procedure/
21. randomized controlled trial/
22. or/5-17
23. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
24. 18 not 19
25. exp fatigue/
26. exp chronic fatigue syndrome/
27. (physical fatigue OR mental fatigue OR muscle fatigue).mp.
28. (energy OR tired* OR sleep* OR drows* OR letharg* OR lassitude OR weari*).mp.

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29. (exhaust* OR listless* OR apath* OR malaise).mp.
30. ((asthenia OR asthenic) adj3 syndrome).tw.
31. ((lack OR loss OR lost) adj3 (energy OR vigo* OR vitality).tw.
32. 25 or 26 or 27 or 28 or 29 or 30 or 31
33. 4 AND 24 AND 32

Appendix 3. Cochrane Library search strategy

#1 MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
#2 crohn*
#3 ulcerative colitis
#4 colitis
#5 proctitis
#6 ileitis
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 MeSH descriptor: [Fatigue] explode all trees
#9 "chronic fatigue" or "physical fatigue" or "mental fatigue" or "muscle fatigue"
#10 energy or tired* or sleep* or drows* or letharg* or lassitude or weari* or exhaust* or listless* or apath* or malaise
#11 #8 or #9 or #10
#12 #7 and #11

Appendix 4. CINAHL search strategy

1. (TI fatigue or AB fatigue) OR (TI energy or AB energy) OR (TI sleep* or AB sleep*) OR (TI drows* or AB drows*) OR (TI lethargy* or AB lethargy*) OR (TI lassitude or AB lassitude) OR (TI weari* or AB weari*) OR (TI exhaust* or AB exhaust*) OR (TI listless* or AB listless*) OR (TI apath* or AB apath*) OR (TI malaise or AB malaise)
2. (TI inflammatory bowel or AB inflammatory bowel) OR (TI IBD or AB IBD) OR (TI Crohn* or AB Crohn*) OR (TI CD* or AB CD*) OR (TI colitis* or AB colitis*) OR (TI UC or AB UC) OR (TI proctitis or AB proctitis) OR (TI ileitis or AB ileitis)

Appendix 5. PsycINFO search strategy

1. TI(fatigue OR energy OR sleep* OR drows* OR lethargy* OR lassitude OR weari* OR exhaust* OR listless* OR apath* OR malaise) AND TI(inflammatory bowel OR IBS OR Crohn* OR CD OR colitis OR UC OR proctitis OR ileitis)

Appendix 6. clinicaltrials.gov search strategy

(fatigue OR energy OR sleep* OR drows* OR lethargy* OR lassitude OR weari* OR exhaust* OR listless* OR apath* OR malaise) | (inflammatory bowel OR IBS OR Crohn* OR CD OR colitis OR UC OR proctitis OR ileitis)

CONTRIBUTIONS OF AUTHORS

Dawn Farrell: content expert, conceived the project, developed the protocol, coordinated authors, and will be responsible for the full review and update.

Christine Norton: content and methodological expert, contributed to review of the protocol.

Eileen Savage: methodological expert, contributed to review of the protocol.

Lars P Jelsness-Jørgensen: content expert, contributed to review of the protocol.

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DECLARATIONS OF INTEREST

Dawn Farrell has received support from a Cochrane Fellowship awarded by the Health Research Board Ireland and infrastructure support from University College Cork, Ireland to conduct this review.

Eileen Savage: None known

Christine Norton: None known

Lars-Petter Jelsness-Jørgensen has received unrestricted research grants from Ferring Pharmaceuticals and Tillots Pharma. and has also acted as consultant and speaker for Abbvie. All of these activities are outside the submitted work.

Wladyslawa Czuber-Dochan: None known

Micol Artom: None known

SOURCES OF SUPPORT

Internal sources

- University College Cork, Ireland.

Provided infrastructure support to the primary author to carry out the Cochrane review

External sources

- Health Research Board, Ireland.

Provided a Cochrane Fellowship to the primary author

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