Ther Adv Chronic Dis
2019, Vol. 10: 1–12
DOI: 10.1177/2040622319838439

Randomized controlled trial: a pilot study of a psychoeducational intervention for fatigue in patients with quiescent inflammatory bowel disease

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Abstract

Introduction: Fatigue is a frequent, debilitating symptom of inflammatory bowel disease (IBD). Despite this, studies report dissatisfaction among IBD patients regarding how little attention is given to fatigue-related issues during consultations. We performed a pilot randomized controlled trial (RCT) to assess whether a brief, structured, multidisciplinary psychological support program improved fatigue, mood and quality of life indices in patients with quiescent IBD.

Methods: The intervention consisted of three small-group psychoeducational sessions over 6 months. Primary outcomes were effect on fatigue severity and impact scores. Secondary outcomes included effect on depression, anxiety, somatization scores, generic and disease-specific quality of life.

Results: Twenty-three patients were enrolled, 10 in the intervention arm and 13 controls. Mean fatigue severity and impact scores improved for patients in the intervention group (by 14.5–13.1 and 49.7–45.8, respectively), and worsened in controls (by 11.5–12.6 and 33.5–35 respectively). Mean Short Form 36 (SF-36) scores for role limitations due to physical health decreased from 44.4 to 38.9 in the intervention group, but increased from 44.2 to 51.9 among controls. Energy scores in the intervention group improved from 17.8 to 26.6, but only from 31.4 to 31.7 among controls. Short IBD questionnaire scores improved in both groups, from 46.2 to 45.2 in controls compared with 44.4–40 in the intervention group.

Discussion: In this small pilot RCT, positive effects were demonstrated on fatigue, energy levels and other quality of life outcomes. Larger, adequately powered studies with longer follow up are required.

ClincialTrials.gov identifier: NCT02709434.

Keywords: Crohn's disease, fatigue, inflammatory bowel disease, quality of life, ulcerative colitis

Received: 1 October 2018; revised manuscript accepted: 22 February 2019.

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Key summary

What is already known about this subject?

- Fatigue is common in inflammatory bowel disease (IBD), but patients report considerable dissatisfaction as to how little attention is given to fatigue by their treating physicians.
- Randomized controlled trial (RCT) data on nonpharmacologic interventions for fatigue in IBD are sparse, and especially so among patients in clinical and biochemical remission.
- Psychological interventions resulting in improvements in quality of life have been

shown to result in significant reductions in subsequent healthcare usage.

What are the new findings?

- We assessed the efficacy of a brief, structured, multidisciplinary program of psychological support in fatigue management.
- This study adds to a small body of literature of RCTs in IBD that use fatigue and energy scores as primary endpoints.
- There were positive effects on fatigue, energy levels and a range of other quality of life outcomes, in spite of disease parameters that did not improve.
- This is the first RCT to report improved disease-specific quality of life scores following treatment of fatigue in a cohort of patients in clinical and biochemical remission.

How might it impact on clinical practice in the near future?

- Larger, adequately powered studies with a longer duration of follow-up, and which recruit IBD patients with fatigue, regardless of disease activity, are required.

Key summary

- Fatigue is common in IBD, but patients report considerable dissatisfaction as to how little attention is given to fatigue by their treating physicians. RCT data on nonpharmacologic interventions for fatigue in IBD are sparse, and especially so among patients in clinical and biochemical remission.
- We assessed the efficacy of a brief, structured, multidisciplinary program of psychological support in fatigue management.
- This is the first RCT to report improved fatigue and energy levels, and disease-specific quality of life scores following treatment of fatigue in a cohort of patients in clinical and biochemical remission.
- Larger, adequately powered studies with a longer duration of follow up, and which recruit IBD patients with fatigue, regardless of disease activity, are required.

Introduction

Fatigue is a frequent and debilitating symptom in inflammatory bowel disease (IBD). More than 40% of patients with IBD, even when in remission, suffer from fatigue and this rises to 86% when the disease is active.[1] In one study, mean Multidimensional Fatigue Inventory scores of these patients were comparable with the mean scores reported in cancer patients who had completed chemotherapy.[2] In a survey of perceived health status, fatigue ranked third on a 25-item rating form of concerns among IBD patients, after uncertainties about the disease, and the effects of medication.[3]

Despite this, studies have reported considerable dissatisfaction among patients with IBD as to how little attention is given to fatigue-related issues in their consultations, as well as in the range of interventions available to enable them to manage these symptoms effectively.[4–6] In spite of the efforts of both patients and their advocacy organizations to highlight fatigue as a major concern, published evidence for treatment strategies is sparse. A systematic review on the topic in 2013 criticised the inconsistent definitions used across the literature, and noted that none of the reviewed studies asked patients to describe the experience of fatigue in their own words.[7] A further systematic review of 43 studies found that IBD fatigue was consistently associated with disease activity, depression, anxiety and sleep difficulties but was unable to conclude on causation and found an inconsistent relationship between biochemical factors, such as anaemia and inflammation, and fatigue.[8] The same study identified solution-focused therapy, thiamine and exercise as potential targets to improve fatigue in IBD. Regarding these therapeutic interventions, three small randomized controlled trials (RCTs) reported a favourable effect of infliximab and adalimumab on fatigue in IBD.[9–11]

In other chronic disease areas such as cancer, rheumatoid arthritis and multiple sclerosis psychotherapeutic interventions have been shown clearly to be beneficial.[12–14] However, data from the IBD literature are sparse, with only one study reporting a benefit from a stress management program,[15] and two RCTs from the same group suggesting that a strategy known as solution-focused therapy may also be superior to treatment as usual.[16,17] We therefore performed a pilot RCT, which aimed to assess whether or not fatigue, energy and quality of life indices could be improved in a group of patients with quiescent

IBD, who reported fatigue, *via* the delivery of a brief and simple structured multidisciplinary program of psychological support.

Materials and methods

Patients and setting

We performed a pilot RCT in patients with IBD recruited from outpatient clinics at Leeds Teaching Hospitals NHS Trust, UK, between December 2016 and April 2017. All patients received information about the study and gave written informed consent. The study was approved by the local research ethics committee (Reference Number: 16/YH/0235). The study was registered on ClincialTrials.gov (identifier: NCT02709434). All recruited individuals provided blood for complete blood count, urea and electrolytes, liver function tests, thyroid function tests, ferritin, vitamin B_{12}, folate, vitamin D, calcium, magnesium, phosphate and C-reactive protein (CRP), as well as stool for faecal calprotectin (FC) (Immundiagnostik, Bensheim, Germany).

Data collection and synthesis

Demographic and disease-specific data. Once informed consent was obtained, demographic data included gender, age, ethnicity, marital status, educational level, tobacco and alcohol use, weight (in kilograms) and height (in metres), which were used to calculate body mass index (BMI), were collected. Medication history, including current use of 5-aminosalicylates (5-ASAs), glucocorticosteroids, immunosuppressants or biologic therapies, and disease location and behaviour for Crohn's disease (CD) or distribution for ulcerative colitis (UC), as defined by the Montreal classification,[18] were also recorded.

IBD activity data. Assessment of IBD activity was performed by physician using the Harvey–Bradshaw index (HBI) for CD,[19] and the Simple Clinical Colitis Activity Index (SCCAI) for UC,[20] with a score <5 used to define clinical remission for both, as recommended previously.[21,22] In addition, we used an FC cut off of <250 μg/g of stool to define no evidence of mucosal inflammation, in line with the European Crohn's and Colitis Organisation consensus on the use of FC to measure disease activity.[23]

Fatigue data

Fatigue was assessed using the IBD fatigue self-assessment scale,[24] consisting of two main sections. Section one assesses frequency and severity of fatigue, and section two the impact of fatigue on daily activities. Higher scores represent higher fatigue severity, and a greater impact on daily life.

Mood, somatization and quality of life data

Anxiety and depression data were collected using the Hospital Anxiety and Depression Scale (HADS),[25] with severity categorized, according to total HADS score, into normal (total HADS depression or anxiety score 0–7), borderline normal[8–10] and abnormal ($\geqslant$11), as previously validated.[25] Somatization data were collected using the Patient Health Questionnaire-15 (PHQ-15), which is derived from the validated full PHQ,[26,27] which enquires about the presence of 15 somatic symptoms (or symptom clusters) over the last 4 weeks, with severity categorized as recommended previously.[28]

Finally, generic quality of life data were collected via the medical outcomes study 36-item Short Form (SF-36) health survey, a validated questionnaire used to assess physical and mental health status,[29] and disease-specific quality of life using the Short Inflammatory Bowel Disease Questionnaire (SIBDQ).[30]

Inclusion and exclusion criteria

To be included patients had to have quiescent IBD, both according to clinical (HBI or SCCAI <5) and biochemical (CRP <5 mg/l and FC <250 μg/g) indices no more than 1 month prior to randomization, and report fatigue by virtue of scoring 1 or more on Section I of the Crohn's and Colitis UK IBD fatigue self-assessment scale. Patients were excluded if they had any correctable electrolyte (sodium, potassium, magnesium, calcium), vitamin (B12 or D) or iron deficiency anaemia (defined as Hb <11.5 g/dl for a woman or <13 g/dl for a man with ferritin <20 μg/l), or active disease according to either clinical or biochemical criteria. Pregnancy, inability to conduct intervention in English language and severe psychological comorbidity were other contraindications.

Randomization

After baseline assessment, eligible patients were randomized by selection of sequentially numbered

opaque sealed envelopes by the research fellow to either a standard of care group, which consisted of treatment as usual, or to participate in the multidisciplinary psychoeducational intervention group, using lists drawn from a computer-generated series of random numbers. Allocation of treatment was concealed by the use of opaque, sealed envelopes. Blinding was not possible, as patients were clearly aware of the treatment arm they were assigned to such was the nature of the intervention.

Intervention

The standard of care group received standard medical care, as per their responsible gastroenterologist, with no additional psychological interventions. This consisted of planned review every 6 or 12 months depending on disease characteristics with demand-led appointments on top of that for active symptoms. The active intervention consisted of a series of three small-group psychoeducational sessions, delivered every 8 weeks over a period of 6 months. Each session lasted 1 hour. There were five patients in each group. The programme ran twice in parallel and the groups stayed together and did not overlap. The sessions were structured around psychological and physical interventions, which were geared towards understanding fatigue, energy conservation, management strategies and improving relaxation techniques tailored to the specific needs of patients with IBD. Sessions were facilitated by a senior occupational therapist with experience in fatigue management and small group work in chronic disease management, as well as nurse specialists in IBD and psychological medicine. The interventions used methods which have long been used in other patient groups with chronic diseases such as fibromyalgia, multiple sclerosis and inflammatory arthritis and drawing on the experience of gastroenterologists and specialist nurses in IBD the therapeutic intervention was modified to focus on the specific aspects of fatigue management in patients with IBD. The first session focused on analysing activity diaries the patients had brought with them to identify their patterns of activity, exercise, work, sleep and recreation over the week prior to the intervention. Core skills for managing fatigue such as grading, pacing, purposeful rest, time management strategies, enjoyable activities, sleep hygiene and a relaxation practice (diaphragmatic breathing) were taught and emphasized. The session finished with the setting of goals for them to work on before the next session, with pro-forma sheets provided to document these. Participants were also asked to complete the same activity diary for another 1 week in the week prior to their next session. Patients were provided with written material germane to the learnings at the end of every session.

The second session started by reflection on both the activity diaries, and how people had been able to progress on the strategies and goals identified in the first workshop, as well as including problem solving for any barriers that arose. This session also focused on managing external expectations and relationships, and discussed assertiveness, linked with themes from the previous session. The session finished with a different relaxation practice (visualisation) and further goal setting. Participants were again asked to complete an activity diary for 1 week.

The third and final session started by reflecting on the goals set and activity diaries, and then focused on the recognition and management of relapse of fatigue. A relapse plan booklet was devised by each patient, focusing on the core skills that had been particularly helpful to them, and what they could do to maintain their progress. The session finished with a third relaxation practice (progressive muscular relaxation), and further goal setting for the future.

Outcomes

The primary outcomes were the effect of the active and control interventions on fatigue severity and impact scores. Secondary outcomes included the effect on IBD activity indices, depression, anxiety and somatization scores, and generic and disease-specific quality of life. Questionnaires were administered at study entry and repeated at 6 months.

Statistical analysis

All questionnaire data at baseline and 6-month follow-up, including fatigue severity and impact, HADS scores, PHQ-15 scores and generic and disease-specific quality of life indices were analysed using means. Owing to the small number of patients in each treatment arm, we did not compare these

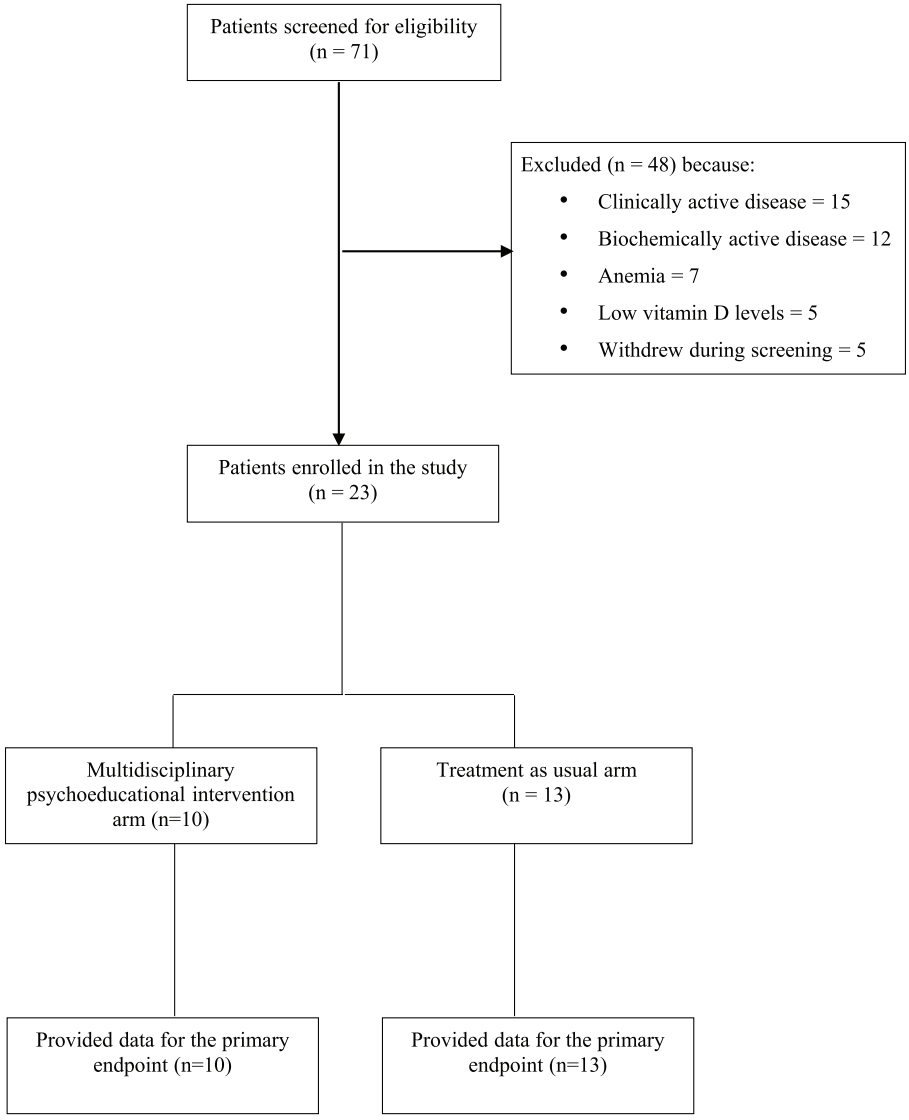

Figure 1. Flow of participants through the study.

using statistical testing, in order not to make spurious claims about efficacy of the intervention.

Results

Patient and disease characteristics

In total, 71 patients (31 male, 40 female) who reported fatigue were screened for entry into the trial. In total, 48 patients were screened but were not eligible for randomization (Figure 1). Reasons included abnormal clinical disease activity indices in 15, abnormal biochemical activity indices in 12, anaemia in seven, low vitamin D levels in five and failure to provide a stool sample in four. A further five patients withdrew during screening, one due to a family emergency, and the other four without giving a reason. Therefore, 23 patients were enrolled, with 10 in the active intervention arm and 13 in the control arm. The age range among those randomized was 19–61 years, and 6 men and 17 women were randomized. No significant differences were found between the treatment arms with respect to mean age, marital status, smoking status, educational attainment or disease activity, and distribution. Baseline characteristics of both groups are provided in Table 1. Attendance rates at the sessions were 86.7% overall. There were no patients lost to follow up.

Table 1. Baseline characteristics of subjects in the active intervention and control arms.

			Control ($n = 13$)	Active Intervention ($n = 10$)	All patients ($n = 23$)
Mean age			39.9	39.7	39.8
Mean BMI			23.8	24.9	24.3
Gender (%)	Male		30.8	20.0	26.1
	Female		69.2	80.0	73.9
Marital status(%)	Married/cohabiting		76.9	60	69.6
	Divorced/separated		7.7	20.0	13.0
	Never married		15.4	20.0	17.4
Smoker (%)	Yes		46.2	10.0	30.4
	No		53.8	90.0	69.6
Alcohol use (%)	Yes		92.3	60.0	78.3
	No		7.7	40.0	21.7
Educational level (%)	Secondary school		23.1	40.0	30.4
	Some technical school/college		7.7	20.0	13.0
	Technical school/college graduate		15.4	10.0	13.0
	Some university		0	20.0	8.7
	University graduate		30.8	10.0	21.7
	Postgraduate		23.1	0	13.0
Previous surgery (%)	Yes		53.8	60.0	56.5
	No		46.2	40.0	43.5
Type of IBD (%)	CD		84.6	90.0	87.0
	UC		15.4	10.0	13.0
Disease location or extent (%)	CD	Ileal	15.4	40.0	
		Colonic	15.4	10.0	
		Ileocolonic	46.2	40.0	
	UC	Proctitis	7.7	0	
		Left-sided	7.7	0	
		Extensive colitis	0	10.0	
Treatments (%)	5-ASAs		0	10.0	4.3
	Immunosuppressants		69.2	50.0	60.9
	Biologics		84.6	70.0	78.3
	Glucocorticosteroids		0	10.0	4.3

BMI, body mass index; CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Influence of the multidisciplinary psychoeducational intervention on fatigue severity and impact scores

Baseline fatigue scores for both fatigue severity and impact of fatigue on daily activities were worse at baseline in the active intervention group compared with the control arm. Following the intervention, both fatigue severity and impact scores improved for patients in the multidisciplinary psychoeducational intervention group (by 9.7% and 7.3%, respectively), whereas these worsened in controls (by 9.4% and 4.4% respectively). These data are provided in Table 2.

Influence of the multidisciplinary psychoeducational intervention on clinical disease activity and psychological parameters

There were not enough patients with UC randomized to calculate any data on SCCAI, but for patients with CD HBI did not improve, and actually worsened among patients in the active intervention group (mean score 2.4 at baseline, compared with 5.4 at follow up). Among controls, mean HBI at baseline was 2.8, compared with 3.8 at follow up. Anxiety and depression scores worsened slightly from baseline to 6 months in both the control arm and the multidisciplinary psychoeducational intervention arm (4.2–5.3 and 5.7–6.9, respectively, for anxiety and 7.7–8.5 and 6.6–8.7, respectively, for depression). Somatisation scores were stable among both controls and the multidisciplinary psychoeducational intervention group between baseline and 6 months (10.5–11.2 and 11.8–11.7, respectively).

Influence of the multidisciplinary psychoeducational intervention on generic and disease-specific quality of life

The SF-36 questionnaire provided subcategory data on generic quality of life according to physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy, emotional wellbeing, social functioning, pain and perception of general health (Table 2). Physical functioning worsened in both arms, by 5.4% in controls and by 6.4% in the intervention arm. Role limitations due to physical health decreased by 12.5% in the intervention group and increased by 17.4% among controls. Role limitations due to emotional problems remained the same in the control arm, and increased by 30.3% in the intervention group. Energy scores in the intervention group were improved by 49.4%, but by only 0.9% among controls. Emotional wellbeing was improved by 4.6% in the intervention group, but worsened by 4.4% among controls. Social functioning was broadly unchanged in both groups, increasing by 0.4% in controls and 1.7% in the intervention group. Pain scores worsened by 9.3% in controls, but improved by 3% in the intervention arm. Finally, perception of general health worsened by 6.1% among controls, but improved by 9.2% in the intervention arm. In terms of disease-specific quality of life, SIBDQ scores improved in both groups, but by only 2.2% in controls compared with 9.9% in the intervention group.

Discussion

We present data from a pilot RCT, in which a multidisciplinary psychoeducational intervention focusing on fatigue management in patients with quiescent IBD, the majority of whom had CD, was compared with a standard of care control group. Although this was a small pilot study, we were able to demonstrate positive effects on fatigue, energy levels and a range of other quality of life outcomes. This was in spite of disease parameters that, if anything, appeared to worsen, with an increase in HBI scores among those with CD. This is the first RCT to report improved SIBDQ scores in a cohort of patients with IBD in clinical and biochemical remission, following a fatigue intervention.

The multidisciplinary psychoeducational intervention did not improve anxiety, depression or somatization scores, nor was it designed to. However, by improving energy and fatigue levels, such interventions may be of benefit to the unmet needs of the many patients with quiescent IBD who report debilitating levels of fatigue, with a consequent negative impact on quality of life. The observed natural history of previous longitudinal studies of patients with IBD does not suggest an improvement in fatigue scores over time, regardless of their disease course.[31,32] Therefore, the improved outcome for fatigue levels in patients undergoing the intervention, albeit in a relatively small group, is encouraging.

Limitations of this study include its small sample size, and the fact that it was unblinded, and therefore patients were aware of the treatment arm

Table 2. Fatigue, clinical disease activity, and quality of life scores at baseline and 6-month follow-up among subjects in the active intervention and control arms.

		Control ($n = 13$)	Active Intervention ($n = 10$)	Cohen's D/ rYl
Mean fatigue severity score	Baseline	11.5	14.5	0/0
	Follow up	12.6	13.1	
Mean fatigue impact score	Baseline	33.5	49.7	0.091/ 0.045
	Follow up	35.0	45.8	
Mean HBI	Baseline	2.8	2.4	–0.119/ 0.059
	Follow up	3.8	5.4	
Anxiety score	Baseline	4.2	5.7	0.629/ 0.300
	Follow up	5.3	6.9	
Depression score	Baseline	7.7	6.6	–0.847/ 0.390
	Follow up	8.5	8.7	
Somatization score	Baseline	10.5	11.8	–0.716/ 0.337
	Follow up	11.2	11.7	
SF-36 physical functioning score	Baseline	73.6	77.4	0.490/ 0.238
	Follow up	69.6	72.4	
SF-36 role limitations due to physical health score	Baseline	44.2	44.4	–0.135/ 0.067
	Follow up	51.9	38.9	
SF-36 role limitations due to emotional problems score	Baseline	59.0	37.0	–0.224/ 0.111
	Follow up	59.0	48.2	
SF-36 energy score	Baseline	31.4	17.8	–0.442/ 0.216
	Follow up	31.7	26.6	
SF-36 emotional wellbeing score	Baseline	70.5	58.8	0.040/ 0.020
	Follow up	67.4	61.5	
SF-36 social functioning score	Baseline	64.4	61.5	–0.044/ 0.022
	Follow up	64.7	62.6	
SF-36 pain score	Baseline	65.6	57.0	–0.274/ 0.136
	Follow up	71.7	55.3	
SF-36 general health score	Baseline	44.2	36.1	0.024/ 0.012
	Follow up	41.5	39.4	
SIBDQ score	Baseline	46.2	44.4	0.569/ 0.274
	Follow up	45.2	40.0	

HBI, Harvey–Bradshaw index; SF-36, 36-item Short Form health survey; SIBDQ, Short Inflammatory Bowel Disease Questionnaire.

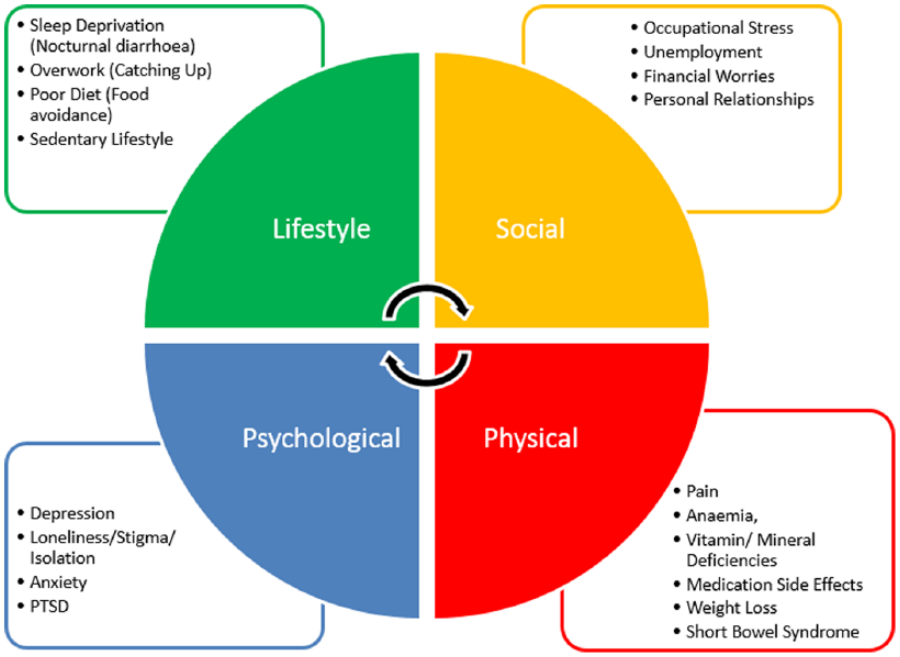

Figure 2. Factors contributing to fatigue in inflammatory bowel disease.

they were assigned to. This may have led to a high placebo response rate among those randomized to the active treatment, and disappointment among those who received the control intervention, which may have led to a worsening of their fatigue symptoms. In addition, we were unable to repeat CRP and FC measurements at the end of the study. We had initially intended to randomise 40 patients but delays in the ethics process meant we were only able to randomize 23 suitable patients in the lifetime of the grant. A longer period of follow up after the end of the study would also have been desirable. Some previous studies of psychological therapies in patients with IBD have shown a lack of durability of their beneficial effects, with regression to the mean over time, once the intervention has been completed.[15,33–35] Nonetheless, we believe that this study adds to a small body of literature of RCTs in IBD that use fatigue and energy scores as primary endpoints, and utilize validated questionnaires to define quality of life parameters.

Fatigue in IBD is a complex, multidimensional problem for patients requiring an accessible, multidisciplinary response from providers. Whether fatigue represents true inflammatory activity, anaemia, mood disorder or symptom-reporting in general remains unclear.[36,37] The many factors leading to fatigue in IBD probably reflect the ability of both CD and UC to interfere across many domains of life (Figure 2). We would therefore argue that, given the complexity of fatigue in IBD, the multidisciplinary approach piloted in this trial, encompassing gastroenterology, psychology and occupational therapy, may be more likely to provide comprehensive and durable benefits to patients with IBD. These issues are of significant concern to both patients and practitioners in IBD, because fatigue and impaired quality of life appear to be related to an increased risk for relapse or symptoms of the disease.[38–42]

Although most of the available evidence on interventions to reduce fatigue comes from trials of biologic therapies, nonpharmacological interventions, such as physical activity and psychosocial interventions, have been applied in IBD populations, but these have mainly focused on mental health symptoms or overall quality of life.[15,34,35,43,44] Many of these studies have used nonvalidated questionnaires and are therefore difficult to reliably interpret. One study reported that stress management techniques had a beneficial effect on tiredness, compared with treatment as usual in patients with CD.[15] In another study, solution-focused therapy, directed at adequacy of existing coping abilities of patients with fatigue, had a positive effect on both

fatigue and generic and disease-specific quality of life in patients with IBD, but the effect diminished during follow up.[17] This study involved seven visits, making the strategy considerably more labour intensive than the one we report, which carries clear cost implications. The advantages of affordable strategies for fatigue management are self-evident, as psychological interventions resulting in improvements in quality of life have been shown, in some studies, to result in significant reductions in subsequent healthcare usage.[45,46] Other studies have shown physical exercise and activity to be beneficial,[47–49] but it may be more difficult in practice to tailor such interventions to a diverse group of patients with chronic IBD.

The results of this pilot RCT will hopefully lead to larger studies of fatigue management strategies, which investigate whether the signals we observed, in terms of improvements in fatigue severity, impact and quality of life, are replicated. These should be adequately powered, with a longer duration of follow up, and assess the cost-effectiveness of strategies for fatigue management. We selected patients with troublesome fatigue whose disease was in both clinical and biochemical remission not only because they are a group of patients with significant unmet needs, but also to reduce the confounding effect of disease activity in a small cohort. Larger studies that recruit patients with IBD with fatigue would be particularly welcome. Ultimately, an ideal future scenario may be one where a multidisciplinary team is able to tailor a bespoke suite of solutions for patients with IBD and fatigue, which may include exercise, pharmacologic, nutritional and psychoeducational measures to fit the patient's profile and disease characteristics.

Author contributions

AOC, PJH, DP, AE and LW conceived and drafted the study. RR, LW, DJG and RCS collected all data. ACF and AOC analysed and interpreted the data. AOC and ACF drafted the manuscript. All authors commented on drafts of the manuscript. All authors have approved the final draft of the manuscript.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by Crohn's and Colitis UK (Reference Number: SP2015/3).

Conflict of interest statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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