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ECCO Topical Review

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European Crohn's and Colitis Organisation Topical Review on Complementary Medicine and Psychotherapy in Inflammatory Bowel Disease

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Abstract

Patients with inflammatory bowel disease [IBD] increasingly use alternative and complementary therapies, for which appropriate evidence is often lacking. It is estimated that up to half of all patients with IBD use various forms of complementary and alternative medicine during some point in their disease course. Considering the frequent use of such therapies, it is crucial that physicians and patients are informed about their efficacy and safety in order to provide guidance and evidence-based advice. Additionally, increasing evidence suggests that some psychotherapies and mind–body interventions may be beneficial in the management of IBD, but their best use remains a matter of research. Herein, we provide a comprehensive review of some of the most commonly used complementary, alternative and psychotherapy interventions in IBD.

Key Words: Inflammatory bowel disease; alternative medicines; complementary medicines; psychotherapy

1. Introduction

Inflammatory bowel disease [IBD] is a chronic disease in which both medical and psychological factors have a major impact on the patient's quality of life [QoL]. Many patients seek alternative and complementary therapies,[1] for which appropriate evidence is often absent. However, considering the increasing use of such therapies, it is important that physicians are ready to provide evidence-based advice on their efficacy and potential risks.

High levels of psychological and emotional distress, fatigue, anxiety and depression are common among IBD patients, all of which are complex symptoms that require integrative and appropriate management.[2,3] Psychotherapies and mind–body interventions may have beneficial impact on coping skills and stress management, but their best use remains undetermined.

The aim of this topical review is to provide an overview on the most commonly used complementary, alternative and psychotherapy interventions used in IBD.

2. Methods

The European Crohn's and Colitis Organisation [ECCO] organized a topical review consensus group on the issue of Complementary Medicine and Psychotherapy in IBD. ECCO topical reviews are developed from expert opinion consensus and are endorsed by ECCO. As controlled data are absent, a topical review is distinct from ECCO consensus guidelines and is intended to provide guidance in clinical areas where scientific evidence is lacking. An open call was announced to all ECCO members; 15 individuals were selected based on their expertise in the topic. Three subgroups were formed. Working Group 1 focused on biologically based practices with the goal of reviewing products such as herbal medicines, probiotics, marijuana, vitamins and other dietary supplements. Working Group 2 focused on mind–body practices and psychotherapy interventions, with the goal of reviewing the main psychological domains that are altered in IBD [anxiety, depression, fatigue, etc.]. The available evidence for the use of hypnosis, yoga and psychotherapy interventions was reviewed. Finally, Working Group 3 focused on manipulative and body-based practices such as acupuncture and exercise.

All working groups performed a systematic literature search of their topic. Discussions of the published evidence among the working group members and a preliminary voting round took place. The working parties met in Vienna in February 2018 to agree on the statements. Statements were accepted when 80% or more of the participants were in agreement; statements were henceforth termed an agreed *Current Practice Position*. The group leaders and their respective working group wrote the final section for each subgroup. It is intended that the statements are read in context, with qualifying comments, and not in isolation. The final text was edited for consistency of style by the steering committee and one member of the Guidelines Committee of ECCO who were not involved in the consensus. We recognize that not all products or interventions have been included in this review as we chose to focus only on those that are most widely used.

3. Herbal Therapies and Dietary Supplements

Many studies have assessed a wide range of herbal therapies and different herbal preparations in IBD. These are summarized in Table 1.

3.1. Cannabis and other herbal therapies

Current Practice Position 3.1

Although the use of cannabis may be associated with a reduction of some symptoms in IBD, there is no good evidence to show that it positively affects the course of disease

A retrospective observational study on 30 patients showed promising results for *Cannabis* for the treatment of active Crohn's disease [CD].[4] A randomized controlled trial [RCT] assessed 22 patients who received either *Cannabis sativa* or placebo cigarettes.[5] Response rates and QoL, but not remission rate or reduction of C-reactive protein [CRP], were higher in the intervention group.[5] Side effects did not differ between the groups.

Two small controlled studies reported on the use of *Artemisia absinthium* [wormwood], a herbaceous plant, compared to placebo[6] or standard treatment[7] for the treatment of active CD [Table 1].

Current Practice Position 3.2

Curcumin as a complementary therapy to 5-aminosalicylic acid [5-ASA] may be effective in inducing remission in mild-to-moderately active ulcerative colitis [UC]. Curcumin, psyllium, and a herbal preparation consisting of myrrh, chamomile and coffee charcoal may be effective as complementary maintenance therapy in UC

For maintenance of remission in CD, a *Boswellia* extract compared to placebo was investigated in an RCT of 82 patients. There were no significant differences between the groups after 12 months. There were no serious adverse events in either group.[8] Another study tested the effects of a traditional Japanese herbal preparation [*daikenchuto*] compared to 5-ASA and azathioprine among patients who underwent surgery. The results of this study indicated a significantly lower 3-year reoperation rate in the *daikenchuto* group.[9]

High doses of *Tripterygium wilfordii* Hook F, a plant widely used in Chinese traditional medicine, led to prolonged remission and was well tolerated.[10–13] For prevention of postoperative recurrence, *T. wilfordii* was less effective than azathioprine in the long term.[10–13]

For treatment of active UC, no differences regarding disease activity or remission rates were observed with curcumin enema plus oral mesalamine, as compared to placebo enema plus oral mesalamine.[14] Oral curcumin plus oral mesalamine compared to placebo plus oral mesalamine resulted in more patients achieving endoscopic remission at the end of the 1-month treatment period and more patients showed clinical improvement in the curcumin group.[15] The incidence of adverse effects was not different between the treatments.

A study on 44 patients compared *Aloe vera* gel to placebo and showed significant improvements in clinical signs and QoL after 4 weeks. Reductions in histological score were also observed. No serious adverse events were reported.[16]

Two studies evaluated the effects of the oral drug HMPL-004 [*Andrographis paniculata*].[17,18] No significant differences were found in one study, while in the other study higher response rates were observed with HMPL-004. The effects of pomegranate [*Punica granatum*] peels plus standard treatment were compared to placebo plus standard treatment in a study on 79 patients.[19] Clinical treatment response was higher in the *P. granatum* group, although this was not statistically significant.

Table 1. Characteristics of included trials on herbal medicine sorted by disease condition

Induction CD	Author	*N* [subjects, groups]	Study type	Intervention	Control	Results
	Naftali *et al* [2011]	30, 1 group	Retrospective observational study	*Cannabis*	—	• Improvement of disease activity [VAS] • Decrease in Harvey–Bradshaw index, bowel movements, and need for other drugs
	Naftali *et al* [2013]	22, 2 groups	RCT placebo-controlled double-blind	*Cannabis sativa* cigarettes [115 mg THC per cigarette]; 2 per day	Placebo	• Significant differences in favour of cannabis: response rate [CDAI] and quality of life [SF-36] • n.s.: remission rate [CDAI], CRP
	Omer *et al* [2007]	40, 2 groups	RCT placebo-controlled double-blind	*Artemisia absinthium* [AA] + steroid or prednisolone; 6 × 250 mg/day	Placebo + steroid or prednisolone	• Significant differences in favour of AA: clinical improvement [CDAI], subjective well-being [VAS] • n.s.: IBDQ and HDS
	Krebs *et al* [2010]	20, 2 groups	RCT standard care controlled open-label	AA + standard treatment; 9 × 250 mg/day	Standard treatment	• Significant differences in favour of AA: TNF-α, clinical activity [CDAI], IBDQ, HDS
Maintenance of remission in CD	Holtmeier *et al* [2011]	82, 2 groups	RCT placebo-controlled double-blind	*Boswellia serrata* extract PS0201Bo; 6 × 400 mg/day	Placebo	• n.s.: maintenance of remission, time to relapse, clinical activity [CDAI], IBDQ • No serious adverse events
	Kanazawa *et al* [2014]	258, 2 groups		Dried extract powder of *daikenchuto*, *Zingiberis rhizoma*, *Ginseng radix* and *Zanthoxyli fructus*; 7.5–15 g/day	Azathioprine or 5-ASA	• Significant in favour of *daikenchuto*: 3-year reoperation rates • No serious adverse events
	Ren *et al* [2007]	20, 1 group	Open, prospective study	*Tripterygium wilfordii* Hook F pills; 3 × 4 10 mg capsules/day	-	• Decline in clinical activity [CDAI] • Endoscopic response [CDEIS] • Decrease in CRP, TNF-α and IL-1β levels
Induction UC	Singla *et al* [2014]	45, 2 groups	RCT placebo-controlled double-blind	Standardized curcumin preparation enema [NCB-02] + oral 5-ASA	Placebo + oral 5-ASA	• n.s.: Disease activity [UCDAI], remission rate [UCDAI <3] and endoscopic disease activity
	Lang *et al* [2015]	50, 2 groups	RCT multicentre placebo-controlled double-blind	Oral curcumin capsules; 2 × 3 g/day	Placebo	• Significant in favour of curcumin: clinical remission [SCCAI], clinical improvement [SCCAI], endoscopic remission • 3 serious adverse events [n.s. between groups]
	Langmead *et al* [2004]	44, 2 groups	RCT placebo-controlled double-blind	*Aloe vera* gel; 2 × 100 mL/day	Placebo	• Significant in favour of *Aloe vera*: disease activity [SCCAI] and histological results • Significant in favour of placebo: IBDQ • n.s.: remission, physician's global assessment, sigmoidoscopic examination, laboratory testing [Hb, platelet count, CRP, serum albumin] • No serious adverse events

Table 1. *Continued*

Induction CD	Author	*N* [subjects, groups]	Study type	Intervention	Control	Results
	Tang *et al* [2011]	120, 2 groups	RCT controlled double-blind	*Andrographis paniculata* [HMPL- 2004]; 3 × 400 mg/day	Mesalamine	• Significant improvements in both groups: clinical efficacy [DAI], EI and histological efficacy
	Sandborn *et al* [2013]	224, 3 groups	RCT placebo-controlled double-blind	*Andrographis paniculata* extract [HMPL-004] + mesalamine; 3 × 1200 mg or 1800 mg/day	Placebo + mesalamine	• Significant differences in favour of HMPL-004: clinical response • n.s.: clinical remission, mucosal healing, Mayo score
	Kamali *et al* [2015]	2 groups	RCT placebo-controlled double-blind	*Punica granatum* peel extract; 6 g/day	Placebo	• Significant reduction in both groups: Lichtiger Colitis Activity Index • Clinical response higher in favour of *Punica granatum* at week 4 but not 10
	Ben-Arye *et al* [2002]	24, 2 groups	RCT placebo-controlled double-blind	Wheat grass [WG] juice; 100 mL/day	Placebo	• Significant differences in favour of WG: DAI, rectal bleeding, physician's global assessment, patients' retrospective evaluation and abdominal pain • n.s.: stool frequency, sigmoidoscopic score, mucus, abdominal bloating, number of bowel movements • No serious adverse events
	Tong *et al* [2010]	126, 3 groups	RCT placebo-controlled single-blind	*Sophora* colon-soluble capsules; 18 or 12 × 960 mg/day	Mesalamine	• n.s.: clinical efficacy, fibrocolonoscopic examination, stool sample
	Biedermann *et al* [2013]	13, 1 group	Open pilot trial	Bilberry [*Vaccinium myrtillus*] preparation; 4 × 40 g/day with an average anthocyanin dose of 840 mg/day	-	• 63.4% achieved remission [CAI] • 90.9% response rate [CAI] • Significant changes in favour of bilberry in Mayo score, short IBDQ and faecal calprotectin • n.s.: acute inflammatory activity as defined by biopsy, serum markers [CRP, leukocytes, neutrophil granulocytes, and thrombocytes], electrolytes, markers of renal and liver function
	Patel *et al* [2013]	50, 1 group	Non-randomized observational clinical study	Oral administration of herbal drugs [*Holarrhena antidysenterica*, *Ficus glomerata*, *Cyperus rotundus*, *Mesua ferrea* and *Symplocos racemosa*] + rectocolonic administration of *Ficus glomerata* and ayurvedic dietary advice	—	• Reduction in frequency of bowel movements, presence of blood in stool, requirement for conventional drugs, symptoms [abdominal pain, weakness and weight loss] • Improvement in Hb, ESR, erythrocytes and cells in stool • No serious adverse events
	Huber *et al* [2007]	16, 1 group	Open-label, dose-escalating study	Tormentil extracts; 1200, 1800, 2400 and 3000 mg/day	—	• CAI and CRP improved during therapy with 2400 mg tormentil/day • Neither undegraded nor metabolized tannins could be detected in patient sera

Table 1. *Continued*

Induction CD	Author	*N* [subjects, groups]	Study type	Intervention	Control	Results
Maintenance of remission in UC	Hanai *et al* [2006]	89, 2 groups	RCT placebo-controlled double-blind	Curcumin + sulfasalazine or mesalamine; 2 g/day	Placebo + sulfasalazine or mesalamine	• Significant improvements in favour of curcumin: CAI, EI and recurrence rate • No serious adverse events
	Langhorst *et al* [2013]	97, 2 groups	RCT double-blind double-dummy	4 tablets Myrrhinil intest [100 mg myrrh, 70 mg chamomile extract and 50 mg coffee charcoal], 3× day + 1 tablet placebo/3× day	Mesalamine	• n.s.: clinical colitis index [CAI], modified CAI, EI, faecal markers, laboratory measures [CRP, white blood cells, Hb] • 10 [Myrrhinil] vs 8 [mesalamine] serious adverse events, no causal relationship to therapy
	Rastegarpanah *et al* [2015]	80, 2 groups	RCT placebo-controlled double-blind	Oral silymarin; 140 mg/day	Placebo	• Significant improvements in favour of silymarin: Hb, ESR, increase in butyrate concentrations and disease activity [DAI] • Not reported: symptoms [abdominal pain, diarrhoea, fatigue, anorexia, joint or eye complications]
	Johari and Gandhi [2016]	30, 3 groups	RCT placebo-controlled single-blind	*Holarrhena antidysenterica* tablet or *Holarrhena antidysenterica* tablet + mesalamine; 2 tablets/day	Mesalamine	• Herbal tablets alone: maximal reduction in abdominal pain, diarrhoea, and bowel frequency and stool consistency scores • Herbal tablet alone and in combination with mesalamine: significantly reduced stool infection; no adverse events

Abbreviations: CAI, Clinical Colitis Activity Index; CD, Crohn's disease; CDAI, Crohn's disease activity index; CDEIS, Crohn's Disease Index of Severity; CRP, C-reactive protein; DAI, Disease Activity Index; EI, endoscopic efficacy; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; HDS, Hamilton depression scale; IBDQ, Inflammatory Bowel Disease Questionnaire; n.s., not significant; RCT, randomized controlled trial; SCCAI, Simple Clinical Colitis Activity Index; SF-36, Short form [36] health survey; UC, ulcerative colitis; UCDAI, Ulcerative Colitis Disease Activity Index; VAS, visual analog scale.

Wheat grass showed positive effects on disease activity, rectal bleeding and abdominal pain.[20] Another study on 126 patients assessed *Sophora* colon-soluble capsules or mesalamine over a period of 8 weeks.[21] There were no significant differences between groups regarding disease activity or laboratory measurements.

For maintenance of remission in UC, curcumin had positive effects on disease activity and recurrence rate at 6 months.[22] Curcumin is only available as an over-the-counter food supplement and relevant quality concerns regarding the preparation of the herbs may be an issue.

Treatment with a herbal preparation of myrrh, chamomile and coffee charcoal vs mesalazine exhibited no significant differences between the treatment groups regarding relapse rates, relapse-free time, endoscopy and faecal biomarkers.[23] The herbal preparation was well tolerated and had a good safety profile. This preparation is available as a drug at least in single countries in Europe.

A study on 80 patients revealed that silymarin in addition to standard therapy had positive effects on haemoglobin levels, erythrocyte sedimentation rate and disease activity.[24] However, no significant differences between groups were reported.

Preliminary evidence indicates that *Holarrhena antidysenterica* might be effective although the study quality was very low.[25]

Traditional Chinese medicine [TCM] herbs are individualized based on symptoms and treatments are often based on classification of disease patterns. Accordingly, a conclusion regarding TCM herbs cannot be provided. However, TCM shows promising evidence.[26–29]

Other herbs not yet evaluated by RCTs show promise in treating IBD. An open pilot study explored the effects of an anthocyanin-rich bilberry preparation in 13 patients with active UC. Over half [63.4%] of the patients achieved remission and 90.9% showed a response.[30]

An open-label, dose-escalating study on 16 patients with active UC assessed tormentil in escalating doses for 3 weeks. During tormentil treatment, Colitis Activity Index decreased with highest effect sizes for 1800, 2400 and 3000 mg/day.[31]

A non-randomized observational clinical study assessed an ayurvedic preparation [extract of *Holarrhena antidysenterica*, decoction of *Ficus glomerata*, powder combination of *Cyperus rotundus*, *Mesua ferrea* and *Symplocos racemose*, and *Ficus glomerata* decoction] in UC patients. Reductions in bowel movements, blood in the stool and abdominal pain and improvements in general well-being and reduced intake of aminosalicylates were observed.[32]

In summary, only a few, small trials of limit quality have investigated the role of herbs in the therapy of IBD patients, and this probably limits their routine use in the clinic.

3.2. Vitamins and minerals

Current Practice Position 3.3

There is insufficient evidence to support the use of vitamins and minerals to induce or maintain remission in CD and UC

Therapy with vitamin D,[14,33–56] vitamin B[57–59] and vitamin K[60] has been examined regarding their possible involvement in inflammatory pathways in IBD.

Vitamin D deficiency is multifactorial in IBD and ranges between 10% and 75% across studies.[61] The causes of vitamin D deficiency in patients with IBD include inadequate exposure to sunlight from reduced physical activity, inadequate dietary intake, impaired absorption and impaired conversion of vitamin D.[61] The use of vitamin D as a therapy has been explored in vitamin D-deficient interleukin-10 [IL-10] knockout mice, which develop a rapidly progressive form of IBD. Disease was attenuated when these mice were given a high calcium and vitamin D diet.[62] Some human studies have examined the role of vitamin D in IBD treatment.[35,36,40,63] A study on the use of vitamin D as maintenance therapy in CD patients in remission demonstrated that only 13% of the patients in the vitamin D replacement group relapsed during the 12-month study period compared to 29% in the placebo arm [$p = 0.06$].[36] Another group compared the therapeutic effects of vitamin D replacement on bone health and CD activity and reported significant improvement during the 6-week follow-up period.[35] An accelerated supplementation protocol for patients with CD or UC led to significant improvement in symptom-based activity [CDAI] scores but not in objective markers of inflammation.[55]

A recent meta-analysis revealed that levels of vitamin B12 were significantly lower in IBD patients than in healthy controls (standardized mean difference [SMD] −0.57 pg/mL; $p < 0.001$). However, there was significant heterogeneity in the included studies.[59] Mortimore and Florin reported the impact of high-dose vitamin B12 on the treatment of ten consecutive IBD patients with dermatoses and showed improvement in cutaneous manifestations in six patients but not in those with only fistulizing CD.[58]

A recent review reported the prevalence of vitamin K deficiency in 111 paediatric IBD patients as 54% [CD] and 43.7% [UC], which correlated with higher disease activity and was probably due to malabsorption and malnutrition.[64] In a study from the Framingham Offspring population, vitamin K levels were inversely correlated with inflammatory markers [such as CRP]; it was postulated that vitamin K may have anti-inflammatory properties.[65] One study reported no significant effects of vitamin K supplementation on bone health status in patients with CD.[60] No study has investigated the effects of vitamin K supplementation on disease activity in IBD.

3.3. Dietary supplements

Current Practice Position 3.4

There is insufficient evidence to support the use of diet supplements or specific diets to induce or maintain remission in CD and UC. However, future research should focus on diet as a complementary therapy

This section is focused on dietary supplements other than enteral or parenteral nutrition. A more comprehensive review on diet and nutrition has been published in a separate Topical Review.[66]

Common nutritional and dietary supplements comprise dietary fibre supplements [including prebiotics such as fructo-oligosaccharides] and fatty acids. The theorized mechanism underpinning the pathogenesis of IBD is an aberrant response by the mucosal immune system to microbiota in genetically susceptible individuals.[67] Short-chain fatty acids such as butyrate, arising from anaerobic fermentation of dietary fibre, are thought to positively influence the gut microbial composition and enhance colonic epithelial barrier function.[68–80] The tested forms of fibre delivery in IBD range from dietary advice[81] to fibre supplementation. Such supplementation includes psyllium[67,81,82] and germinated barley.[83–85] A systematic review of three RCTs in UC and one study in pouchitis revealed positive results for the use of fibre supplementation.[67] No studies in CD showed added benefit,[86–88] while others showed equivalence.[89,90] The trials examined showed conflicting results. Treatment of UC patients with germinated barley revealed a significant reduction in CRP but not in clinical activity indices.[83] However, a separate study on UC patients revealed a significant reduction in clinical indices, but not CRP, after administration of germinated barley.[85]

Fructo-oligosaccharides are prebiotics that are non-digestible, selectively fermentable, short-chain carbohydrates that stimulate the growth or activity of selected beneficial microbial species, such as *Faecalibacterium prausnitzii* and Bifidobacteria, resulting in potential health benefits to the host.[88] An open-label pilot study on CD patients revealed a significant reduction in Harvey–Bradshaw index [HBI] and a non-significant reduction in inflammatory markers [CRP].[91] This study was followed up with an adequately powered RCT that did not show a statistically significant different clinical response.[88] Another RCT showed a significant reduction in HBI compared with baseline.[92]

Specific diets, such as a diet high in salmon,[93] have been examined for the treatment of IBD. The purported benefit of salmon is its high *n*-3 polyunsaturated fatty acid [PUFA] content [omega-3], with the additional benefit of peptides and phospholipids that accompany the fish [see also next paragraph].[93] *n*-3 PUFAs are thought to produce an anti-inflammatory effect through the reduction of pro-inflammatory cytokines.[93] A single-arm open-label pilot study on 12 patients that assessed the efficacy of a salmon-rich diet in patients with mild-to-moderate UC revealed that an intake of 600 g of salmon weekly over 12 weeks significantly reduced disease activity [$p < 0.01$], was associated with a trend towards lower CRP, and increased the anti-inflammatory fatty acid index in biopsies and plasma.[93]

Despite the current deficiency of quality data for diet supplements or specific diets in IBD, dietary therapies have the potential to be a meaningful complementary treatment and should be the focus of future research.

3.4. Fish oil – omega-3 fatty acids

Current Practice Position 3.5

Omega-3 fatty acids might be beneficial in maintaining remission in CD. However, study quality and the heterogeneity of trials limit these findings

Fish oil, or *n*-3 PUFA, is thought to reduce production of IL-1, IL-6 and tumour necrosis factor [TNF].[94] Oxidative stress, caused by an imbalance between the formation of reactive oxygen species and

counteracting antioxidants, occurs in several chronic inflammatory conditions, including IBD. Increasing the antioxidant level might reduce tissue damage and the inflammatory process. Fish and fish proteins may have such an antioxidant potential.[95–97] A beneficial effect of fish oil and fish protein has been shown in some animal models.[95] Fish oil is found predominately in oily fish and in commercially produced fish oil capsules. Several studies have been conducted to test the effect of omega-3 fatty acid [FA] supplementation [also called *n*-3 or ω-3 FA] on biochemical and clinical outcomes in IBD.

Among CD patients, two studies[98,99] assessed the effect of *n*-3 FA compared with *n*-6 FA on biochemical and clinical markers of inflammation as adjuvant therapy to corticosteroid treatment in patients with active disease. Nielsen *et al*. [*N* = 31] showed that *n*-3 FA had immunomodulatory properties and might inhibit the increase of proinflammatory cytokines in contrast to *n*-6 FA.[98] Eivindson *et al*. [*N* = 31] showed that disease activity and CRP decreased from baseline to week 9 in both the *n*-3 and the *n*-6 group.[99]

A Cochrane review[94] that assessed *n*-3 FA for the maintenance of remission in CD found a marginal benefit for *n*-3 FA over placebo in preventing relapse after 1 year (relapse rate, *n*-3 group 39% vs placebo 47%, six studies, 1039 patients, relative risk [RR] 0.77, 95% confidence interval [CI] 0.61–0.98). The same trend was also found in two other systematic reviews.[100,101] Patients with CD had a significant reduction of relapse risk within 1 year compared with placebo in favour of *n*-3. However, there was heterogeneity in the pooled analyses, publication bias and small negative trials were underestimated. In addition, no reduction in 1-year relapse rate was observed in the two high-quality studies, namely EPIC1 and EPIC2.[102]

In patients with UC, two systematic reviews found no difference in the relapse rate between *n*-3 FA supplementation and control groups.[100,103] These studies did not record significant adverse events.

An RCT on 211 patients assessed the effect of a combination of a nutritionally balanced oral supplement enriched with fish oil, fructo-oligosaccharides, gum arabic, vitamin E, vitamin C and selenium on disease activity and medication use in adults with mild-to-moderate UC. This study revealed similar rates of improvement of disease activity score and need for corticosteroids over a 6-month period as placebo.[104] Studies assessing the effect of fish oil on extra-intestinal manifestations [such as joint pain] via administration of seal oil have shown promising results.[105–107] A study that compared seal oil and cod liver oil found a tendency toward improvement in several joint pain parameters for both oils.[107] Another study found positive results for duodenal administration of seal oil [rich in *n*-3 FAs] compared with soy oil [rich in *n*-6 FAs]. Soy oil tended to aggravate joint pain.[105]

3.5. Probiotics

Current Practice Position 3.6

There is no evidence to support the use of prebiotics, probiotics or both in patients with CD, either in the induction or the maintenance of remission. There is no evidence to support the use of prebiotics, probiotics or both in the postoperative CD patient

A recent overview summarized the evidence for probiotics in IBD patients.[108] Two trials [*N* = 37] evaluated the efficacy of probiotics in the induction of remission in CD.[109,110] Both studies failed to show a clinical benefit. Studies evaluating maintenance of remission in quiescent CD patients [*N* = 195] also failed to show a statistically significant benefit.[111,112] The role of probiotics in preventing relapse in CD patients in remission following surgically induced remission [*N* = 333] remains controversial and no recommendations on their use can currently be given.[113–116] In summary, there is little evidence for the use of probiotics in the treatment of CD.

Current Practice Position 3.7

Escherichia coli Nissle 1917 may be effective in inducing and is effective in maintaining remission in UC. A multistrain probiotic containing a combination of lactic acid bacteria, streptococcus and bifidobacteria may be effective in inducing and maintaining remission in UC

Eight studies evaluated the efficacy of probiotics in inducing remission in patients with active UC.[117–124] One study compared non-pathogenic *Escherichia coli* Nissle 1917 b.d. for 12 weeks with mesalazine for 12 weeks [*N* = 116].[121] There was no statistically significant difference between the two groups. The other seven studies [*N* = 535] were RCTs that compared probiotics with placebo.[117–120,122–124] Three of these trials [*N* = 319] used a multistrain probiotic containing eight different probiotics [*Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus bulgaricus*, *Streptococcus thermophilus*].[119,122,124] A recent systematic review[108] calculated on those three studies showed a number needed to treat of 5 for this multistrain probiotic [95% CI 4–10]. Six RCTs evaluated the efficacy of probiotics [*Bifidobacterium longum*, *Lactobacillus acidophilus*, *Bifidobacterium animalis* subsp. *lactis* BB-12, *Escherichia coli* Nissle 1917, *Streptococcus faecalis* T-110, *Clostridium butyricum* TO-A and *Bacillus mesentericus*] in the maintenance of remission in quiescent UC.[125–130] Of these trials, three compared probiotics with 5-ASAs [*N* = 555][126,127,130] and three compared probiotics with placebo [*N* = 122].[125,128,129] In summary, probiotics showed efficacy in maintaining remission in UC patients. Since probiotics are usually well tolerated, they are useful alternatives to conventional medical therapy especially in UC patients.

4. Mind–Body Medicine and Psychotherapeutic Interventions

A significant proportion of IBD patients report or suffer from depression, anxiety or both. The prevalence rates of these disorders have been evaluated in four systematic reviews[131–134] and two large observational studies,[135,136] where they were compared between IBD and healthy and medically ill controls.

4.1. Anxiety

Current Practice Position 4.1

There are data showing higher rates of anxiety preceding the diagnosis of IBD in adult patients

Current Practice Position 4.2

Anxiety is common in IBD, particularly during flares, with higher rates than in healthy controls but not in medically ill controls. Anxiety is slightly more common in CD than in UC

Adults with IBD are more likely to develop anxiety before IBD onset; 70% of those with IBD and a lifetime history of anxiety or a mood disorder had a first episode of an anxiety disorder 10 years or more before the IBD diagnosis, whereas just 8% developed anxiety ≥2 years after IBD onset.[136]

The pooled prevalence estimate for anxiety disorders in adult IBD patients is 20.5% [95% CI 4.9–36.5%].[133] In CD, the pooled rate of anxiety-related symptoms is 19.1% [±3.63, 95% CI], 28.2% [±2.7, 95% CI] during remission, and 66.4% [±7.8, 95% CI] during flares [37% [±9.9, 95% CI]].[132] In UC the pooled rate of anxiety symptoms is 31% [±14.2, 95% CI] as compared to 9.6% [±1.94, 95% CI] in healthy controls.[132]

In studies in which IBD cases were compared with medically ill controls, the pooled average rate of anxiety symptoms was 41.9% [±9.2, 95% CI] for IBD and 48.2% [±31.1, 95% CI] for medically ill controls.

4.2. Depression

Current Practice Position 4.3

There are data showing higher rates of depression preceding IBD diagnosis in adult patients

Current Practice Position 4.4

Depression is common in IBD, particularly during flares, with higher rates than in healthy controls but not in patients with other chronic diseases

Similar to anxiety, 54% of adult IBD patients with a lifetime history of anxiety or mood disorders had an onset of depression ≥2 years before IBD onset while 23% developed depression ≥2 years after IBD onset.[136]

The pooled prevalence of depressive disorders in adults is 15.2% [95% CI 9.9–20.5%]. The pooled mean rate of depressive symptoms in IBD is 21.2% [±2.9, 95% CI] compared with 13.4% [±1.9, 95% CI] for healthy controls,[132] with a higher prevalence in CD [25.3%, 95% CI 20.7–30%] than in UC [16.7%, 95% CI 12.0–21.4%] and a higher prevalence in active [40.7%, 95% CI 31.1–50.3%] vs inactive disease [16.5%, 95% CI 7.4–25.5%].[133] In the studies with medically ill controls, the pooled mean depression rate was 14.5% [±10.5, 95% CI] in IBD vs 28.4% [±17.7, 95% CI] in medically ill controls.

4.3. Stress

Patients often report stress as a major trigger of both disease and flares; this association has been examined in several studies.[3,137–142] In a population-based study [*N* = 704], only high perceived stress was associated with an increased risk of flares (adjusted odds ratio [OR] 2.40, 95% CI 1.35–4.26).[140] In two prospective studies[3,142] each approximately with almost 500 participants, perceived stress was associated with symptomatic activity for both CD and UC. Patients with persistently active disease reported significantly higher stress than the persistently inactive group [mean stress at 3-month follow-up 23.64, 95% CI 21.81–25.46 vs 17.46, 95% CI 16.46–18.45].[142] A smaller prospective study on CD patients [*N* = 101] also found stress, when paired with avoidance coping, as a significant predictor of flare.[141]

Current Practice Position 4.5

There is some evidence that stress is associated with a higher risk of relapse in IBD. There are no data on stress contributing to the aetiology of IBD

4.4. Fatigue

Current Practice Position 4.6

Even if inconsistently defined in the literature, fatigue is common in IBD patients and affects social functioning and QoL. Fatigue is associated with anxiety or depression, disease activity, sleep disturbances, reduced physical activity, medication use, and anaemia

Despite being extensively studied,[2,143–160] fatigue has been inconsistently defined in the literature and commonly reported as a secondary outcome.[144] Vogelaar *et al.* found that several immune parameters were higher in fatigued patients, including TNF-α [$p = 0.02$] and IL-12 [$p < 0.001$]; IL-6 was lower in these patients [$p = 0.002$].[156]

The reported fatigue prevalence in IBD ranges between 22% and 48% in remission and between 44% and 86% in moderate-to-severe active disease.[2,143,149] Almost 50% of newly diagnosed patients report fatigue.[150] Severe anaemia can cause fatigue,[146,147] but this is not the case with iron deficiency without anaemia.[152] Other contributors include nutritional deficiency, smoking, and immune and genetic factors.[145,146,148,156] In an observational study of 631 patients, 50% with anaemia experienced daily fatigue, irrespective of disease activity.[153] In a cross-sectional survey [*N* = 5382], prolonged use of corticosteroids was associated with fatigue vs non-use [55% vs 51%; $p = 0.001$] in patients aged >60 years.[154] In a systematic review,[148] depression, stress, sleep disturbances and anxiety [in this order] were associated with IBD fatigue. Fatigued patients reduce physical activity, with an estimated effect size of 1.02 [$p = 0.04$].[155] Exercise programmes could address the physical component of IBD fatigue.[155,158] Fatigue reduced QoL in three studies [*N* = 84].[147] Low QoL can in turn increase fatigue.[151]

4.5. Irritable bowel syndrome and functional symptoms in IBD

The evidence on functional gastrointestinal disorders is mostly limited to irritable bowel syndrome [IBS]-type symptoms.[161–166] The pooled prevalence of IBS in IBD is approximately 39% [95% CI 30–48%],[166] and is slightly lower during remission [35%, 95% CI 25–46%] than during flares [44%, 95% CI 24–64%]. When compared with controls, the OR for IBS was 4.89 [95% CI 3.43–6.98] in all IBD patients, 4.39 [95% CI 2.24–8.61] in remission and 3.89 [95% CI 2.71–5.59] in active disease. The prevalence of IBS in CD was higher than in UC [46% vs 36%; OR 1.62, 95% CI 1.21–2.18]. In a recent cross-sectional study [*N* = 6309], Abdalla *et al.*[161] observed a 20% rate of self-reported IBS diagnosis. Two large studies [*N* = 1321 with IBS-like symptoms, *N* = 6401 for all IBD patients] revealed worse QoL, higher levels of anxiety, depression, fatigue,

sleep disturbances, pain interference and decreased social satisfaction in patients with IBS-like symptoms.[161,165]

A cross-sectional study on children [*N* = 184][162] found that the prevalence of IBS-type symptoms was highly dependent on the definition of remission.

Current Practice Position 4.7

IBS is common in IBD and is associated with adverse patient-reported outcomes. IBS is slightly more common in CD than in UC

4.6. Sleep

Evidence regarding sleep disturbance in IBD is based on two case-control studies,[167,168] five cohort studies[169–172] and one cross-sectional study.[173]

The prevalence of sleep disorders in IBD ranges between 44% and 66% [vs 27–55% in healthy controls and 67–73% in IBS].[168,169,171,173] Even in remission, IBD patients [*N* = 119] report significantly more sleep disturbance [prolonged sleep latency, frequent sleep fragmentation, high use of sleeping pills and poor overall sleep quality] than healthy controls; however, rates were similar to IBS.[167] Sleep disturbance is slightly more common in CD than in UC.[167] Two prospective cohort studies[171,172] [*N* = 3214] found an association between poor sleep quality and disease activity. Several cohort studies [*N* = 1468] suggest an association between poor sleep quality and an increased risk of IBD relapse at 6 months to 1 year.[169,171,174]

Current Practice Position 4.8

There is limited evidence on the frequency of sleep disturbance in IBD. Some studies report higher rates of sleep disturbance in IBD than in healthy controls

In summary, anxiety and depression are common in IBD. High perceived stress is associated with a higher risk of relapse. Fatigue is common in IBD and is associated with higher disease activity and increased rates of anxiety and depression. IBS is common in IBD and is associated with poorer patient-reported outcomes. There is limited evidence on the frequency of sleep disturbance in IBD and further studies focused on sleep in IBD are needed.

4.7. Cognitive behavioural therapy

Current Practice Position 4.9

Cognitive behavioural therapy [CBT] has a short-term beneficial effect on QoL in adults with IBD. There is limited evidence on the efficacy of CBT in adolescents; early reports are promising in terms of QoL and coping

CBT is a type of psychotherapy that teaches patients to identify and modify unhelpful negative thinking styles and maladaptive behaviours. It has a shorter duration than traditional psychotherapies [6–12 weeks].[139] Common elements of CBT include exploration of the links between cognitions and emotions, cognitive restructuring and challenging unhelpful thoughts, psycho-education, coping and relaxation.

The evidence on the effectiveness of CBT in IBD has been summarized in two meta-analyses[138,175] and two systematic reviews.[139,176] CBT seems to improve short-term QoL in adults [*N* = 254, SMD 0.37, 95% CI 0.02–0.72],[175] albeit with little or no effect on disease activity, anxiety, depressionor perceived stress.[139,176] A positive short-term effect of CBT on QoL [SMD 0.70, 95% CI 0.21–1.18] and coping [SMD 0.75, 95% CI 0.26–1.25] was noted in adolescents [*N* = 71].[138]

4.8. Hypnotherapy

Current Practice Position 4.10

There is limited evidence on the efficacy of hypnotherapy to reduce IBD symptoms, maintain clinical remission and increase QoL in UC

The effectiveness of hypnotherapy [treatment involving deep relaxation, focused attention and an enhanced ability to follow suggestions] has been studied in IBD.[138,139,175,177] A small study showed an immune-modulating effect of a 50-min session of gut-directed hypnotherapy in 17 patients with active UC.[139,177] Three pre-post hypnotherapy studies [*N* = 2, CD, with a 6-month follow up; *N* = 8, IBD; *N* = 15, severe UC with 5.4-year follow up] and one trial in UC [*N* = 23] have shown that hypnotherapy improves QoL and reduces bowel symptoms.[139,177] One RCT in quiescent UC [*N* = 54] showed that gut-directed hypnotherapy maintains clinical remission [68% for hypnosis vs 40% of controls maintained remission for 1 year; $p = 0.04$].[139,175,177]

4.9. Other psychotherapies

Current Practice Position 4.11

Psychodynamic therapy may reduce depressive and anxiety symptoms. Stress management has only modest benefits in reducing IBD symptoms and improving mental health or QoL. Solution-focused therapy [SFT] might be beneficial for patients with fatigue

The evidence on the effectiveness of psychodynamic therapy as well as SFT in IBD is based on two meta-analyses and two systematic reviews.[138,139,175,176] Other psychotherapies such as psychodynamic [PD] therapy and stress management [SM] interventions have also been investigated in IBD.[138,139,175,176] PD is derived from traditional psychoanalysis and focused on working with transference [i.e. the redirection of childhood emotions to a therapist]. Common elements of PD are interpretation, empathic validation, free association, and analysis of transference, regression and resistance.[139] PD must be used as a long-term therapy [20–52 weeks in IBD trials]. SM is focused on developing strategies to manage stress and includes breathing exercises, relaxation, biofeedback and problem solving [typically 6–8 sessions]. SFT uses the patient's past experiences to address current difficulties and relies on identifying solutions that worked in the past and finding exceptions to the patient's problems [typically 5–6 sessions]. No or minimal effects of PD, SM and SFT on long-term disease activity have thus far been observed.[138,139,175,176] Significant short-term improvements in QoL and fatigue were observed in patients with elevated fatigue scores receiving SFT.[175] There is limited evidence for SM and PD to improve mental health and QoL.[139,176]

4.10. Meditation, mindfulness and relaxation

Current Practice Position 4.12

Meditation and relaxation may improve QoL and possibly decrease inflammatory activity in IBD. There is limited evidence on the effectiveness of mindfulness-based interventions on disease activity

Meditation is a broad term encompassing practices aimed at reaching a heightened level of consciousness and concentration. Mindfulness is a type of meditation dedicated to being present in the moment. It involves activities where one focuses on a particular sensation, such as taste or smell, and brings the mind to breathing. Relaxation is a process of reducing tension in the body and mind and may involve breathing activities or tensing and relaxing different muscle groups. Meditation, mindfulness and relaxation are often used as part of psychotherapies but also as standalone treatments to promote well-being.

While older trials in IBD [N = 136] reported improvements in symptoms, psychosocial well-being and QoL using relaxation and stress management, recent trials found benefit on QoL only [two RCTs, N = 121].[178] Two recent studies[179,180] [N = 29 and N = 60, respectively] showed that mindfulness improved psychological and physical symptoms in IBD and reduced CRP levels.[179] Norton *et al.*[181] showed pain reduction using relaxation, meditation, or both in four out of six studies. Timmer *et al.*[138] showed no evidence for the efficacy of relaxation in unselected adults with IBD.

4.11. Yoga

Current Practice Position 4.13

There is limited evidence on the efficacy of yoga to reduce IBD symptoms. Yoga improves QoL in adults with IBD

The largest survey performed to date [N = 235][182] reported that 16.3% of paediatric IBD patients [aged 2–22 years] practised yoga, meditation or tai chi, while the second survey [N = 67, aged 12–19 years] reported that 10% of patients practised yoga.[183] One trial[184] [N = 60, UC; N = 40, CD; all adults in remission] compared an 8-week yoga intervention to treatment as usual [TAU]. The study showed yoga to be no different than TAU, except for colic pain which was reduced in the yoga group [$p < 0.05$]. Another RCT[185] [N = 77; adults with UC in remission] on patients with impaired QoL who received 12 sessions of yoga or written self-care advice showed yoga to be effective in improving QoL after 12 and 24 weeks [$p = 0.018$ and $p = 0.022$, respectively]. Yoga also improved disease activity after 24 weeks [$p = 0.029$].

In summary, CBT improves QoL in IBD over the short term. Although the evidence on the efficacy of hypnotherapy to reduce IBD symptoms is limited, the efficacy of hypnotherapy in functional gut disorders[186] warrant future studies in IBD. PDT and SM may reduce symptoms of depression and anxiety, but not IBD severity. SFT might be beneficial for patients with fatigue. Meditation and relaxation may improve QoL and potentially reduce inflammatory activity in IBD. Evidence on the effect of mindfulness-based interventions on disease activity is limited and the role of this intervention in IBD management should be further explored. There is limited evidence on the efficacy of yoga to reduce IBD symptoms, but yoga may improve QoL in adults with IBD.

5. Manipulative and Body-Based Interventions

5.1. Moxibustion and acupuncture

Current Practice Position 5.1

There is insufficient evidence to support the use of moxibustion and acupuncture [either in monotherapy or in combination] for the treatment of active UC or CD

The term acupuncture [AP] refers to the insertion of needles for remedial purposes into specific points [acupoint receptors].[187] Moxibustion is a procedure involving the use of heat generated by burning material, which is then applied to certain areas of the body [usually AP points[187]] where it stimulates superficial and deep tissues of the skin.[188] Several burning materials can be used, the most usual being moxa [a herbal preparation containing *Artemisia vulgaris*]. Direct moxibustion involves direct application to the skin around an AP point, whereas indirect moxibustion or herb-partitioned moxibustion [HPM] is performed with some insulating materials between the moxa cone and the skin.[187–189] AP and moxa are often used in combination.[187] Several human studies have assessed the clinical benefit of these interventions in IBD [Supplementary Table 1].

5.1.1. Moxibustion alone

A systematic review and meta-analysis assessed the evidence of moxibustion alone for the treatment of UC;[189] five RCTs conducted in China were included, three of which compared moxibustion with sulfasalazine [SASP] and the remaining two compared moxibustion to SASP and other drugs [antibiotics, steroids]. The efficacy of moxibustion was based on the physician's assessment [recovery, marked improvement, improvement and no change] or endoscopy. The meta-analysis suggested a small favourable effect of moxibustion when compared with SASP alone [RR 1.23, 95% CI 1.04–1.46; $p = 0.01$] or SASP combined with steroids or antibiotics [RR 1.33, 95% CI 1.11–1.59; $p = 0.002$] with overall low heterogeneity. However, all trials were non-blinded and reported incomplete outcome measures, and were therefore considered to have a high risk of bias.[189] Furthermore, non-standard measures of clinical and endoscopic activity were used, thus greatly limiting the conclusions.

5.1.2. Acupuncture vs moxibustion

Moxibustion and e-AP electro-acupuncture were compared as separate treatments in a randomized study of CD patients in sustained remission. Thirty-six patients were randomly assigned to electro-acupuncture or moxa treatment over 12 weeks. In both arms there was a significant reduction of CDAI and a significant increase in the Inflammatory Bowel Disease Questionnaire [IBDQ] score; no significant difference was seen between both interventions.[190]

5.1.3. Acupuncture combined with moxibustion

The efficacy and safety of AP with moxibustion were evaluated in patients with mild-to-moderate CD; 92 subjects were randomly assigned to receive either active treatment [HPM with AP] or placebo [wheat-bran-partitioned moxa combined with superficial

needle application in non-acupoints] over 12 weeks. Both groups had a significant reduction in the CDAI and IBDQ score at week 12, which was significantly greater in the active treatment arm [$p < 0.001$]. Patients in the active treatment group also showed a significant improvement in haemoglobin [$p = 0.026$], CRP levels [$p = 0.008$] and histopathological scores [$p = 0.029$] when compared with placebo. No significant difference was found in endoscopy.[191]

Another randomized, single-blind trial evaluated the efficacy of the combined methods in reducing CDAI after 4 weeks of treatment. Patients with mild-to-moderate CD were randomly assigned to receive ten AP sessions over 4 weeks or sham AP. All patients in the AP arm were treated with *Artemisia* moxa. Fifty-one patients were treated [27 in the active arm and 24 in the control arm]. While CDAI reduction was significantly higher in the treatment arm [$p = 0.003$], the overall remission rates were not statistically different between the two arms. QoL was improved in both arms although the difference did not reach statistical significance [$p = 0.064$].[192]

Two large studies assessed the efficacy of AP combined with moxibustion in UC.[193,194] In one study, 121 patients were randomly assigned to receive either AP [$N = 76$] or SASP 1 to 2 g four times/day [$N = 45$] over a period of 20–60 days. In the intervention group, 59% of patients entered remission as compared with 39% of patients in the control group. Low-quality trial design affected the validity of these results.[193] In another study on 123 patients with mild-to-moderate UC, HPM with AP was compared with sham intervention [bran-partition moxibustion].[194] A significant improvement [defined as disappearance of clinical symptoms and normal colonic mucosa by sigmoidoscopy] was observed in 52.5% of patients treated with HPM vs 24.5% of patients who received sham intervention. No baseline description of patient features was provided [such as extent of colitis, Mayo score, concomitant therapies during the trial], making the results difficult to interpret.[194] In another small RCT in mild-to-moderate UC, 29 patients were randomly assigned to receive AP plus moxibustion or sham AP for 5 weeks. Disease activity was measured by the Colitis Activity Index [CAI] and QoL with IBDQ and a ten-point visual analog score. The treatment group showed a significant decrease in CAI after treatment [$p < 0.001$] and the benefit was maintained throughout the 16-week follow-up [$p < 0.001$]. Although patients in the control group showed an improvement in disease activity, treatment was significantly superior [$p = 0.048$]. In the treatment group, CAI was statistically lower than that at baseline [$p < 0.001$]. QoL was improved in both groups.[195]

Finally, a meta-analysis examined the clinical efficacy of AP and/or moxibustion compared with SASP for the treatment of UC.[196] The overall efficacy of AP alone, moxibustion alone or AP combined with moxibustion was greater than the efficacy of SASP [RR 5.42, 95% CI 3.38–8.68; $p < 0.0001$]. However, the trials were underpowered and were mostly of low quality with subjective assessments of efficacy.[196] Additionally, whether true blinding is even possible was questioned, as the acupuncturist always knows if the needle is inserted in an acupoint or not. Moreover, needle insertion can lead to non-specific physiological responses and this could explain why in some studies an improvement was also obtained with sham acupuncture.[197]

In summary, the low quality of the published studies, even if with positive results, precludes any valid conclusion and recommendations.

5.2. Chiropractic treatment and osteopathy

Current Practice Position 5.2

There is minimal evidence on the efficacy of chiropractic and osteopathy in the management of active CD

Chiropractic and osteopathy are two different types of complementary and alternative medicine [CAM]. Chiropractic treatment involves manual therapy, usually spinal manipulation therapy, but also manipulations of other joints and soft tissues. Osteopathy involves massage, stretching, pressure and mobilization of various tissues or organs.[198,199] A summary of the major studies on chiropractic and osteopathy can be found in Supplementary Table 2.

In a longitudinal, population-based study of health outcomes in an IBD cohort, among patients who used CAM, 14% used chiropractic treatament.[200,201] In a study from Sweden, 5.4% of IBD patients made use of chiropractic therapy compared with 5.7% of the normal population.[202]

There are limited data on the use and benefit of chiropractic and osteopathy as CAM in IBD, with only two randomized trials published. In a single-blind study, CD patients in remission were randomized into two groups. The aim of the study was to determine if there was an improvement in IBDQ score following visceral osteopathic treatment. Fourteen patients received a visceral osteopathic technique at the root of the mesentery. The root of the mesentery gives rise to the mesentery of the small intestine and is the region connected to the structures in front of the vertebral column. The control group [$N = 13$] did not receive any osteopathic treatment and received virtual manipulation, which consisted of palpation of the small intestine and colon without action on the vasculature and innervations. Change in QoL was assessed using the IBDQ. The IBDQ score increased significantly [$p < 0.001$] in the group treated with osteopathy; no significant change was observed in the control group [$p = 0.22$].[199] In another study, 38 CD patients who were in remission receiving infliximab were randomly assigned 2:1 to receive osteopathic or sham therapy at 15, 30 and 45 days after infliximab infusion. The severity of IBS-like symptoms was significantly reduced in patients receiving osteopathy [$p = 0.01$, $p = 0.04$ and $p = 0.05$ at day 30, 45 and 60, respectively].[203]

There are currently no published studies evaluating chiropractic and osteopathy in patients with UC or IBDU.

5.3. Exercise

Current Practice Position 5.3

Exercise can have beneficial effects on overall health, physical well-being, perceived stress and QoL of IBD patients. There is promising but limited evidence on the role of exercise both in protection from IBD development and in disease management

Regular exercise exerts anti-inflammatory effects, which may be mediated through a reduction in visceral fat mass [with a consequent decreased release of adipokines] and the induction of an anti-inflammatory environment.[204,205]

In a retrospective database analysis, a sedentary occupation was associated with a two-fold increase in IBD incidence.[206] In two large

prospective female cohorts, physical activity was inversely associated with risk of CD but not of UC.[207] Compared with women with low physical activity, the multivariate adjusted hazard ratio [HR] of CD among women with very high physical activity was 0.64 [95% CI 0.44–0.94].[207] Active women with at least a 27 metabolic equivalent task [MET] hours/week of physical activity had a 44% reduction [HR 0.56, 95% CI 0.37–0.84] in the risk of developing CD compared with sedentary women with <3 MET hours/week.[207] In a case-control study the RR of CD was inversely related to regular physical activity [weekly exercise, RR 0.6, 95% CI 0.4–0.9; daily exercise, RR 0.5, 95% CI 0.3–0.9].[208] Furthermore, in a recent meta-analysis it was demonstrated that physical activity has a protective effect against developing CD.[209] No significant inverse association between physical activity and UC was observed.

Exercise could be used in the treatment of IBD either for its anti-inflammatory potential or for symptom relief.[210] Several studies have been performed on IBD patients [Table 2][179,207,208,211–216] and have shown that exercise could be beneficial via a positive effect on QoL. However, these studies were limited by small sample size. In the largest study to date, 117 CD patients in remission where randomized to either a low-impact exercise programme or no prescribed exercise. The primary end point was bone mineral density [g/cm^2] measured at baseline and at 12 months at the hip and spine [L2–L4] by dual-energy X-ray absorptiometry. This study revealed that exercise was associated with increasing bone mineral density. Effects on disease activity were not measured.[211] A prospective study[216] on CD patients in remission [CDAI < 150] revealed that those with higher exercise levels were significantly less likely to develop active disease at 6 months. In UC patients in remission, those with higher exercise levels were also less likely, albeit non-significantly, to develop active disease at 6 months.

Data are lacking regarding the intensity and type of exercise. Furthermore, for active disease there is a possibility that exercise could exacerbate symptoms, as more rigorous exercise may cause

Table 2. Studies on exercise and IBD

Study [year]	*N*	Study type	Results
Elsenbruch *et al* [2005]	30	RCT, either low-impact exercise programme of increasing intensity or no exercise prescribed	Significantly greater improvement in the IBDQ than in the control group
Gerbarg *et al* [2015]	29	RCT, either Breath–Body–Mind Workshop or control [educational seminar]	Significant improvements in psychological and physical symptoms, QoL and CRP
Klare *et al* [2015]	30	RCT, either supervised moderate-intensity running 3× a week for 10 weeks or a control group [no prescribed exercise]	IBDQ improved 19% in the intervention group and 8% in the control group [$p = 0.081$]; scores for the IBDQ social sub-scale were significantly improved in the intervention group compared with controls [$p = 0.026$]
Ng *et al* [2007]	32	RCT, either low-intensity walking at an interval of 3× per week for a duration of 3 months [each walking session was 30 min] or a control group [no prescribed exercise]	Patients in the exercise group experienced a statistically significant [$p < 0.05$] improvement in QoL
Loudon *et al* [1999]	12	Open label, a supervised, 3× week, 12-week walking programme	IBD Stress Index, the IBDQ, the Harvey–Bradshaw Simple Index, the Canadian Aerobic Fitness Test and VO_2 Max all showed statistically significant improvements at study end
Robinson *et al* [1998]	117	RCT, low-impact exercise programme of increasing intensity or a control group who were not prescribed any exercise.	In fully compliant patients, bone mineral density [BMD] increased. Compared with controls, gain in BMD at the greater trochanter was statistically significant; increases in BMD were significantly related to the number of exercise sessions completed
Patricia *et al* [2015]	1308 CD, 549 UC or indeterminate colitis in remission	Prospective observational study, Crohn's and Colitis Foundation of America Partners' internet-based cohort using the validated Godin leisure-time activity index	In patients with CD in remission, those with higher exercise levels were significantly less likely to develop active disease at 6 months; in patients with UC/IC in remission, patients with higher exercise levels were less likely to develop active disease at 6 months [not statistically significant]
Persson *et al* [1993]	152 CD, 145 UC, and 305 controls	Case-control study, postal questionnaire based on the population of Stockholm County during 1980–1984; information on physical activity and other lifestyle indices [oral contraceptives, previous diseases, childhood characteristics]	The relative risk of CD was inversely related to regular physical activity and estimated at 0.6 (95% confidence interval [CI] 0.4–0.9) and 0.5 (95% CI 0.3–0.9) for weekly and daily exercise, respectively
Khalili *et al* [2013]	284 CD, 363 UC [from 3 421 972 person-years of follow up]	Prospective cohort study, 194,711 women enrolled in the NHS II data on physical activity and risk factors every 2–4 years since 1984 in the NHS and 1989 in the NHS II and followed up through 2010	In two large prospective cohorts of US women, physical activity was inversely associated with risk of CD but not of UC

BMD, bone mineral density; CD, Crohn's disease, CRP, C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; NHS, Nurses' Health Study; QoL, quality of life; RCT; randomized controlled trial; UC, ulcerative colitis; IC, indeterminate colitis.

gastrointestinal symptoms such as bloating, cramps, and urgency to defecate.[217] A trial assessing two exercise regimens in adults with inactive or mildly active CD is currently underway.[218] New technology, including next-generation wearable physical activity trackers, could potentially improve exercise studies and might be used to promote physical activity[219] in IBD patients.

6. Conclusion

Various types of CAMs and psychotherapy interventions are available. However, for most of them, the lack of rigorously conducted trials has hampered their use. Regarding psychotherapy and mind–body interventions, a positive effect on QoL has been reported; effect in disease activity is less clear. Physicians should be informed about the evidence behind most frequently used CAMs and be ready to provide advice to their patients. Further research is needed before strong recommendations can be made.

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Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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