

# Third-wave therapies in inflammatory bowel disease: the outline therapy to reduce psychological stress, anxiety and depression in IBD adult patients

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## ABSTRACT

Inflammatory bowel diseases (IBD) are chronic immune-mediated disorders affecting the gastrointestinal tract, including Crohn's disease and ulcerative colitis. Numerous studies have demonstrated the bidirectional relationship between psychological disorders and IBD. However, although very useful, psychological assessment and psychotherapeutic intervention by specialized psychologists are not always performed in these patients.

Psychological treatments used with IBD patients include a wide spectrum of different interventions, such as psychodynamic therapies, cognitive-behavioral approaches, and third-wave therapies, with the aim of modifying the course of disease of affected patients, improving their quality of life, and reducing symptoms of anxiety and depression.

Third-wave therapies, such as Mindfulness-based intervention and Acceptance Commitment Therapy, are new forms of psychotherapy, which, based on scientific evidence, have been widely demonstrated to be effective in IBD patients. This narrative review provides an overview of the current state of the art regarding the use of third-wave therapies in the management of adult IBD patients, suggesting that they may represent a therapeutic option for the management of psychological stress, anxiety, and depression in these patients.

## INTRODUCTION

Inflammatory bowel diseases (IBD) are a group of chronic immune-mediated disorders that affect the gastrointestinal tract, including Crohn's disease (CD) and ulcerative colitis (UC). They are usually characterized by a relapsing-remitting course, with periods of latency alternated at phases of exacerbation<sup>1</sup>. IBD affects more than 5 million people worldwide, mostly in Western countries; their worldwide incidence is dramatically increasing especially in newly industrialized countries<sup>2</sup>, with a great impact on the quality of life of affected patients<sup>3</sup> and a significant direct and indirect healthcare burden<sup>4</sup>.

Although the pathogenesis of IBD remains still unclear, their development is considered the result of genetic, gut microbiota, environmental, and immune response factors. They probably derive from a dysregulation of the innate and adaptive immune system, which leads to

## KEYWORDS

THIRD-WAVE THERAPIES

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ACCEPTANCE COMMITMENT THERAPY

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an abnormal inflammatory response against commensal bacteria of the gut microbiota, in a genetically susceptible individual.

CD usually presents with abdominal pain, diarrhea, fatigue, and weight loss, while patients with UC usually develop hemorrhagic diarrhea, colicky abdominal pain, urgency, tenesmus, and fecal incontinence<sup>5</sup>. Nevertheless, IBD not only affects the gastrointestinal (GI) tract, but also may involve many other organs of the body. These manifestations of disease, referred to as extraintestinal manifestations (EIMs), occur with varying frequency depending on the affected organ. EIMs most commonly involve the skin (e.g., pyoderma gangrenosum, erythema nodosum, and aphthous stomatitis), musculoskeletal system (e.g., sarcopenia, asthenia, peripheral and axial arthritis, enthesitis), hepatobiliary tract (primary sclerosing cholangitis) and eyes (episcleritis, anterior uveitis, and iritis). They can significantly impact the quality of life (QoL) of IBD patients, even more than the underlying IBD<sup>6</sup>.

The goal for IBD treatment is a complete disease control, which requires both clinical and endoscopic remission through the inhibition of the inflammatory pathways involved in its pathogenesis. It is based on corticosteroids (for the acute phases), mesalamine (mostly for UC), traditional immunosuppressants and targeted therapies, including anti-tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), anti-integrin, anti-interleukin (IL) 12/23 and Janus kinases (JAK) inhibitors<sup>7,8</sup>.

The relatively low levels of clinical response rate, not exceeding 60% of patients<sup>9,10</sup>, together with the typical long-life lasting of the disease, the typical exacerbation stages, the ongoing concerns about the potential loss or reduction of control of bowel function, the possible need for medical surgery, the restrictive diets to be followed, the possible side effects of pharmacological therapies, and subsequent lifestyle changes can easily explain the impaired quality of life experienced by patients affected by IBD<sup>11,12</sup>.

Indeed, mental health problems concurrent with IBD are common and could represent another therapeutic opportunity for treatment<sup>13</sup>. Numerous studies demonstrated the bidirectional relationship between psychological disorders and IBD. Nowadays it is increasingly considered a disease of brain-gut interaction, with emerging evidence of bidirectional brain-gut and gut-brain links<sup>14</sup>. Moreover, when a person develops IBD, his susceptibility to anxiety and/or depression increases. These links result in higher rates of anxiety and depression in people with IBD compared with the general population<sup>15</sup>. For example, as many as 28% and 20% of people report, respectively, symptoms of anxiety and depression, during remission,

while these rates rise to 66% and 35% during IBD relapses<sup>15</sup>. Consistent with brain-gut linkages, these episodes of anxiety and depression have a significant impact on disease outcomes, including IBD flare-ups, hospital readmissions, and surgeries.

Furthermore, a recent systematic review and meta-analysis<sup>16</sup> showed that symptoms of anxiety and depression were significantly associated with future adverse outcomes in patients with IBD; in particular, they were related to future risk of flare, escalation of therapy, hospitalization, emergency room attendance, and surgery. On the other hand, the review shows that clinically active disease at baseline was associated with the future development of symptoms of anxiety or depression.

The complex gut-brain interaction involves the communication of neuroendocrine pathways with the hypothalamic-pituitary-adrenal axis and the central, peripheral, and autonomic nervous systems. Activation of these pathways was observed in murine models with quiescent colitis, whereby induction of depression reactivated the inflammatory response of the gut<sup>17</sup>. Induction was associated with attenuation of the vagal response and led to suppression of proinflammatory cytokine release by macrophages, mediated by  $\alpha 7nAChR$  on these cells.

Clinical and experimental evidence suggest that the enteric microbiota has an important impact on the gut-brain axis, interacting not only locally with intestinal cells and enteric nervous system, but also directly with the central nervous system through the neuroendocrine and metabolic pathways<sup>18-21</sup>. Several bacterial compounds present in human gut microbiota can modulate brain functions: the molecules released in the intestinal lumen in response to psychological stress can lead to altered intestinal permeability and gastrointestinal motility, thereby changing the gastrointestinal environment and the composition of the microbiome<sup>22</sup>.

The strong comorbidities and reciprocal influence between IBD and psychiatric disorders suggest the importance of a psychological evaluation of IBD patients; and, if appropriate, a therapeutic intervention by specialized psychologists. In fact, despite the obstacles sometimes present within standard gastroenterology care, which limit effective screening and treatment, it is now known that psychological intervention contributes to promote engagement and addressing the psycho-socio-welfare needs of people with IBD<sup>23-26</sup>. Indeed, several studies demonstrated the efficacy of psychotherapy in improving the quality of life and depression in IBD patients<sup>27</sup>.

The British Society of Gastroenterology consensus guidelines on the management of IBD in adults suggest that psychological therapies including

cognitive behavioral therapy (CBT), hypnotherapy and mindfulness should be offered to patients, particularly those with psychopathological symptoms, chronic pain and disabling fatigue, as adjunctive therapy to improve symptom control and quality of life<sup>28</sup>.

NICE Quality Standards and expert opinion<sup>29-31</sup> recommend a multidisciplinary approach in the management of IBD patients, in which the figure of the psychologist should always be included.

### Psychological treatments in IBD

Psychological treatments used with IBD patients include a broad spectrum of different interventions, such as psychodynamic therapies, cognitive-behavioral approaches and third-wave therapies<sup>32</sup>.

The aim of psychotherapy in patients with IBD may be to modify the course of the disease, improve their quality of life, or reduce symptoms such as anxiety and depression.

To date, publications in the literature show encouraging, although contradictory, results on the beneficial effect of psychotherapy in IBD. Interventions based on stress management show conflicting evidence of effectiveness. Some studies have shown an improvement in disease activity<sup>33,34</sup>, while others found no significant differences compared to the control group<sup>35,36</sup>. Regarding the effect on anxiety symptoms, one study<sup>37</sup> showed an improvement, while others found no difference<sup>34,36</sup>.

Evidence on the psychodynamic approach was mixed due to limitations related to a lack of intervention details and methodological limitations<sup>38</sup>. Jantschek et al explored the effect of psychodynamic psychotherapy on patients with Crohn's disease with regard to disease course and psychological symptoms<sup>39</sup>. After 2 years, 30% of the experimental group and 23% of the control group had not relapsed, while 17% of the experimental group and 29% of the control group had undergone surgery.

Some studies demonstrated an improvement in mental health after psychodynamic treatment<sup>40,41</sup>, while others have found no significant differences<sup>39,42,43</sup>.

Regarding the efficacy of hypnotherapy on IBD, Mawdsley et al demonstrated a 50-minute gut-focused hypnotherapy session to patients with active UC and assessed the systemic inflammatory response by measuring serum concentrations of interleukin (IL)-6 and IL-13, production of tumor necrosis factor-alpha and IL-6 by lipopolysaccharide-stimulated whole blood, leukocyte counts, natural killer cells, degree of platelet activation, and platelet-leukocyte aggregate formation<sup>44</sup>. Patients in the intervention group reported reductions in several components of the systemic inflammatory response. Reductions in serum interleukin-6 concentrations and decreased rectal

mucosal release were observed, based on associated changes in substance P, histamine, and general mucosal blood flow. However, another study<sup>45</sup> that proposed gut-directed hypnotherapy shows no significant changes about disease severity and quality of life in IBD patients after 20 weeks. Studies that have focused on CBT showed more consistent results than other types of approaches<sup>38</sup>. Mussell et al found lower rates of anxiety and depression nine months after the end of CBT for a group of patients with IBD<sup>46</sup>. One study demonstrated that a cognitive behavioral approach improved bowel and systemic symptoms<sup>45</sup>.

Szigethy et al compared the effect of CBT with that of non-directive supportive therapy in the treatment of adolescents with IBD in comorbidity and depression and found that both therapies had a significant impact in improving depression, while CBT was associated with a greater reduction in disease activity<sup>47</sup>. Reigada et al showed reductions in anxiety, pain and disease severity after a CBT intervention program for adolescent with IBD<sup>48</sup>.

A recent systematic review evaluated the efficacy of psychotherapy in the management of fatigue in IBD<sup>49</sup>. All approaches considered showed preliminary efficacy in improving fatigue. However, the most effective psychotherapy was CBT, with a greater reduction in fatigue severity.

The authors of a review<sup>32</sup> concluded that IBD patients are more probable to benefit from psychological therapy if it is individualized, holistic, targeted to psychological symptoms and individual life stressors and based on CTB.

Third-wave therapies are new forms of psychotherapy that naturally evolve from CBT, which has accumulated most of the evidence of effectiveness to date. The link with psychology as a basic science is maintained, with a focus on experimental verification, progress and individual patient change.

Third-wave therapies aim to work on the cognitive processes that support and maintain the various symptoms from which mental distress arises. They promote acceptance, defusion, shifting attention, and mindfulness and pay special attention to the therapeutic relationship to implement psychological well-being<sup>50</sup>.

### Mindfulness-based intervention

Mindfulness-based intervention (MBI) is a form of intervention that focuses on the body and mind. The principle of mindfulness consists in the ability to be present and aware of what is happening to us in a non-judgmental way<sup>51</sup>.

Historically, mindfulness has been called "the heart" of Buddhist meditation<sup>52</sup>, residing at the core of Buddha's teaching<sup>53-55</sup>. Despite specific differences within the

various currents, the Buddha explains that mindfulness is the central teaching and forms the foundation upon which all currents of Buddhist meditative practice rest. The founding theorist of Western mindfulness is Jon Kabat-Zinn, who in 1979 introduced the mindfulness-based stress reduction (MBSR) program at the University of Massachusetts Medical Center to manage chronic pain and stress-related disorders. According to the definition of Jon Kabat-Zinn (2003), mindfulness is defined as “the awareness that emerges through paying attention, on purpose, and non-judgmentally to the unfolding of experience moment by moment” (p. 145). If the mind remains anchored in the here and now, it does not tire of chasing the future and ruminating on the past. The founding principle of mindfulness in Buddhism – relieving suffering and cultivating compassion – suggests that it may be the recommended approach for patients with chronic diseases<sup>56</sup>.

Many studies have evaluated the effectiveness of MBI on chronic diseases<sup>57-59</sup>. A recent review<sup>60</sup> shows that the main benefit of mindfulness for patients with chronic diseases, such as cardiovascular disease, cancer, HIV, diabetes and musculoskeletal conditions is the reduction of psychological stress, while the effects on objective measures of disease are not significant. Indeed, the practice of mindfulness in chronic inflammatory conditions appears to have a protective role against the effects of stress on local neurogenic inflammation<sup>56</sup>.

Mindfulness-based interventions have been of particular interest, mostly in chronic diseases that often occur in comorbidity with psychiatric disorders<sup>61,62</sup>, as several studies demonstrated their effectiveness in treating anxiety and depression<sup>63-65</sup>. Furthermore, mindfulness showed to be associated with changes in specific biomarkers of immune system activity<sup>66</sup> and alterations in biological pathways, such as the autonomic nervous system and neuroendocrine function<sup>67</sup>.

Studies have shown that mindfulness practice, in addition to having a positive effect on mental health, helps reduce nausea, pain, and fatigue<sup>68</sup>.

Managing physical pain or emotional distress is a burden often present in people with IBD. Acceptance of chronic pain, however difficult, is extremely helpful in reducing the associated suffering. In fact, emotional reactivity to pain has the effect of making the individual anxiously watch over its possible presence and sensitizing the brain circuits responsible for processing this experience, so that they will register the pain even more. The same happens with emotions: if a depressive thought or feeling reaches awareness and is not accepted, a vicious cycle can be triggered in which mental rumination on these experiences only fuels them. On the other hand, along with acceptance and

non-reactivity, the ability to relinquish control of the flow of unpleasant physical or emotional experiences and become less involved with them also matures.

Most published studies that have used mindfulness intervention in patients with physical illnesses have applied the MBSR group program born from the work of Kabat-Zinn<sup>69</sup>.

MBSR training, designed for patients with chronic pain or terminal illness, has been shown to lead to increases in QoL and mental and physical health. There are eight mindfulness meditation group meetings with weekly frequency, lasting about two and a half hours, plus an intensive day of practice. In addition to moments of mindfulness meditation, the path also includes moments of sharing experiences and exercises to be done at home through materials and audio tracks. During sessions, therapists encourage patients to awareness, paying attention to the experience of the moment, usually by maintaining focus on the breath and observing distracting mental states. Furthermore, patients are instructed to develop an attitude of acceptance and non-reactivity to the momentary experience, with a gentle, patient, and non-judgmental attitude, even for painful physical and psychological experiences.

Another widely used intervention is Mindfulness-Based Cognitive Therapy (MBCT)<sup>70</sup>. This protocol is a reworking of Jon Kabat-Zinn’s work on the MBSR program. The MBCT program is structured, like MBSR, into eight meetings lasting about 2 hours and one full-day meeting. MBCT combines mindfulness meditation with cognitive therapy to alleviate distress associated with depression, anxiety, and psychosomatic problems through increased awareness of bodily sensations, thoughts, and emotions.

### Acceptance and Commitment Therapy

A related treatment to Mindfulness is Acceptance and Commitment Therapy (ACT). It is an approach based on Relational Frame Theory (RFT), combining the aspects of CBT and MBT, which can help patients develop psychological flexibility and improve coping strategies<sup>71,72</sup>.

Psychological flexibility is increased through the use of acceptance and mindfulness strategies, along with action engagement and behavior modification strategies.

ACT is a third-generation psychotherapy that aims to help the patient be more aware of their automatic thoughts, emotions and behaviors. It also emphasizes the role of personal values in the treatment path, encouraging committed actions and behaviors in line with what really matters to the patient, even in the presence of difficult or unpleasant emotions and thoughts<sup>73</sup>.

Psychological inflexibility emerges from experiential avoidance, cognitive fusion, conceptualized self, loss of contact with the present, and the consequent inability to take the necessary behavioral steps in accordance with core values. ACT, perhaps more than any other therapeutic approach, clearly expresses this concept: pathology is not in the topography of behavior but in the function. The patient is not asked to change because his behavior is incorrect but rather to persist or change behavior in order to achieve his goals and to be in touch with the things that matter to him. These things will give direction and not a preconception of pathology.

ACT demonstrates similar efficacy to CBT for the improvement of psychological distress in the general population<sup>50,63</sup> and in patients with pain related to chronic disease.

### **Mindfulness-based intervention for the management of IBD patients**

To date, Mindfulness interventions are increasingly being used as part of the integrated treatment of patients with IBD, but there are limited data and a lack of consensus on effectiveness.

A meta-analysis of 2019, on eight studies, showed that yoga and Mindfulness interventions were effective in reducing stress, depression and anxiety and improving quality of life, although they did not lead to significant improvements in physical symptoms of IBD<sup>74</sup>. Interestingly, the study also showed further decreases in stress scores on long-term follow-up, which is unusual in other psychotherapy research, where positive results usually fade with time.

Particularly, a controlled study on a group mindfulness intervention for IBD patients showed interesting results<sup>75</sup>. The study included adults with IBD being treated at the St. Vincent's Hospital Melbourne IBD Clinic. Thirty-three patients participated in the mindfulness-based intervention (adapted MBSR protocol). Twenty-seven patients were selected in the control group, receiving only standard medical care. Results showed that patients who participated in the mindfulness program reported statistically significant improvements in anxiety, quality of life and mindfulness. The improvements in quality of life and mindfulness were maintained at six months follow-up after the group intervention.

Mazaheri et al proved the effectiveness of mindfulness-based cognitive therapy on the perception of positive dimension of stress in UC patients<sup>76</sup>. Indeed, MBI can help patients with UC reduce cognitive distortions involved in the perception of stress, changing their evaluation of events so that they can better manage stressful events, increasing their ability to cope effectively with the disease.

Accordingly, a study exploring the benefits of online mindfulness-based interventions in IBD patients showed significant improvement in dispositional mindfulness and mindful eating and a significant decrease on measures of depression, stress and anxiety<sup>77</sup>. In contrast, no improvements were found in the quality-of-life measure in the test sample. Although this result may appear contrasting with the improvement in symptoms of anxiety, depression and stress found in this study, it is consistent with other evidence, in which the mindfulness-based interventions did not lead to significant overall improvements in the quality of life<sup>78</sup>. Interestingly, a recent study evaluated whether the psychological characteristics of CD patients were associated with their inflammatory status and whether a 3-month integrated cognitive-behavioral approach and mindfulness-based stress reduction trial (COBMINDEX) have an impact on their inflammatory process. The study showed that CD patients had a characteristic immunological profile that correlated with well-being, stress, and the disease process. COBMINDEX has been demonstrated to reduce daily psychological stress and to cause significant changes in patients' well-being. The positive outcomes of the patient after the group intervention were correlated with inflammatory changes, such as a reduction of IL-17 and an increase of IFN $\alpha$ , and with changes in cortisol, the "stress hormone", indicating that COBMINDEX may affect stress resilience and thus could enhance the immunoregulatory role of cortisol. Therefore, COBMINDEX exercise during relapse could act to reduce inflammatory tone. Finally, authors identified both biological, such as baseline higher levels of cortisol and lower of TNF $\alpha$ , and psychological markers that predicted the success of the proposed intervention, thus providing a personalized treatment plan for CD patients<sup>79</sup>.

A recent study<sup>80</sup> involving 40 patients with IBD compared the efficacy of a group intervention focusing on empowerment education combined with mindfulness meditation training in a subgroup of twenty patients with the control group. The results showed that the proposed intervention can effectively improve patients' negative emotions and their quality of life.

Recently, for the first time, the relationships between depression, disease symptoms and mindfulness in IBD patients have been considered within the theory of subjective well-being (SWB) homeostasis in an interesting study by K. Lyall et al. According to this theory, SWB is normally maintained by a homeostatic system around a fairly stable set point range, with normal values between 70-90, but it can fail when psychological challenges dominate consciousness.

As hypothesized by the authors, participants with IBD experienced lower levels of subjective well-being than the healthy population, demonstrating that the chronic stressors they are subjected to, lead to the defeat of SWB homeostasis. The study showed that engagement in mindfulness practice – including focused breathing, body scans, yoga exercises and guided meditations – doubled the Crohn's disease participants' odds reporting SWB within the normal homeostatic range after controlling for psychological, physical and demographic variables<sup>81</sup>. Therefore, this study provided initial evidence for an association between mindfulness and SWB homeostatic resilience in an IBD population. Interestingly, González-Moret et al conducted a study in which the focus, for the first time, was on the effect of a mindfulness-based therapy on several biomarkers among patients with inflammatory bowel disease. Specifically, the between-groups analysis showed that the group of patients who participated in the mindfulness intervention reported significant reductions in fecal calprotectin and C-reactive protein levels at six months follow-up, compared with the group who followed only standard medical therapy<sup>82</sup>.

One study<sup>83</sup> focused on the effectiveness of Multiconvergent Therapy – which combines CBT and mindfulness – on IBD patients with symptoms of irritable bowel syndrome. In this subgroup of patients, the analysis showed a significant improvement in the quality of life of affected patients compared with the control group that did not participate in group therapy.

### **Acceptance and commitment therapy for the management of IBD patients**

ACT is a therapy that has only recently been introduced as a pathway to complement normal clinical practice for the treatment of distress of patients with IBD. Therefore, although the constitutive theoretical model of ACT appears very useful for the treatment of the specific psychological difficulties of this category of patients, to date, only few studies have examined its efficacy.

A randomized controlled trial investigated the effect of an 8-week ACT-program on stress symptoms, anxiety and depression in patients with IBD. In the treatment group, there were reduced stress levels compared with patients in the control group. Furthermore, positive effects were found on the measures of perceived stress, depression, and the quality-of-life domain of general well-being. Conversely, no significant effect of treatment was found on anxiety symptoms. However, this result may be influenced by the characteristics of the participants who, overall, had relatively low levels of anxiety at baseline; therefore, no significant changes could be detected<sup>84</sup>.

Considering the recent interest in the ACT model for IBD patients, interventions were developed during the COVID-19 pandemic and, thus, short, and online protocols were also designed.

The study by Lavelle et al described two different brief ACT interventions offered to patients with IBD. The first group of patients was offered a single session ACT intervention, delivered face to face and lasting about two hours, targeting stress and experiential avoidance. Anyway, the results indicated that a single session ACT intervention failed to provide the expected results, because it was probably too short. A brief telehealth ACT intervention of two sessions delivered via a video conferencing platform and lasting approximately 4 hours was proposed to a second group of patients, with the aim of targeting stress and increasing psychological flexibility. Results indicated that around half of the participants experienced reduced stress, improved engagement in valued action, and increased functioning<sup>85</sup>.

Despite the great potential of ACT as a complementary treatment for the management of IBD patients, due to its role in promoting acceptance of situations that cannot be solved, such as persistent physical symptoms, to date, only few studies examined ACT in the treatment of IBD in adult patients. Nevertheless, recently two clinical trials, the ACT for IBD programme and the LIFE with IBD are currently ongoing<sup>86,87</sup>.

### **Discussion and future perspectives**

Patients with inflammatory bowel disease (IBD) express the need for additional psychotherapy; however, psychological support is usually not incorporated into the routine care of people with IBD.

The incorporation of mental health professionals into gastroenterology centers is critical to promoting patient-centered, biopsychosocial care<sup>88</sup>.

Multidisciplinary management allows the creation of complete treatment programs which, as demonstrated in the literature<sup>89</sup>, in addition to improving patient satisfaction, can reduce unexpected care, improve disease outcomes, increase the quality of life and reduce opioid consumption.

Among the various psychotherapeutic proposals that it is possible to propose, both ACT interventions and interventions based on mindfulness are particularly suitable for the management of patient with chronic illness. Furthermore, these approaches are particularly applicable to group therapeutic programs both as short-term and long-term therapy, as well as through telemedicine. In fact, brief group therapy is more sustainable in a hospital setting than individual pathways.

**Table 1.** Summary of included studies characteristics.

Author	Study design	N. participants N. groups	Type and duration of intervention	Follow-up	Outcome measures	Results
Neilson, 2016	Non-randomized controlled trial	60 IBD, 2 groups [33 experimental group; 27 control group]	MI-IBD 8 weeks 2.5 hours sessions; a 7-hour weekend session	- Baseline - Post-intervention - 32 weeks	<u>Psychological outcomes</u> - Quality of life (WHOQoL-BREF) - Depression and anxiety (HADS) - Mindfulness (FFMQ)	- Significant greater improvements in the MI-IBD group on anxiety, quality of life, and mindfulness after intervention; - Reduction of depression and improvements of quality of life, and mindfulness maintained at 6 months after intervention.
Mazaheri, 2020	RCT	17 UC, 2 groups [9 experimental group; 8 control group]	MBCT 10 weeks 120-minute sessions	- Baseline - Post-intervention	<u>Psychological outcome</u> - Perceived stress (PSS-10)	- Significant effect of MBCT on positive dimension of stress; - No significant effect on the negative dimension.
Forbes, 2021	RCT	33 IBD, 2 groups [7 self-guided; 26 supported]	Online MBIs 8 hours 2 hours per week	- Baseline - Post-intervention	<u>Psychological outcomes</u> - IBD quality of life (IBDQ) - Anxiety (BAI) - Perceived Stress (PSS) - Depression (PHQ-9) - Mindfulness (MAAS) - Mindful Eating (MES) - Obstacles (OBS) - Intrusive Thoughts (RTQ)	- No significant differences regarding psychological outcomes between the two groups; - A significant difference group was found in terms of rate of completion, with 44.1% of the supportive group completing the protocol compared to 11.7% of the self-guided.
Schoultz, 2015	RCT	44 IBD, 2 groups [22 experimental group; 22 wait-list control group]	MBCT 16 hours 8 consecutive weeks plus guided home practice and follow-up sessions	- Baseline - Post-intervention - 6 months	<u>Psychological outcomes</u> - Depression (BDI-II) - Anxiety (STAI) - Dispositional mindfulness (MAAS) - IBD quality of life (IBDQ)  <u>Physical outcomes</u> - CD activity (CDAI) - UC activity (SCCAI)	- Significant improvement of proposed scores in the MBCT group compared to the control for depression, trait anxiety and dispositional mindfulness, at follow-up.
Nemirovsky, 2022	RCT	171 individuals, 3 groups [55 healthy controls; 55 CD patients taught COBMINDEX; 61 CD patients on wait-list]	COBMINDEX 3 months	- Baseline - Post-intervention	<u>Psychological outcomes</u> - Quality of life (SF-12) - IBD quality of life (SIBDQ) - Mental fatigue (FACIT-F) - Psychological symptoms (BSI) - Perceived stress (PSS-4)  <u>Physical outcomes</u> - CD activity (HBI) - Signs of inflammations and hormones in peripheral blood	- COBMINDEX was accompanied by changes in inflammatory markers that coincided with changes in cortisol - Inflammatory markers of CD patients at baseline predicted COBMINDEX efficacy: higher levels of distinct cytokines and cortisol at baseline correlated negatively with changes in disease activity and psychological distress after COBMINDEX.
Xi, 2022	RCT	40 IBD, 2 groups [20 experimental group; 20 control group]	Empowerment education combined with mindfulness meditation training 3 months Once a day, 30 min per time	- Baseline - Post-intervention	<u>Psychological outcomes</u> - Anxiety (SAS) - Medication Compliance (MMAS) - IBD quality of life (IBDQ) - Lifestyle compliance (Lifestyle compliance questionnaire)	- No significant differences in anxiety and quality of life between the two groups; - Significantly lower anxiety in the experimental group after authorization education combined with mindfulness meditation training; - Significantly higher quality of life in the experimental group.

**Table 1.** Summary of included studies characteristics. (continues)

Author	Study design	N. participants N. groups	Type and duration of intervention	Follow-up	Outcome measures	Results
Lyall, 2022	Cross-sectional study	739 IBD	Regularity of mindfulness practice	NA	<u>Psychological outcomes</u> - Subjective Wellbeing (PWI) - Depression and Stress (items derived from DASS) - Mindfulness (regularity of mindfulness practice)  <u>Physical outcomes</u> - CD activity (CD-PRO/SS) - UC activity (UC-pro/SS)	- Significantly lower SWB than normative data; - Mindfulness practice doubled the Crohn's disease participants' odds of reporting SWB within the normal homeostatic range, after controlling for psychological, physical, and demographic variables; - A one-point increase of patient-reported bowel symptoms reduced the participant's odds of reporting SWB in the normal homeostatic range by about a third -The influence of mindfulness or disease symptoms on SWB was not observed for people with ulcerative colitis.
González-Moret, 2020	RCT	57 IBD, 2 groups [37 experimental group; 20 control group]	Mindfulness-based intervention.  4 internet-based therapy modules (60-90 minutes each); 4 face-to-face support sessions (two hours each)	- Baseline - 6 months	<u>Physical outcomes</u> - Fecal calprotectin (primary outcome) - C-reactive protein - Cortisol levels measured in hair samples	- Significant decrease in fecal calprotectin and in C-reactive protein levels in the mindfulness-based intervention group compared to the standard medical therapy group at the six-month follow-up
Berrill, 2014	RCT	66 IBD in remission with IBS-type symptoms or a high perceived stress level, 2 groups [33 experimental group; 33 control group]	MCT  16 weeks 6 face-to-face sessions, each lasting for 40 min	- Baseline - Post-intervention - 8 months - 12 months	<u>Psychological outcomes</u> - IBD quality of life (IBDQ) - Life stressors (RDHS) - Perceived stress (PSQ) - Coping (WCC) - Crystallized intelligence (NART) - Personality (BFI) - Perceived availability of social resources (ISEL) - Anxiety and depression (HADS)  <u>Physical outcomes</u> - IBS symptom severity (IBS-SSS) - CD activity (modified Harvey-Bradshaw index) - UC activity (Simple Clinical Colitis Activity Index) - Fecal calprotectin	- Higher IBDQ score in the active group compared to controls at 4-month assessment; - No difference between groups in relapse rate based on faecal calprotectin measurement.
Wynne, 2019	RCT	122 IBD, 2 groups [61 experimental group; 61 control group]	ACT  8 weeks 90-minute sessions	- Baseline - Post-intervention - 20 weeks	<u>Psychological outcomes</u> - Anxiety and depression (DASS-21) - Perceived stress (The stressometer) - Psychological flexibility (AAQ-II) - Quality of life (Short Health Scale)  <u>Physical outcomes</u> - CD activity (short CDAI) - UC activity (short Mayo score) - C-reactive protein, hemoglobin, leucocyte and serum albumin concentration - Fecal calprotectin - Cortisol concentration in hair	- Reduction in stress at wk 8 and wk 20; - Reduction in perceived stress and depression, but not anxiety; - Improved of overall well-being quality-of-life domain; - Hair cortisol concentration correlated with stress and anxiety at baseline but not at follow-up.



**Table 1.** Summary of included studies characteristics. (continues)

Author	Study design	N. participants N. groups	Type and duration of intervention	Follow-up	Outcome measures	Results
Lavelle, 2022	Single-case experimental design (SCED) with randomized multiple baseline designs	STUDY 1: 7 IBD STUDY 2: 12 IBD	STUDY 1: single-session face-to-face ACT intervention 2 hours  STUDY 2: brief telehealth ACT intervention 4 hours	- Baseline - Post-intervention	<u>Psychological outcomes</u> - Depression Anxiety (DASS-21) - Stress (Adapted Stressometer) - experiential avoidance (AAQ-II and EA).	STUDY 1: a single-session ACT intervention was an insufficient dosage to reduce stress and experiential avoidance. STUDY 2: half of participants experienced reduced stress, increased engagement in valued action, and increased functioning
Evans, 2022	RCT controlled with active control conditions (study PROTOCOL)	50 IBD, 2 groups [25 The ACTforIBD programme; 25 The active control group programme]	ACTforIBD programme  8 weeks 1-hour sessions, first three sessions and last one-to-one with psychologist, other sessions self-directed online	- Baseline - Post-intervention - 3 months	<u>Psychological outcomes</u> - Measure of mental health (K10, DASS-21, EQ5D5L, Brief Resilience Scale, General Self-efficacy Scale, Acceptance and Action Scale) - Satisfaction (A 0-10 satisfaction rating scale, Open-ended questions, The Credibility/Expectancy Questionnaire) - Safety  <u>Physical outcomes</u> - Health-related questions - IBD activity (IBD Control Scale, Manitoba index, PRO3 for Crohn's disease, item re usual bowel function, PRO2 for ulcerative colitis) - Pain (A Numeric Rating Pain Scale, guts) - Fatigue (Fatigue Symptom Inventory) - Therapy	Ongoing
Trindade, 2021	RCT controlled with medical treatment according to ECCO guidelines (Study PROTOCOL)	61 IBD, 2 groups [32 experimental group; 29 control group]	LIFewithIBD  9 weeks 2-hour sessions	- Baseline - Post-intervention - 3 months - 12 months	<u>Psychological outcomes</u> - Anxiety and depression (DASS-21) - Self-compassion (SCS) - Psychological flexibility (CompACT) - Functional impairment (WSAS) - General quality of life (EUROHIS-QOL 8-item index) - Health-Related quality of life (IBDQ-UK) - Chronic illness-related shame (CISS)  <u>Physical outcomes</u> - IBD symptom perception (IBD symptoms scale ) - CD activity (Harvey-Bradshaw Score) - UC activity ( Mayo score) - Inflammation-biomarkers - Gut microbiota diversity	Ongoing

Furthermore, the intervention protocols are structured and therefore have a good ability to return consistent and replicable results.

In this narrative review, we showed that mindfulness-based interventions are a group of effective strategies in mitigating psychological stress, anxiety and depression in IBD patients both in the short- and the long-term. Most but not all included studies also indicated an improvement in the overall quality of life of affected patients after MBI. Probably, the conflicting results observed in this field derive from the exclusion in most part of the studies of participants with significant mental illness and active IBD, thus, resulting in the enrolment of participants with low levels, at baseline, of both psychological and biological parameters, making more difficult to demonstrate their improvement. Indeed, only two studies showed statistically significant variation of biological markers, such as inflammatory cytokines, cortisol levels, C-reactive protein, or fecal calprotectin in IBD patients treated with MBI, compared with controls<sup>82</sup>.

ACT represents another promising third-wave therapy in the field of IBD. As previously explained, ACT promotes acceptance of situations that cannot be resolved, such as persistent physical symptoms, and is taught as an alternative to experiential avoidance. The application of acceptance processes, together with commitment and value-driven behavior change processes, aims to increase psychological flexibility, such as being fully present in the actual moment, without trying to avoid/combat unwanted thoughts/feelings<sup>90</sup>. The psychological flexibility offered by ACT is associated with reduced psychological distress in debilitating chronic illnesses<sup>91</sup>. ACT is known to derive from CBT. Both therapies support adaptive emotion regulation, but while CBT focuses on the regulation of antecedent emotions, ACT targets maladaptive regulation strategies, such as suppression<sup>92</sup>. CBT has been shown to be effective in reducing symptoms of depression and improving the quality of life in IBD patients<sup>27</sup>. ACT demonstrates similar efficacy to CBT in improving psychological distress in the general population and in those with chronic disease-related pain<sup>90</sup>. Therefore, we believe that its role should be deeply analyzed in the IBD population through larger and high-quality clinical trials.

## CONCLUSIONS

Overall, this narrative review showed that third-wave therapies may be an option for managing psychological stress, anxiety and depression in adults with IBD.

Definitely, at the current state of art, further high-quality research is needed, before these therapeutic approaches can be implemented in daily clinical practice and to assess whether early psychological intervention after diagnosis can increase coping strategies and improve psychological well-being throughout the life course.

However, concomitant nonpharmacological interventions and pharmacological treatment are recommended for the management of depression and anxiety in adult patients with IBD and to improve their quality of life. Therefore, we believe that all healthcare providers in the acute or outpatient setting should promote discussion with IBD adult patients about the availability of these interventions to manage their stress, anxiety, and depression.

We believe that both IBD patients with severe symptoms and patients with psychopathological morbidities should be screened and referred to the most appropriate nonpharmacological intervention, since anxiety and depression are risk factors for disease recurrence in the population with IBD.

## Conflict of Interest

The authors declare that they have no conflict of interest regarding this article.

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