Pain Ther (2024) 13:1447–1469
https://doi.org/10.1007/s40122-024-00672-9

REVIEW

Abdominal Pain in Inflammatory Bowel Disease-Epidemiology, Pathophysiology, and Management: A Narrative Review

Wei-wei Tan · Zi-xuan Liu · Xiao-Yan Liu · Wei-bing Zhang · Lie Zheng · Ya-Li Zhang · Yan-Cheng Dai

Received: September 3, 2024 / Accepted: October 4, 2024 / Published online: October 28, 2024

ABSTRACT

Abdominal pain is a major symptom of inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, and has a significant impact on patients' quality of life. Given the evolving understanding of IBD pathology and management strategies, there is an urgent need to review the recent research findings. In this review, we have analyzed the epidemiology, pathophysiology, and management of abdominal pain in IBD over the past decade. We draw on the current literature and highlight emerging trends, challenges, and advances in this field. By synthesizing key findings, this review provides insights into the complex interplay between abdominal pain, disease progression, and therapeutic interventions for IBD.

Keywords: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Abdominal pain; Pathophysiology; Management

Key Summary Points

Abdominal pain is a major symptom of inflammatory bowel disease (IBD), significantly impacting patients' quality of life.

This study aimed to review recent research findings on the epidemiology, pathophysiology, and management of abdominal pain in IBD.

The study highlighted the complex interplay between abdominal pain, disease progression, and therapeutic interventions for IBD.

Emerging trends and challenges in managing IBD-related abdominal pain were identified, emphasizing the need for patient-centered approaches and integrative therapies to improve quality of life.

INTRODUCTION

Inflammatory bowel disease (IBD) comprises a group of chronic, non-specific inflammatory

Wei-wei Tan and Zi-xuan Liu contributed equally to this work.

W. Tan · Z. Liu · X.-Y. Liu · W. Zhang · Y.-C. Dai (✉)
Department of Gastroenterology, Shanghai Traditional Chinese Medicine-Integrated Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200082, China
e-mail: daiyancheng2005@126.com

L. Zheng
Department of Gastroenterology, Traditional Chinese Medicine Hospital of Shaanxi Province, Xi'an 710003, China

Y.-L. Zhang
Institute of Digestive Diseases, Long Hua Hospital Shanghai University of Traditional Chinese Medicine, Shanghai 200032, China

intestinal disorders with unclear etiology, which primarily include ulcerative colitis (UC) and Crohn's disease (CD) [1]. Both UC and CD lead to intestinal inflammation and ulcers, which clinically manifest as presenting symptoms such as diarrhea, bloody stools, and abdominal pain. The distinction is mainly based on the location, extent, depth, pattern, and complications of the lesions [2]. Abdominal pain is common in IBD patients, with studies indicating a high incidence rate and a duration of up to 1–2 years, significantly affecting patients' quality of life (QoL) [3].

Currently, there are no specific medications for IBD-related abdominal pain. Patients are usually administered acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids for pain relief [4]. The long-term use of these medications can lead to adverse effects. For example, opioids [5, 6], such as morphine, tramadol, hydromorphone, and fentanyl, can cause hepatotoxicity, renal dysfunction, slowed intestinal motility, and exacerbated symptoms of IBD. NSAIDs [7], such as ibuprofen, naproxen sodium, and diclofenac sodium can cause intestinal damage, ulcer formation, and bleeding, and increase the risk of IBD occurrence or recurrence. Acetaminophen can potentially cause damage to the cardiovascular system with long-term use [8, 9]. In addition, the side effects of these treatments exacerbate symptoms and reduce patient compliance [10].

In addition to the economic burden, abdominal pain and/or fear have a negative impact on the quality of life (QoL) of patients with IBD [11]. Recent studies have shown that an increasing number of patients on mesalazine, a commonly used IBD treatment, experience intolerable symptoms, including worsened diarrhea and abdominal pain [12]. As there are currently no effective and safe treatments for IBD-associated abdominal pain, thorough research into the pathogenesis and intervention mechanisms of IBD-associated abdominal pain, the development of practical, patient-centered intervention strategies, and the safe, rational, appropriate, and effective use of relevant medications for IBD are of great importance [13, 14].

In a longitudinal study on the association between abdominal pain and the increased risk of future medical resource utilization (HRU) in IBD, 162 consecutively enrolled IBD patients (mean age 44.0 years; 99 female, 63 male; 115 CD, 45 ulcerative colitis UC, two indeterminate colitis) were included. A total of 121 patients (74.7%) exhibited HRU (mean age 43.6 years; 73 female: 48 male; 84 CD, 36 UC, one IC) preceding the follow-up appointment. Abdominal pain (OR = 2.18, 95% CI 1.04–4.35, $p = 0.04$) at the index appointment was the only study variable significantly associated with HRU on bivariate analysis [15]. These findings reinforced the importance of regularly screening for and effectively treating abdominal pain in IBD. Therefore, it is important for both clinicians and researchers to gain a better understanding of this abdominal pain symptom to develop effective and targeted therapeutic interventions. This review summarizes the current knowledge on the pathophysiology of abdominal pain in IBD and also reviews the current evidence behind therapies and interventions for the management of abdominal pain.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

DEFINITION AND EPIDEMIOLOGY OF ABDOMINAL PAIN IN IBD

Abdominal pain is an important reason for patients with IBD to seek treatment. Abdominal pain in IBD manifests differently between patients with CD and UC. CD primarily presents as cramping pain in the right lower abdomen and around the navel, often occurring after meals and temporarily subsiding after bowel movements. In acute cases, there may be persistent abdominal pain with tenderness and rebound tenderness, which requires differentiation from acute appendicitis. Abdominal pain in UC is usually localized to the lower abdomen, although the pain locations vary slightly depending on the location of the lesions. For example, pain occurs in the cecum and ascending colon in the right lower abdomen, pain in the descending colon in the left lower abdomen,

and pain in the sigmoid colon and rectum in the lower abdomen, pubic region, and perineal area. Lower abdominal pain in UC is often accompanied by a feeling of urgency, and pain subsides after defecation [16].

Abdominal pain in IBD can be classified as either chronic or acute. Chronic abdominal pain refers to persistent or recurrent visceral pain lasting longer than 3 months, with IBD-induced abdominal pain falling under the category of chronic secondary abdominal pain [17]. Acute abdominal pain is caused by non-traumatic reasons lasting no more than 5 days [18].

Symptoms of abdominal pain occur in 62% of patients in IBD [19]. Studies suggest that patients with CD are more likely to experience abdominal pain than patients with UC [20]. Conversely, other studies have indicated a comparable frequency of abdominal pain in these IBD subtypes [3]. Abdominal pain is more common in female patients with IBD than in male patients [21]. Abdominal pain is also common in pediatric patients with IBD, with over 50% of adolescent patients with IBD experiencing abdominal pain [22]. A survey conducted in the UK found that up to 50% of patients with CD and 37% of those with ulcerative colitis reported pain, irrespective of whether IBD was in relapse or in remission. Of those reporting pain, a high level of pain (pain ≥ 7/10) was scored by 54% of patients with CD and 42% with UC.4. In a survey of people with IBD from 21 European countries ($n = 4990$), 62% reported daily pain and 28.5% reported regular analgesic use between flares [9].

IMPACT OF ABDOMINAL PAIN ON PATIENTS WITH IBD

Abdominal pain is a common symptom in patients with IBD. It occurs not only in the active phase but also during remission and has a lasting impact on patients' daily lives. A study conducted in the United States found that 50–70% of IBD patients experience abdominal pain, making it the most common reason for emergency room visits [23].

In-depth interviews conducted by Newton et al. with 21 adults and 14 adolescents about their summary health-related quality of life (HRQoL) and their experience of symptoms in UC revealed that all patients experienced abdominal pain symptoms, which lead to emotional and psychological distress, such as anxiety, fear, and depression, thus impairing the patient's QoL [24]. In the Swiss IBD Cohort Study (SIBDCS), Zeitz et al. surveyed 2152 IBD patients for pain intensity, location of pain, and the impact of pain on daily life and social activities. The study found that 71% of the patients experienced pain during the course of the disease, with abdominal pain (59.5%) and back pain (38.3%) being the main causes [3]. In addition, patients with pain had a significantly lower overall QoL than patients without pain. A retrospective cohort study of 303 IBD patients conducted by Venkata Subhash Gorrepati et al. found that IBD-related abdominal pain leads to weight loss and malnutrition among patients [25]. Barnes et al. conducted an online survey with 670 respondents from three tertiary IBD centers, social media, and the Crohn's & Colitis Australia (CCA) association on factors associated with insomnia in patients with IBD. The results of this study suggest that abdominal pain is one of the most important contributing factors to insomnia [26].

Numerous studies have shown that abdominal pain impairs the QoL and health of patients with IBD. Therefore, there is an urgent need for treatment interventions that target abdominal pain in patients with IBD. A study of 400 patients with IBD by Louis et al. found that abdominal pain was the most important factor in assessing treatment preferences, with a relative attribute importance (RAI) of 33%. To reduce abdominal pain from severe to moderate or mild, patients were willing to accept an additional risk of mild-to-moderate side effects of 18.8% and 30.6%, respectively [27].

DIAGNOSIS AND EVALUATION OF ABDOMINAL PAIN IN IBD

Pain is a subjective sensation experienced by humans. Therefore, the methods for recognizing and evaluating abdominal pain in IBD differ significantly from other signs and must be understood by asking patients about the degree, frequency, intensity, and characteristics of abdominal pain. Clinically, objective methods are also being sought to quantify the diagnosis of abdominal pain. Therefore, there are numerous scales or questionnaires that have been developed for the diagnosis of IBD and the severity of abdominal pain based on the degree of pain or IBD. In addition, imaging techniques such as magnetic resonance imaging have also been applied to diagnose and evaluate abdominal pain in IBD.

Visual Analog Scale (VAS)

The VAS returns to the visual analog scale proposed by Hayes et al. in 1971 for clinical pain assessment [28]. In recent years, Chinese pain experts have conducted research on the status and validity of international and national pain scales and published the "Chinese Expert Consensus on the Application of Pain Assessment Scales (2020 Edition)" [29]. Pain scales are divided into three categories: unidimensional, multidimensional, and neuropathic pain screening. The VAS is a unidimensional pain intensity assessment scale that is characterized by accuracy, simplicity, and high sensitivity. The VAS is a simple self-assessment method consisting of a 10-cm horizontal line with no pain at the left end and the most intense pain at the right end. Patients mark their pain intensity on the line, and the score is calculated in centimeters. VAS questionnaires can be customized as needed. For example, researchers seeking to assess gastrointestinal symptoms and well-being in patients with irritable bowel syndrome(IBS) have developed a series of seven 100-mm visual analog scales to assess abdominal pain, diarrhea, constipation, bloating, vomiting, nausea, psychological well-being, and the impact of intestinal symptoms on daily life [30]. More recently, some researchers have pointed out the limitations of the VAS, such as subjectivity, measurement error, limitation of a single item, and lack of description, and have proposed the VAS-RRR, which can simultaneously collect ratings, rankings, and data from pairwise comparisons [31].

Eleven-point Numeric Rating Scale (NRS-11)

The NRS-11 requires patients to describe their pain intensity using 11 numbers from 0 to 10, with 0 being no pain, 0–3 being mild pain, 3–7 being moderate pain, > 7 being severe pain, and 10 being the most intense pain [32]. The NRS is a numerical representation of the VAS method, with the advantage of being more intuitive. Patients are asked to express their perceived pain intensity using numbers (0–10), which is easy to understand and express, and convenient to record. Farrar et al. analyzed data from ten double-blind, placebo-controlled, multicenter clinical trials on chronic pain, involving 2724 patients. The study showed that a reduction of about 2 points or about 30% on the NRS-11 usually represents a clinically significant change, providing a standard definition for chronic pain treatment clinical trials, andenhancing the comparability, validity, and clinical applicability of research results [33]. Janssen et al. used the NRS-11 to assess abdominal pain symptoms in 429 out of 559 (76.7%) patients with IBD in remission. The study found that 198 out of 429 (42.6%) had abdominal pain symptoms (score ≥ 3), which were related to psychosocial factors [34]. More comprehensive treatment methods for IBD patients with abdominal pain can improve the quality of care and subjective well-being. The NRS-11 is also used in various clinical studies on abdominal pain [32, 35].

Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

The SIBDQ is a simplified version of the Inflammatory Bowel Disease Questionnaire (IBDQ) by Irvine et al., which reduces the original 32 questions of the IBDQ to ten questions, covering the four dimensions of intestinal symptoms,

emotional status, social function, and systemic symptoms [36]. The advantages of the SIBDQ are its brevity and ease of completion and scoring. Some researchers examined patients with UC simultaneously with the SIBDQ and the Simple Clinical Colitis Activity Index (SCCAI) and analyzed the internal consistency, test–retest reliability, sensitivity, and criterion validity of the SIBDQ. It was found that the SIBDQ can sensitively reflect changes in disease activity in patients with UC and is highly correlated with SCCAI. It is considered an effective, reliable, and responsive assessment method for measuring the HRQoL of patients [37]. In China, researchers also had 201 patients with IBD complete the Chinese version of the Short Inflammatory Bowel Disease Questionnaire (C-SIBDQ) [38] to assess its reliability, validity, and stability. They concluded that the C-SIBDQ has high reliability, validity, and stability and can be used as a rating scale to assess the QoL of patients with IBD.

Magnetic Resonance Imaging Technology

Bao et al. used functional magnetic resonance imaging (fMRI) and found that patients with CD with abdominal pain showed lower regional homogeneity (ReHo) values in the insula, middle cingulate cortex (MCC), and auxiliary motor area, while showing higher ReHo values in the temporal pole. Patients without abdominal pain have lower ReHo values in the hippocampus/parahippocampal cortex and higher ReHo values in the dorsomedial prefrontal cortex, which indicates a close correlation between abnormal activity in the insula and MCC and the severity of CD with and without abdominal pain [39]. Lv et al. determined the changes in metabolites in the bilateral anterior cingulate cortex (ACC) of CD patients with abdominal pain by using proton magnetic resonance spectroscopy (1H-MRS). The results showed that the levels of glutamic acid (Glu)/(creatine + phosphocreatine, total creatine, tCr) and glutamic acid + glutamine (Glx)/tCr in the bilateral ACC of CD with abdominal pain were higher than those without abdominal pain, and were closely related to the pain VAS score [40]. Some scholars have also applied blood-oxygen level-dependent (BOLD6) fMRI for abdominal pain perception to determine the immune response of anti-tumor necrosis factor (TNF) therapy in CD patients [41].

PATHOPHYSIOLOGY MECHANISMS OF ABDOMINAL PAIN IN IBD

Transient Receptor Potential Vanilloid 1 (TRPV1)

TRPV1 receptors are also involved in visceral hypersensitivity. Upon activation, TRPV1 elicits burning and pain sensations and releases neuropeptides that trigger neurogenic inflammation, including calcitonin gene-related peptide (CGRP) and substance P (SP), from the peripheral terminals [42–45]. Alterations in TRPV1 expression and functionality have been associated with various gastrointestinal disorders such as gastroesophageal reflux disease, IBS, and active IBD.

In their study, Ayesha Akbar et al. found that the number of TRPV1-positive nerve fibers in the rectosigmoid mucosa of patients with IBD showing symptoms of IBS was significantly higher than that of patients with IBD without IBS symptoms and the control group. This number was positively correlated with the scores for abdominal pain. However, there were no significant differences between the three groups in terms of other neuromarkers and inflammatory indicators. Multiple linear regression analysis showed that TRPV1 was the only significant predictor of abdominal pain [46]. Yiangou et al. investigated the density of TRPV1 in the colon tissue of patients with IBD and the control group using immunoblotting and immunostaining methods. They found a significant increase in the immunoreactivity of TRPV1 in the colonic nerve fibers of patients with IBD during active disease, suggesting that TRPV1 plays an important role in IBD-related pain and gastrointestinal motility disorders [47].

Studies have shown upregulation of TRPV1 expression in patients with acute exacerbations of IBD, acute colitis mouse models, and patients with IBD with chronic abdominal pain or endoscopic remission [48]. Exogenous TRPV1 neurons are involved in the response to abdominal

pain [49]. In addition, TRPV1 sensitization mediates visceral hypersensitivity during UC remission, which contributes significantly to the occurrence of occasional or persistent refractory abdominal pain in some UC patients during endoscopic remission [50].

Acute Inflammatory and Post-inflammatory Abdominal Pain in IBD

Post-inflammatory abdominal pain refers to abdominal pain during the remission phase of IBD. Studies have found that in the same group of IBD patients, post-inflammatory abdominal pain is less severe and of shorter duration compared to abdominal pain during the active phase after relevant drug interventions [51]. During acute inflammation in IBD, an abundance of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α), mediators, for example, SP and serotonin, and neuropeptides, including SP, nerve growth factor, and CGRP are released from damaged tissue or immune cells (mast cells) [52]. These molecules activate visceral afferent neurons, leading to the sensitization of nociceptors [53]. Abdominal pain is triggered by the activation of visceral nociceptors in response to potentially injurious stimuli in the gut, such as bloating, which depolarizes nerve endings and transmits pain signals to the CNS.

Intestinal inflammation often persists during remission in patients with IBD. It impairs intestinal motility and causes either accelerated or slowed bowel movements, leading to abdominal pain, diarrhea, or constipation [54]. Nociceptors become sensitized after tissue damage or inflammation, lowering the pain threshold and making previously ineffective stimuli effective [55]. Peripheral sensitization in IBD results from inflammatory stimuli that excite visceral sensory neurons, lowering the pain threshold and increasing pain perception. Inflammation also leads to central sensitization, which increases the input from visceral sensory neurons to the spinal cord and brain, facilitating the activation of higher-order sensory neurons and amplifying pain signals [56].

TRPV1 is also involved in the development of post-inflammatory pain. SP levels increase during both the acute and recovery phases of colitis. When sensory nerve endings are exposed to SP for prolonged periods, TRPV1 is sensitized, leading to post-inflammatory pain [57]. Ephrin-B2/EphB signaling contributes to post-inflammatory visceral hypersensitivity (VHS). Theofanous et al. [58] demonstrated in mouse models of post-inflammatory TNBS colitis and maternal separation (MS) that Ephrin-B2/EphB signaling contributes to VHS and may represent a novel therapeutic target. Enterochromaffin (EC) cells, which are excitatory enteroendocrine and neuroendocrine cells, recognize environmental and endogenous stimuli that trigger or exacerbate pain, including nutritional stimuli, microbial metabolites, inflammatory factors, mechanical stretch, stress-induced hormones, and neurotransmitters. EC can produce persistent intestinal hypersensitivity in a persistently activated state, even without inflammation [59].

Coexisting Irritable Bowel Syndrome

A common cause of pain in IBD is the simultaneous presence of irritable bowel syndrome, referred to as "inflammatory bowel syndrome (IBS)" or "IBD-IBS" [60, 61].

Chronic abdominal pain in IBD shares common pathophysiological features with IBS and likely represents an overlap between the two processes, including mild mucosal inflammation [62], neuroimmune interactions [63], and alterations in the gut microbiota [64]. Studies have found that patients with IBD and IBS have phenomena such as small intestinal bacterial overgrowth (SIBO), intestinal methanogen overgrowth (IMO), small intestinal fungal overgrowth (SIFO), and mast cell activation syndrome (MCAS) in their intestines, which contribute to the occurrence of abdominal pain [61]. Fecal calprotectin (FC) can be used to distinguish IBS from active IBD. However, the diagnostic threshold of FC for the differentiation between the two is not clear. In addition, chronic pain and discomfort in IBD-IBS abdominal pain are also attributed to dysregulation of the brain–gut axis and neuroendocrine dysfunction [65]. Dysregulation of the brain–gut axis can lead to unfavorable emotional states such as depression and

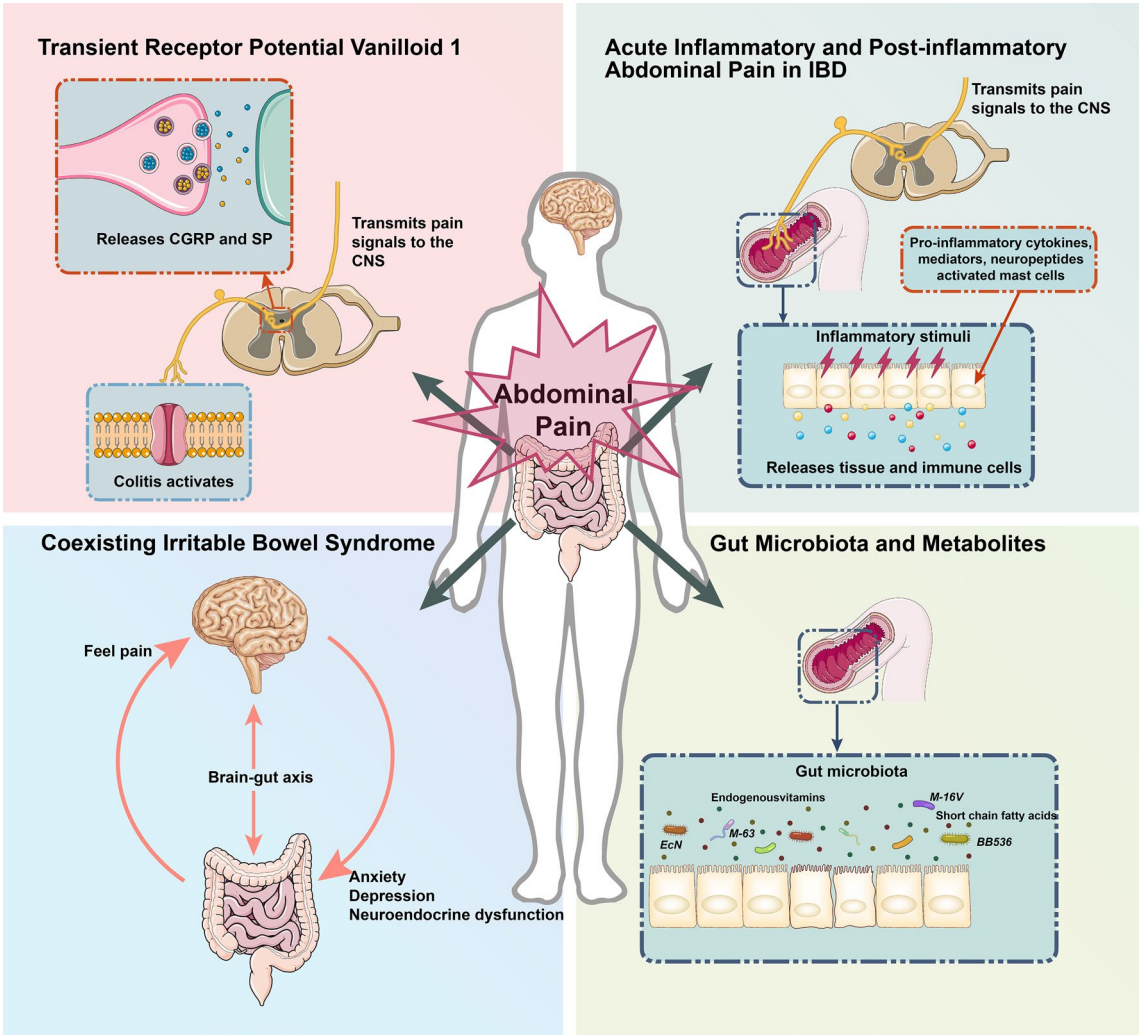

Fig. 1 Pathophysiologic mechanisms of abdominal pain in inflammatory bowel disease (IBD). Transient Receptor Potential Vanilloid 1 (TRPV1); Acute inflammation and post-inflammation; Coexisting irritable bowel syndrome; Gut microbiota and metabolites

anxiety in patients with IBD [66]. Patients with IBD accompanied by anxiety or depression are more prone to symptoms such as IBS-related abdominal pain [67]. The overlap between IBS and IBD may explain why certain medications that relieve IBS symptoms, such as pinaverium bromide and trimebutine, show some efficacy in IBD-related abdominal pain [68]. Despite further confirmation of the causal relationship between IBD and IBS by the randomized Mendel trial, the efficacy of the use of neuromodulators and gut–brain behavioral therapy in patients with IBD-related abdominal pain is not as satisfactory according to IBS guidelines [69].

Gut Microbiota and Metabolites

Signaling molecules from the gut microbiota of many patients with IBD, including microbial by-products, metabolites, neurotransmitters, and neuromodulators, may play a crucial role in mediating abdominal pain through peripheral and central sensitization [70]. Studies have shown that germ-free mice exhibit VHS at birth,

which is associated with an increased expression of spinal Toll-like receptors and cytokines. This decreases after colonization with conventional gut microbiota, indicating a regulatory role of the symbiotic gut microbiota in maintaining the balance of excitability of colonic sensory [71]. Oral administration of specific *Lactobacillus* strains can induce the expression of μ-opioid and cannabinoid receptors in intestinal epithelial cells, mediating an analgesic function in the gut, similar to the effects of morphine [72]. Bacterial overgrowth in the small intestine of children is closely associated with chronic diarrhea and abdominal pain [73].

Several clinical studies have shown that the use of antibiotics alleviates abdominal pain in patients with IBD [74]. Clinical studies have also demonstrated the efficacy of probiotics such as *Lactobacillus rhamnosus GG*, mixtures of *Bifidobacterium infantis M-63*, *M-16 V*, and *BB536*, and *Lactobacillus acidophilus NCFM* in relieving abdominal pain [75]. In addition, metabolites produced by the gut microbiota, such as short-chain fatty acids, can sensitize peripheral pain-sensitive neurons via protein kinase C (PKC), promote histamine and 5-HT secretion, and trigger abdominal pain [76]. Conversely, the probiotic strain *Escherichia coli Nissle 1917 (EcN)* can produce an analgesic peptide, *C12AsnGABAOH*, which can penetrate the epithelial barrier and reduce calcium influx triggered by the activation of nociceptors in sensory neurons via GABAB receptors, thereby alleviating abdominal pain [77]. Overall, these previous studies suggest a link between the gut microbiota, its metabolites, and abdominal pain (Fig. 1).

MANAGEMENT OF ABDOMINAL PAIN IN IBD

Pharmacological Treatment

Modern Medicine Treatment

While there are currently no targeted medications used clinically specifically for abdominal pain in IBD, many researchers are exploring pharmacological treatments tailored to the pathogenesis of abdominal pain in IBD. In a study by Spagnuolo et al., 43 patients with IBD were randomly divided into two groups. The treatment group received mesalazine combined with a mixture of β-glucan, myoinositol, and digestive enzymes, whereas the control group received mesalazine alone. After 4 weeks of treatment, abdominal pain improved significantly in the treatment group, suggesting that a mixture of β-glucan, myoinositol, and digestive enzymes can improve intestinal inflammation and increase intestinal motility, thereby relieving abdominal pain [78].

Opioids are generally used clinically to treat abdominal pain. According to a cross-sectional analysis of data from the National Hospital Ambulatory Medical Care Survey (NHAMCS) from 2006 to 2017, 35.5% of patients with IBD experiencing abdominal pain received opioids in the emergency department [79]. In a survey conducted in the UK, 12% of IBD outpatients had taken opioids within 12 months, and 11% of patients with IBD continued to take opioids after discharge [80]. The long-term use of opioids can have adverse effects on the gastrointestinal tract and central nervous system, including opioid-induced constipation, drug-induced bowel syndrome, and dependence, and there is a lack of clinical evidence for the efficacy of opioids in the treatment of chronic non-cancer abdominal pain [7]. In a study that focused on abdominal pain symptoms in patients with CD, Coates et al. found that opioid medications did not improve abdominal pain symptoms or QoL [81].

Lindstrom et al. found that OLORINAB is a small molecule that selectively activates the cannabinoid receptor 2 (CB2 receptor) and can be administered orally for the treatment of visceral pain associated with IBD [82]. No signs of toxicity were observed in animal studies. Yacyshyn et al. randomly assigned 14 patients with CD to OLORINAB at doses of 25 mg or 100 mg three times daily for 8 weeks. The results showed that at week 8, the mean (SD) change from baseline in average abdominal pain score at peak OLORINAB plasma concentrations was − 4.61 (1.77) in the 25-mg group ($P = 0.0043$) and − 4.57 (2.17) in the 100-mg group ($P = 0.0036$). The change from baseline at week 8 in the mean (SD) number of

pain-free days per week was + 1.60 (2.61) in the 25-mg group and + 2.33 (3.62) in the 100-mg group, and no analgesics were required during the treatment period [83].

Risankizumab, a monoclonal antibody that inhibits inflammatory cytokines, lowers the serum levels of IL-22 in patients with CD by blocking IL-23 signaling, thereby improving clinical symptoms and endoscopic scores. D'Haens et al. randomly assigned 1477 patients with moderate-to-severe UC to either risankizumab 600 mg, 1200 mg, or a placebo administered intravenously every 4 weeks for 12 weeks. The results showed that the clinical remission rates of abdominal pain scores in the risankizumab 600 mg and 1200 mg groups were 35% and 40%, respectively, compared to 19% in the placebo group, confirming the efficacy of risankizumab in improving abdominal pain [84].

Upadacitinib, an oral selective JAK-1 inhibitor, suppresses the JAK-STAT signaling pathway, thereby reducing the production and release of inflammatory cytokines and relieving intestinal inflammation. In a randomized, double-blind, placebo-controlled study by Ghosh et al. [85], 250 patients with moderate UC were divided into five groups that received either placebo or upadacitinib at doses of 7.5, 15, 30, or 45 mg once daily for 8 weeks. Of the patients in the 45 mg upadacitinib group, 37.5% reported no abdominal pain compared to 13.0% in the placebo group, suggesting that upadacitinib at a dose of 45 mg once daily improves the symptoms of abdominal pain in UC. Danese et al. conducted two identical, double-blind, multicenter, placebo-controlled phase III trials in which 660 UC patients were randomly assigned to the upadacitinib treatment group and 328 patients to the placebo (PBO) group and received 15 mg or 30 mg of upadacitinib or PBO once daily over a 52-week treatment period. In this study, at weeks 2, 4, 6, and 8, a larger percentage of UPA-treated patients reported no abdominal pain when compared with PBO-treated patients (30.5 vs. 15.5%, 39.1 vs. 22.3%, 47.5 vs. 23.5%, and 50.2 vs. 23.8%, respectively). The differences at each time point were statistically significant ($P < 0.001$) and maintained improvement in abdominal pain symptoms over the 52-week treatment period (55.3% and 45.9% vs. 20.8% for UPA 15 mg and UPA 30 mg vs. PBO; $P < 0.001$) [86].

Dysbiosis of gut microbiota can be a major contributor to IBD, leading to intestinal barrier damage and inflammation. Therefore, modulation of the gut microbiota is a crucial aspect of IBD treatment, which is usually achieved through the use of antibiotics, probiotics, prebiotics, and transplantation of fecal microbiota [87]. Numerous clinical trials have shown that antibiotic therapy is effective in relieving abdominal pain [74]. In a study by Castiglione et al., 29 patients with CD and small intestinal bacterial overgrowth received either metronidazole 250 mg bid (group A) or ciprofloxacin 500 mg bid (group B) for 10 days, resulting in the improvement of abdominal pain symptoms in 50% of group A patients and 43% of group B patients [88]. In a randomized controlled trial conducted by Palumbo et al. involving 60 patients with moderate-to-severe UC, the control group received mesalazine alone, whereas the observation group received mesalazine combined with probiotics for 2 years [89].

Certain tricyclic antidepressants (TCAs), such as amitriptyline and desipramine, are used to treat neuropathic pain. In a retrospective cohort study of patients with mild or inactive IBD taking TCAs, 85.2% of patients with IBD experienced symptoms of abdominal pain. After TCA treatment, patients with IBD experienced a moderate improvement in overall well-being, while patients with UC showed greater treatment efficacy than patients with CD [90]. In addition, the American Gastroenterological Association recommends the use of antispasmodic medications in patients with IBD experiencing IBS/functional symptoms, which are effective in alleviating abdominal pain symptoms [91].

NSAIDs usually show a favorable response to non-visceral inflammatory abdominal pain and can alleviate axial/peripheral arthritis associated with IBD [92]. Nevertheless, many clinicians approach NSAID therapy for IBD-related abdominal pain with caution [93]. Reports suggest that frequent (≥ 5 times/month) use of NSAIDs is associated with active CD [94].

Mirikizumab, an anti-IL-23p19 antibody, demonstrated efficacy and safety in patients with moderately to severely active UC in the

LUCENT phase 3 trials. At week 4, there was a higher rate of abdominal pain improvement (mirikizumab 45.5% vs. placebo (PBO)27.9%). At week 12, mirikizumab patients versus PBO achieved abdominal pain improvement(66.4 vs. 49.2%). Mirikizumab-treated patients sustained symptom control versus placebo patients in maintenance until week 52 (76.2 vs. 47.2%) [95].

Tofacitinib is an oral, small molecule, JAK inhibitor for the treatment of moderate-to-severe UC that was approved in Europe and the USA in 2018. In a real-world survey in the United States and five European countries, 642 (642/2049) patients with UC received tofacitinib. Abdominal pain/cramps symptoms were reported in the first weeks of treatment, and decreased with time. At week [52+], the mean reduction from treatment initiation to current in abdominal pain symptoms was 2.2 (to a current mean score of 0.9) [96].

Considering the symptom overlap between IBD and IBS, antispasmodic agents (pinaverium bromide, etc.) have also been used to treat abdominal pain. Pinaverium bromide (PB) [*N*-(bromo-2-dimethoxy-4,5-benzyl)-*N*([(dimethyl-6,6 norpinanyl-2)-2 ethoxy]-2 ethyl morpholinium bromide] is a quaternary ammonium derivative that acts as an antispasmodic agent by blocking both muscarinic receptors and calcium channels in the gut smooth muscle cells. In a randomized, placebo-controlled trial, 285 IBS-Rome III patients received at least one dose of PB 100 mg plus simethicone (S) 300 mg or placebo. The results showed that PB + S was superior in abdominal pain (effect size: 31%, $P=0.038$) [97].

TRADITIONAL CHINESE MEDICINE (TCM) TREATMENT

IBD in TCM can be categorized as “Jiu Li”, “Li Ji”, and “Chang Pi”, and results from a weakened spleen due to external pathogens, irregular diet, and emotional imbalance. The main pathological factors include dampness, stagnant heat, and toxic heat [98]. In TCM, abdominal pain in IBD is associated with “inadequate nutrition leads to pain”, “stagnation leads to pain”, and “excessive heat leads to pain”, which is a complex pattern of deficiency and excess [99]. A notable aspect of TCM treatment is syndrome differentiation, in which an appropriate medication is administered based on the patient’s symptoms [100].

Jingwen et al. randomly divided 58 UC patients into a treatment group and a control group, with the control group receiving conventional treatment with modern drugs, while the treatment group received TCM syndrome differentiation treatment in addition to conventional treatment with modern drugs. In the treatment group, various Chinese herbal formulas were selected based on the patients’ TCM differentiation, such as Fuzi Lizhong Tang combined with Sishen Wan, Wumei Pills, Baitouweng Tang, and Tongxie Yaofang combined with Sini San. These formulas have effects such as dispelling cold, relieving pain, warming the middle and stopping diarrhea, and harmonizing Qi, which can alleviate the symptoms of patients’ abdominal pain. The results of the study showed that the scores for abdominal pain in both groups were lower after treatment than before (the study group: before treatment 3.24 ± 0.25, after treatment 1.05 ± 0.26 vs. the control group: before treatment 3.29 ± 0.22, after treatment 2.15 ± 0.32), with the scores in the treatment group being significantly lower than those in the control group ($P<0.05$) [101].

Dai Yancheng et al. conducted a randomized controlled trial to investigate the effects of the spleen-strengthening and bowel-cleansing formula on the QoL of patients with splenic deficiency-moisture syndrome type UC. They divided 120 patients with mild to moderately active UC into an experimental group and a control group, each of which was treated with a spleen-strengthening and bowel-cleansing formula and 5-aminosalicylic acid for 8 weeks. The results showed a significant difference in the relief of abdominal pain between the two groups (total effective rate 94.5% vs. 81.0%), with the experimental group outperforming the control group [102].

In addition to oral Chinese medicine, Chinese medicine enema or retention enema also demonstrates its effectiveness and safety [103]. Retention enemas with Qingchang Decoction

can result in clinical and mucosal remission of left-sided ulcerative colitis [104]. Yuping et al. conducted a randomized controlled trial comparing Qingchang suppositories (experimental group) and mesalazine suppositories (control group) for UC treatment (E1 or E2). The results showed that the comprehensive efficacy rate in the treatment group was 91.49% compared with 87.23% in the control group. Regarding the efficacy of TCM syndrome, the rates were 97.87% and 91.48%, respectively, with the treatment group outperforming the control group. In addition, the Qingchang suppository showed superior efficacy over the SASP suppository in improving symptoms, such as diarrhea, abdominal pain, bloating, tenesmus, and anal burning caused by damp heat in the intestine in mild to moderately active UC below the left half of the colon [105].

Non-pharmacological Treatment

Acupuncture

The potential beneficial mechanisms of acupuncture in the treatment of IBD include increasing vagal nerve activity to reduce disease activity and inflammation, improving malnutrition, restoring intestinal barrier function, reducing VHS, and relieving depression/anxiety and pain in patients [106]. Systematic reviews and meta-analyses have shown that acupuncture alone or combined with conventional medication may be more effective than conventional medication in the treatment of UC compared to conventional medication. In a Swedish study [107] of 147 patients with UC, 48.3% received conventional medical treatment, with 21 of them attempting acupuncture treatment. The feedback on the results showed that most of them (83.1%) found acupuncture helpful, including relieving pain, improving general well-being, and alleviating symptoms [108].

Acupuncture treatment of CD generally targets acupuncture points such as CV12 (Zhongwan), ST37 (Shangjuxu), SP6 (Sanyinjiao), LR3 (Taichong), and KI3 (Taixi) [99]. Chunhui et al. conducted two randomized controlled trials of acupuncture treatment for patients with CD. The observation group received acupuncture and moxibustion, while the control group received sham acupuncture and moxibustion. In both studies, the observation group showed better improvement in abdominal pain than the control group [109, 110]. In another study by Yang Ling et al. [111], it was found that the group receiving moxibustion with herbs (consisting of *Aconiti radix*, *Cinnamomi ramulus*, *Moschus*, *Coptidis rhizoma*, *Salviae Miltiorrhizae* Radix, and *Carthami flos*) was superior to the ginger-separated moxibustion group (consisting of *ginger slices*) in reducing the duration of abdominal pain ($P=0.032$) and improving the scores.

Dietary Management

Diet is a decisive factor influencing the occurrence and course of IBD. Different dietary patterns such as the Mediterranean diet, vegetarian/vegan diet, and a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) can alter the function of the intestinal microbiota, immune system, and intestinal mucosal barrier, thereby influencing inflammatory responses. Certain dietary factors, such as high fat, high sugar, high animal protein, low fiber, and processed foods, can increase the risk of IBD onset and exacerbate the disease, leading to abdominal pain [112]. de Graaf et al. investigated the relationship between the dietary index and intestinal inflammation and gastrointestinal symptoms in patients with IBD [113]. By calculating the Adaptive Dietary Inflammatory Index (ADII) in 238 patients with IBD, the study found a close correlation between the ADII score and abdominal pain in IBD (b=0.194, $p=0.003$).

The FODMAP diet is poorly absorbed by the intestine, leading to osmotic and fermentative effects that cause functional symptoms. The low-FODMAP diet has been shown to be very effective in patients with IBS; therefore, many studies have been conducted in recent years on whether a low-FODMAP diet can improve clinical symptoms in patients with IBD [114]. Tapete et al. conducted a randomized controlled trial in which 30 patients with IBD in remission were divided into a low-FODMAP diet group and a

standard diet group for 6–8 weeks [115]. The results showed a significant improvement in abdominal pain in the low-FODMAP diet group, demonstrating the effectiveness of the low-FODMAP diet in controlling abdominal pain in patients with IBD in remission. Tapete et al. also conducted a study in which 50 patients with IBD were randomly assigned to either a high or low-FODMAP diet for 4 weeks and then switched to the other group for another 4 weeks [116]. The results showed that a low-FODMAP diet significantly reduced abdominal symptoms in patients with IBD.

Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a method of brain stimulation that involves passing a weak current (1–2 mA) across the cortex using at least two electrodes. tDCS has been explored for its potential to alleviate symptoms of psychiatric and neurological disorders, including chronic pain. It is considered a promising treatment due to its cost-effectiveness, portability, safety, and ease of use compared to other neuromodulation methods. Studies have shown that tDCS can influence brain regions associated with pain perception and modulation [117]. Twenty patients with either CD or UC with chronic abdominal pain (CAP) were included in the study aimed to investigate the effects of tDCS. Anodal or sham tDCS was applied over the primary motor cortex for five consecutive days (2 mA, 20 min). The results showed that there was a significant reduction of abdominal pain in the anodal tDCS group compared with sham tDCS (right side of the abdomen (mean of active group: 10.86 kg; pre: 1.53 6 0.81 kg; post: 2.39 6 1.53 kg; vs. mean of sham group: 20.175 kg; pre: 1.78 6 0.84 kg; post: 1.62 6 0.89 kg). This effect was evident in changes in VAS and pressure pain threshold on the left and right sides of the abdomen. In addition, 1 week after stimulation, pain reduction remained significantly decreased in the right side of the abdomen. TDCS proved to be an effective and clinically relevant therapeutic strategy for CAP in IBD [118]. Neeb et al. conducted a study that included 36 patients with IBD and chronic pain in a double-blind, randomized, placebo-controlled trial, assigning participants to either a placebo treatment or tDCS for 5 days. MRI scans were performed before and after the treatment. Compared to the placebo group, the active tDCS group showed significantly higher resting-state functional connectivity within the visual medial network ($p=0.027$) and the right frontoparietal network ($p=0.048$). Increased connectivity was observed in the visual cortex, amygdala, cingulum, and insula. No significant results were found in structural MRI (DTI, VBM). These findings suggest that tDCS can enhance functional connectivity in specific brain networks, potentially offering a novel therapeutic strategy for managing chronic abdominal pain in IBD patients [119].

Psychological Intervention

Hypnotherapy

Hypnotherapy is a form of psychological treatment in which patients are put into a sleep-like state to change their perceptions, emotions, and behaviors. Hypnotherapy can relieve pain in patients with IBD by reducing stress responses, improving emotional states, enhancing self-efficacy, and regulating gut motility [120].

Lee et al. conducted a randomized controlled trial with 40 patients with CD aged 12 to 18 years and divided them into a hypnotherapy intervention group and a waiting control group. The hypnotherapy intervention group received a personal hypnosis session, training in self-hypnosis, and recordings for 8 weeks. The results showed a significant improvement in the severity of abdominal pain in the hypnotherapy intervention group ($P=0.03$), suggesting that hypnotherapy can relieve abdominal pain by modulating the nervous system, improving psychological factors, and controlling inflammatory responses [121].

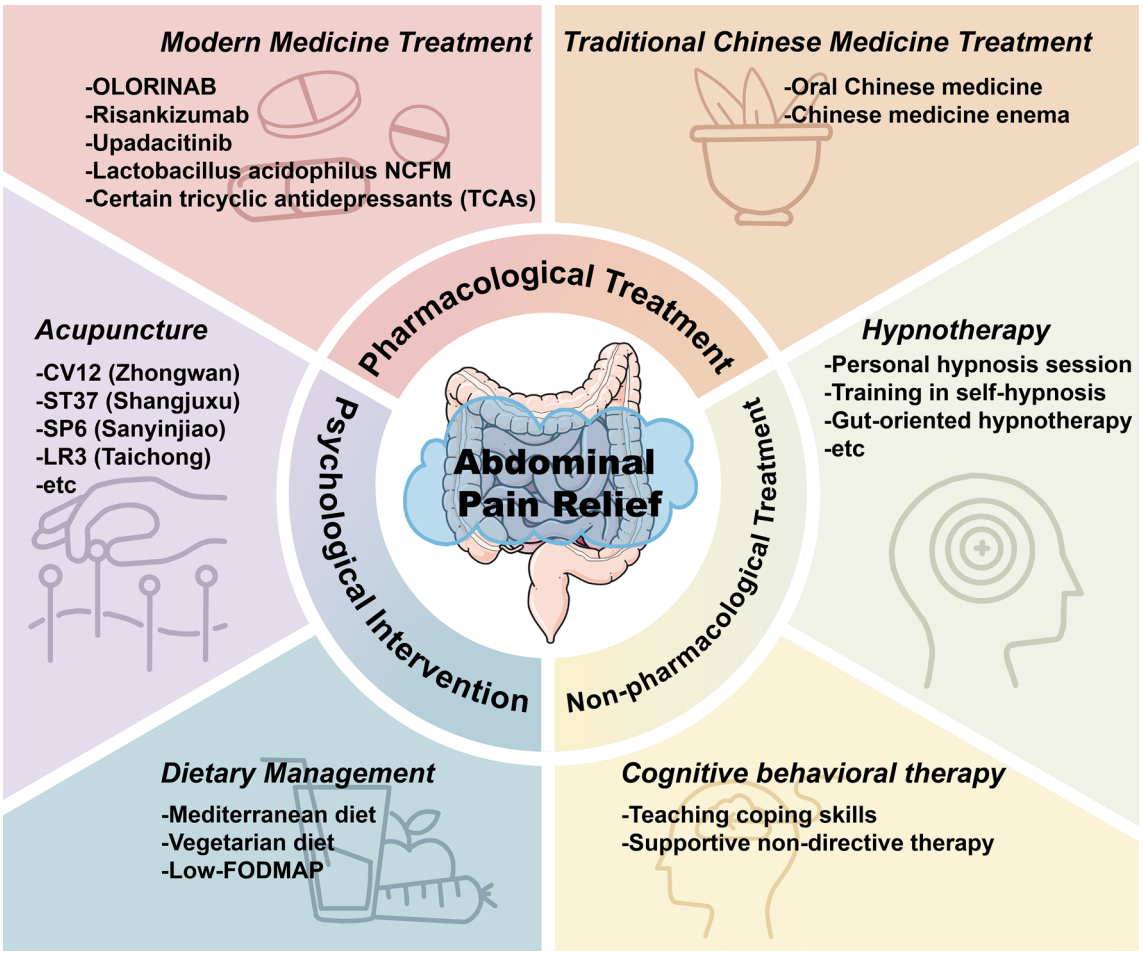

Fig. 2 Suggestions for pain management with pharmacological treatment, non-pharmacological treatment, and psychological intervention for abdominal pain in inflammatory bowel disease (IBD)

Keefer et al. conducted a randomized controlled trial in which 54 patients in remission from UC were treated with gut-oriented hypnotherapy. The observation group received gut-oriented hypnotherapy, whereas the control group received attention-control therapy. Both therapies were conducted by professional psychologists in an outpatient setting once a week for 40 min each, for seven sessions. The results showed that the severity of abdominal pain was lower in the observation group than in the control group both after treatment and at follow-up. It is believed that gut-directed hypnotherapy regulates the muscle tone and peristalsis of the patient's intestines, activates their self-healing power, promotes the repair of the intestinal mucosa, and inhibits the release of inflammatory factors, thereby reducing inflammation and irritation of the intestines by altering symptom perception, improving intestinal motility, and strengthening the immune system [122].

Cognitive behavioral therapy (CBT) is a psychosocial intervention method that aims to reduce pain and improve QoL by changing patients' cognitive and behavioral responses to pain through techniques such as psychoeducation, understanding cognitive behavioral models, relaxation exercises, breathing techniques, and cognitive restructuring. It enables patients to gain better self-management skills,

understand pain and themselves better, and accept pain [123]. A meta-analysis [124] showed that CBT helps reduce anxiety and depression and improves the QoL of patients with IBD. In clinical research, CBT is currently mainly used for sleep disorders in IBD, but there are also several studies in which CBT is used to improve abdominal pain symptoms caused by other diseases, such as functional abdominal pain disorder (FAPD) and IBS [125].

Levy et al. conducted a prospective, randomized longitudinal study over 12 months involving 200 children with FAPD and their parents [126]. The observation group received a social learning and cognitive behavioral therapy (SLCBT) intervention, whereas the control group received an educational and supportive intervention. The results showed that children in the SLCBT group had a more significant improvement in the severity of gastrointestinal symptoms and pain management than those in the educational and supportive groups. Parents in the SLCBT group also showed a significant reduction in attention to their children's symptoms and maladaptive beliefs about their children's pain. Several studies have shown that children and adolescents with IBD are more likely to experience anxiety, depression, social problems (interactions in the social environment), and family dysfunction. CBT, including teaching coping skills or supportive non-directive therapy (SNDT) (therapists listen empathetically and reflect on what the patient presents), provides brief cognitive behavioral interventions for children with IBD and their parents, improving their functioning and QoL. In some patients, it can reduce disease activity and relieve the symptoms of abdominal pain and bloating [127–129]. Therefore, CBT is also a promising direction for research on the treatment of abdominal pain symptoms in IBD (Fig. 2).

CONCLUSIONS

Abdominal pain, one of the most common and distressing symptoms of IBD, has a significant impact on patients' QoL. However, the current understanding and awareness of abdominal pain in IBD remain insufficient in clinical practice [45]. Abdominal pain is mainly diagnosed based on the patient's subjective perceptions, which are assessed using various severity rating scales. Although this method has a certain reference value, it lacks objectivity and accuracy. Therefore, developing more objective and accurate diagnostic tools is important for future clinical practice.

As far as treatment is concerned, the options for treating abdominal pain in IBD are currently limited. Although some medications, such as mesalamine, cannabinoid receptor agonists, and anti-inflammatory drugs, have shown some efficacy in relieving symptoms, these medications are not suitable for all patients and often have side effects. In addition, integrative therapies such as Chinese herbs, acupuncture, dietary management, and psychological interventions have also shown promise in relieving abdominal pain in IBD [130].

In general, the management of abdominal pain in IBD requires a multidisciplinary approach aimed at minimizing patient suffering and improving the QoL. Clinicians should consider individual patient differences during treatment and combine different therapeutic methods to create personalized treatment plans. In addition, patients' psychological status and lifestyle should be included in the treatment to provide comprehensive support and intervention.

ACKNOWLEDGEMENTS

Throughout the writing of this dissertation, I have received a great deal of support and assistance. We thank the participants of the study.

Author Contributions. Wei-wei Tan and Zi-xuan Liu wrote the manuscript; Yan-Cheng Dai and Ya-Li Zhang conceived and designed the study; Xiao-Yan Liu, Wei-bing Zhang, and Lie Zheng proofread and revised the manuscript; and all authors approved the final version to be published.

Funding. This study was supported by the National Natural Science Foundation of China, No. 81873253; the Shanghai Natural Science Foundation, No. 22ZR1458800; the scientific research Project Plan of Shanghai Municipal Health Commission, No. 202240385; and the Science and Technology Innovation Cultivation Program of Longhua Hospital, No. YD202220; the Hongkou District Health Committee, No. HKZK2020A01. The Rapid Service Fee was funded by the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Wei-wei Tan, Zi-xuan Liu, Xiao-Yan Liu, Wei-bing Zhang, Lie Zheng, Ya-Li Zhang, and Yan-Cheng Dai have nothing to disclose.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

REFERENCES

1. Xu L, He B, Sun Y, Li J, Shen P, Hu L, Liu G, Wang J, Duan L, Zhan S, Wang S. Incidence of inflammatory bowel disease in urban China: a nationwide population-based study. Clin Gastroenterol Hepatol. 2023;21(3379–3386):e3329. https://doi.org/10.1016/j.cgh.2023.08.013.

2. Long D. Crohn's disease and ulcerative colitis: from pathophysiology to novel therapeutic approaches. Biomedicines. 2024. https://doi.org/10.3390/biomedicines12030689.

3. Zeitz J, Ak M, Muller-Mottet S, Scharl S, Biedermann L, Fournier N, Frei P, Pittet V, Scharl M, Fried M, Rogler G, Vavricka S, Swiss IBD. Pain in IBD patients: very frequent and frequently insufficiently taken into account. PLoS ONE. 2016;11:e0156666. https://doi.org/10.1371/journal.pone.0156666.

4. Coates MD, Johri A, Gorrepati VS, Maheshwari P, Dalessio S, Walter V, Stuart A, Koltun W, Bernasko N, Tinsley A, Williams ED, Clarke K. Abdominal pain in quiescent inflammatory bowel disease. Int J Colorectal Dis. 2021;36:93–102. https://doi.org/10.1007/s00384-020-03727-3.

5. Camilleri M, Lembo A, Katzka DA. Opioids in gastroenterology: treating adverse effects and creating therapeutic benefits. Clin Gastroenterol Hepatol. 2017;15:1338–49. https://doi.org/10.1016/j.cgh.2017.05.014.

6. Baillie S, Norton C, Saxena S, Pollok R. Chronic abdominal pain in inflammatory bowel disease: a practical guide. Frontline Gastroenterol. 2024;15:144–53. https://doi.org/10.1136/flgastro-2023-102471.

7. Szigethy E, Knisely M, Drossman D. Opioid misuse in gastroenterology and non-opioid management of abdominal pain. Nat Rev Gastroenterol Hepatol. 2018;15:168–80. https://doi.org/10.1038/nrgastro.2017.141.

8. Jozwiak-Bebenista M, Nowak JZ. Paracetamol: mechanism of action, applications and safety concern. Acta Pol Pharm. 2014;71:11–23.

9. Norton C, Czuber-Dochan W, Artom M, Sweeney L, Hart A. Systematic review: interventions for abdominal pain management in inflammatory bowel disease. Aliment Pharmacol Ther. 2017;46:115–25. https://doi.org/10.1111/apt.14108.

10. Takahashi K, Khwaja IG, Schreyer JR, Bulmer D, Peiris M, Terai S, Aziz Q. Post-inflammatory abdominal pain in patients with inflammatory bowel disease during remission: a comprehensive review. Crohns

Colitis. 2021;3:73. https://doi.org/10.1093/crocol/otab073.

11. Szigethy E. Pain management in patients with inflammatory bowel disease. Gastroenterol Hepatol (N Y). 2018;14:53–6.

12. Hiraoka S, Fujiwara A, Toyokawa T, Higashi R, Moritou Y, Takagi S, Matsueda K, Suzuki S, Miyaike J, Inokuchi T, Takahara M, Kato J, Okada H. Multicenter survey on mesalamine intolerance in patients with ulcerative colitis. J Gastroenterol Hepatol. 2021;36:137–43. https://doi.org/10.1111/jgh.15138.

13. Peng S, Xia Y, Wang Y, Yu X, Wu Z, Zhang L, Xu K, Shen L, Luo H. Research hotspots and trend analysis of abdominal pain in inflammatory bowel disease: a bibliometric and visualized analysis. Front Pharmacol. 2023;14:1220418. https://doi.org/10.3389/fphar.2023.1220418.

14. Ford AC, Vanner S, Kashyap PC, Nasser Y. Chronic visceral pain: new peripheral mechanistic insights and resulting treatments. Gastroenterology. 2024. https://doi.org/10.1053/j.gastro.2024.01.045.

15. Zubrzycka I, Bogale K, Stuart A, Cesaire M, Walter V, Dalessio S, Tinsley A, Williams E, Clarke K, Coates MD. Abdominal pain is associated with an increased risk of future healthcare resource utilization in inflammatory bowel disease. Int J Colorectal Dis. 2023;38:213. https://doi.org/10.1007/s00384-023-04510-w.

16. Ananthakrishnan AN, Xavier RJ, Podolsky DK: Inflammatory bowel diseases : a clinician's guide. Chichester, West Sussex, UK ; Hoboken, NJ, John Wiley & Sons, Inc.,; 2017; pp. 27+41.

17. Aziz Q, Giamberardino MA, Barke A, Korwisi B, Baranowski AP, Wesselmann U, Rief W, Treede RD, Pain ITC. The IASP classification of chronic pain for ICD-11: chronic secondary visceral pain. Pain. 2019;160:69–76. https://doi.org/10.1097/j.pain.0000000000001362.

18. Gans SL, Pols MA, Stoker J, Boermeester MA. Guideline for the diagnostic pathway in patients with acute abdominal pain. Dig Surg. 2015;32:23–31. https://doi.org/10.1159/000371583.

19. Hardy PY, Fikri J, Libbrecht D, Louis E, Joris J. Pain characteristics in patients with inflammatory bowel disease: a monocentric cross-sectional study. J Crohns Colitis. 2022;16:1363–71. https://doi.org/10.1093/ecco-jcc/jjac051.

20. Singh S, Blanchard A, Walker JR, Graff LA, Miller N, Bernstein CN. Common symptoms and stressors among individuals with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2011;9:769–75. https://doi.org/10.1016/j.cgh.2011.05.016.

21. Coates MD, Lahoti M, Binion DG, Szigethy EM, Regueiro MD, Bielefeldt K. Abdominal pain in ulcerative colitis. Inflamm Bowel Dis. 2013;19:2207–14. https://doi.org/10.1097/MIB.0b013e31829614c6.

22. Greenley RN, Kunz JH, Schurman JV, Swanson E. Abdominal pain and health-related quality of life in pediatric inflammatory bowel disease. J Pediatr Psychol. 2013;38:63–71. https://doi.org/10.1093/jpepsy/jss097.

23. Ding Z, Patel A, Izanec J, Pericone CD, Lin JH, Baugh CW. Trends in US emergency department visits and subsequent hospital admission among patients with inflammatory bowel disease presenting with abdominal pain: a real-world study from a national emergency department sample database. J Mark Access Health Policy. 2021;9:1912924. https://doi.org/10.1080/20016689.2021.1912924.

24. Newton L, Randall JA, Hunter T, Keith S, Symonds T, Secrest RJ, Komocsar WJ, Curtis SE, Abetz-Webb L, Kappelman M, Naegeli AN. A qualitative study exploring the health-related quality of life and symptomatic experiences of adults and adolescents with ulcerative colitis. J Patient Rep Outcomes. 2019;3:66. https://doi.org/10.1186/s41687-019-0154-x.

25. Gorrepati VS, Soriano C, Johri A, Dalessio S, Stuart A, Koltun W, Tinsley A, Clarke K, Williams E, Coates M. Abdominal pain and anxious or depressed state are independently associated with weight loss in inflammatory bowel disease. Crohns Colitis. 2020;2:47. https://doi.org/10.1093/crocol/otaa047.

26. Barnes A, Andrews JM, Mukherjee S, Bryant RV, Bampton P, Fraser RJ, Mountifield R. Insomnia is common in inflammatory bowel disease (IBD) and is associated with mental health conditions as well as IBD activity. Intest Res. 2024;22:104–14. https://doi.org/10.5217/ir.2023.00028.

27. Louis E, Siegel CA, James B, Heidenreich S, Krucien N, Ghosh S. Patients with inflammatory bowel disease have heterogeneous treatment preferences that are largely determined by the avoidance of abdominal pain and side effects [P-POWER IBD Study]. J Crohns Colitis. 2023;17:231–9. https://doi.org/10.1093/ecco-jcc/jjac130.

28. Yeung AWK, Wong NSM. The historical roots of visual analog scale in psychology as revealed by reference publication year spectroscopy. Front Hum Neurosci. 2019;13:86. https://doi.org/10.3389/fnhum.2019.00086.

29. Li W, Qing Z, Jun C, Bifa F, Chongrong G, Li H, Yi J, Rongguo L, Guijun L, Tao S, Wei T, Jianglin W, Lin W, Jun W, Dasheng W, Xiaoqiu Y. Expert consensus on the application of pain evaluation questionnaires in China (2020). Chin J Painol. 2020;16:8. https://doi.org/10.3760/cma.j.cn101379-20190915-00075.

30. Bengtsson M, Hammar O, Mandl T, Ohlsson B. Evaluation of gastrointestinal symptoms in different patient groups using the visual analogue scale for irritable bowel syndrome (VAS-IBS). BMC Gastroenterol. 2011;11:122. https://doi.org/10.1186/1471-230X-11-122.

31. Sung YT, Wu JS. The Visual analogue scale for rating, ranking and paired-comparison (VAS-RRP): a new technique for psychological measurement. Behav Res Methods. 2018;50:1694–715. https://doi.org/10.3758/s13428-018-1041-8.

32. Vork L, Keszthelyi D, van Kuijk SMJ, Quetglas EG, Tornblom H, Simren M, Aziz Q, Corsetti M, Tack J, Mujagic Z, Leue C, Kruimel JW, Masclee AAM. Patient-specific stress-abdominal pain interaction in irritable bowel syndrome: an exploratory experience sampling method study. Clin Transl Gastroenterol. 2020;11:e00209. https://doi.org/10.14309/ctg.0000000000000209

33. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole MR. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001;94:149–58. https://doi.org/10.1016/S0304-3959(01)00349-9.

34. Janssen LM, Rezazadeh Ardabili A, Romberg-Camps MJL, Winkens B, van den Broek RJ, Hulst J, Verwijs HJA, Keszthelyi D, Jonkers D, van Bodegraven AA, Pierik MJ, Mujagic Z. Abdominal pain in patients with inflammatory bowel disease in remission: a prospective study on contributing factors. Aliment Pharmacol Ther. 2023;58:1041–51. https://doi.org/10.1111/apt.17718.

35. Malec-Milewska MB, Tarnowski W, Ciesielski AE, Michalik E, Guc MR, Jastrzebski JA. Prospective evaluation of pain control and quality of life in patients with chronic pancreatitis following bilateral thoracoscopic splanchnicectomy. Surg Endosc. 2013;27:3639–45. https://doi.org/10.1007/s00464-013-2937-0.

36. Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. Am J Gastroenterol. 1996;91:1571–8.

37. Jowett SL, Seal CJ, Barton JR, Welfare MR. The short inflammatory bowel disease questionnaire is reliable and responsive to clinically important change in ulcerative colitis. Am J Gastroenterol. 2001;96:2921–8. https://doi.org/10.1111/j.1572-0241.2001.04682.x.

38. Sun D, Chi L, Liu J, Liang J, Guo S, Li S. Psychometric validation of the Chinese version of the short inflammatory bowel disease questionnaire and evaluation of its measurement invariance across sex. Health Qual Life Outcomes. 2021;19:253. https://doi.org/10.1186/s12955-021-01890-x.

39. Bao CH, Liu P, Liu HR, Wu LY, Jin XM, Wang SY, Shi Y, Zhang JY, Zeng XQ, Ma LL, Qin W, Zhao JM, Calhoun VD, Tian J, Wu HG. Differences in regional homogeneity between patients with Crohn's disease with and without abdominal pain revealed by resting-state functional magnetic resonance imaging. Pain. 2016;157:1037–44. https://doi.org/10.1097/j.pain.0000000000000479.

40. Lv K, Song W, Tang R, Pan Z, Zhang Y, Xu Y, Lv B, Fan Y, Xu M. Neurotransmitter alterations in the anterior cingulate cortex in Crohn's disease patients with abdominal pain: a preliminary MR spectroscopy study. Neuroimage Clin. 2018;20:793–9. https://doi.org/10.1016/j.nicl.2018.09.008.

41. Hess A, Roesch J, Saake M, Sergeeva M, Hirschmann S, Neumann H, Dorfler A, Neurath MF, Atreya R. Functional brain imaging reveals rapid blockade of abdominal pain response upon Anti-TNF therapy in Crohn's disease. Gastroenterology. 2015;149:864–6. https://doi.org/10.1053/j.gastro.2015.05.063.

42. Wick EC, Hoge SG, Grahn SW, Kim E, Divino LA, Grady EF, Bunnett NW, Kirkwood KS. Transient receptor potential vanilloid 1, calcitonin gene-related peptide, and substance P mediate nociception in acute pancreatitis. Am J Physiol Gastrointest Liver Physiol. 2006;290:G959-969. https://doi.org/10.1152/ajpgi.00154.2005.

43. Szallasi A, Cortright DN, Blum CA, Eid SR. The vanilloid receptor TRPV1: 10 years from channel cloning to antagonist proof-of-concept. Nat Rev Drug Discov. 2007;6:357–72. https://doi.org/10.1038/nrd2280.

44. Defaye M, Abdullah NS, Iftinca M, Hassan A, Agosti F, Zhang Z, Cumenal M, Zamponi GW, Altier C. Gut-innervating TRPV1+ neurons drive chronic visceral pain via microglial P2Y12 receptor. Cell Mol Gastroenterol Hepatol. 2022;13:977–99. https://doi.org/10.1016/j.jcmgh.2021.12.012.

45. Wils P, Caron B, D'Amico F, Danese S, Peyrin-Biroulet L. Abdominal pain in inflammatory bowel diseases: a clinical challenge. J Clin Med. 2022. https://doi.org/10.3390/jcm11154269.

46. Akbar A, Yiangou Y, Facer P, Brydon WG, Walters JR, Anand P, Ghosh S. Expression of the TRPV1 receptor differs in quiescent inflammatory bowel disease with or without abdominal pain. Gut. 2010;59:767–74. https://doi.org/10.1136/gut.2009.194449.

47. Yiangou Y, Facer P, Dyer NH, Chan CL, Knowles C, Williams NS, Anand P. Vanilloid receptor 1 immunoreactivity in inflamed human bowel. Lancet. 2001;357:1338–9. https://doi.org/10.1016/s0140-6736(00)04503-7.

48. Esquerre N, Basso L, Defaye M, Vicentini FA, Cluny N, Bihan D, Hirota SA, Schick A, Jijon HB, Lewis IA, Geuking MB, Sharkey KA, Altier C, Nasser Y. Colitis-induced microbial perturbation promotes postinflammatory visceral hypersensitivity. Cell Mol Gastroenterol Hepatol. 2020;10:225–44. https://doi.org/10.1016/j.jcmgh.2020.04.003.

49. Matsumoto K, Sugimoto F, Mizuno T, Hayashi T, Okamura R, Nishioka T, Yasuda H, Horie S, Kido MA, Kato S. Immunohistochemical characterization of transient receptor potential vanilloid types 2 and 1 in a trinitrobenzene sulfonic acid-induced rat colitis model with visceral hypersensitivity. Cell Tissue Res. 2023;391:287–303. https://doi.org/10.1007/s00441-022-03723-9.

50. Bakshi N, Hart AL, Lee MC, Williams ACC, Lackner JM, Norton C, Croft P. Chronic pain in patients with inflammatory bowel disease. Pain. 2021;162:2466–71. https://doi.org/10.1097/j.pain.0000000000002304.

51. Dubinsky MC, Clemow DB, Hunter Gibble T, Li X, Vermeire S, Hisamatsu T, Travis SPL. Clinical effect of mirikizumab treatment on bowel urgency in patients with moderately to severely active ulcerative colitis and the clinical relevance of bowel urgency improvement for disease remission. Crohns Colitis. 2023;5:44. https://doi.org/10.1093/crocol/otac044.

52. Arendt-Nielsen L, Morlion B, Perrot S, Dahan A, Dickenson A, Kress HG, Wells C, Bouhassira D, Drewes AM. Assessment and manifestation of central sensitisation across different chronic pain conditions. Eur J Pain. 2018;22:216–41. https://doi.org/10.1002/ejp.1140.

53. Drewes AM, Olesen AE, Farmer AD, Szigethy E, Rebours V, Olesen SS. Gastrointestinal pain. Nat Rev Dis Primers. 2020;6:1. https://doi.org/10.1038/s41572-019-0135-7.

54. Keohane J, O'Mahony C, O'Mahony L, O'Mahony S, Quigley EM, Shanahan F. Irritable bowel syndrome-type symptoms in patients with inflammatory bowel disease: a real association or reflection of occult inflammation? Am J Gastroenterol. 2010;105(1788):1789–94. https://doi.org/10.1038/ajg.2010.156.

55. Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. Nat Med. 2010;16:1248–57. https://doi.org/10.1038/nm.2235.

56. Bielefeldt K, Davis B, Binion DG. Pain and inflammatory bowel disease. Inflamm Bowel Dis. 2009;15:778–88. https://doi.org/10.1002/ibd.20848.

57. Lapointe TK, Basso L, Iftinca MC, Flynn R, Chapman K, Dietrich G, Vergnolle N, Altier C. TRPV1 sensitization mediates postinflammatory visceral pain following acute colitis. Am J Physiol Gastrointest Liver Physiol. 2015;309:G87-99. https://doi.org/10.1152/ajpgi.00421.2014.

58. Theofanous SA, Florens MV, Appeltans I, Denadai Souza A, Wood JN, Wouters MM, Boeckxstaens GE. Ephrin-B2 signaling in the spinal cord as a player in post-inflammatory and stress-induced visceral hypersensitivity. Neurogastroenterol Motil. 2020;32: e13782. https://doi.org/10.1111/nmo.13782.

59. Bayrer JR, Castro J, Venkataraman A, Touhara KK, Rossen ND, Morrie RD, Maddern J, Hendry A, Braverman KN, Garcia-Caraballo S, Schober G, Brizuela M, Castro Navarro FM, Bueno-Silva C, Ingraham HA, Brierley SM, Julius D. Gut enterochromaffin cells drive visceral pain and anxiety. Nature. 2023;616:137–42. https://doi.org/10.1038/s41586-023-05829-8.

60. Gajula P, Quigley EM. Overlapping irritable bowel syndrome and inflammatory bowel disease. Miner Gastroenterol Dietol. 2019;65:107–15. https://doi.org/10.23736/S1121-421X.19.02559-5.

61. Lim J, Rezaie A. Irritable bowel syndrome-like symptoms in quiescent inflammatory bowel disease: a practical approach to diagnosis and treatment of organic causes. Dig Dis Sci. 2023;68:4081–97. https://doi.org/10.1007/s10620-023-08095-w.

62. Barbara G, Cremon C, Stanghellini V. Inflammatory bowel disease and irritable bowel syndrome: similarities and differences. Curr Opin Gastroenterol. 2014;30:352–8. https://doi.org/10.1097/MOG.0000000000000070.

63. Kraneveld AD, Rijnierse A, Nijkamp FP, Garssen J. Neuro-immune interactions in inflammatory bowel disease and irritable bowel syndrome: future

therapeutic targets. Eur J Pharmacol. 2008;585:361–74. https://doi.org/10.1016/j.ejphar.2008.02.095.

64. Vich Vila A, Imhann F, Collij V, Jankipersadsing SA, Gurry T, Mujagic Z, Kurilshikov A, Bonder MJ, Jiang X, Tigchelaar EF, Dekens J, Peters V, Voskuil MD, Visschedijk MC, van Dullemen HM, Keszthelyi D, Swertz MA, Franke L, Alberts R, Festen EAM, Dijkstra G, Masclee AAM, Hofker MH, Xavier RJ, Alm EJ, Fu J, Wijmenga C, Jonkers D, Zhernakova A, Weersma RK. Gut microbiota composition and functional changes in inflammatory bowel disease and irritable bowel syndrome. Sci Transl Med. 2018. https://doi.org/10.1126/scitranslmed.aap8914.

65. de Perez AE, Quera R, Beltran CJ, Madrid AM, Nos P. Irritable bowel syndrome in inflammatory bowel disease. Synergy in alterations of the gut-brain axis? Gastroenterol Hepatol. 2022;45:66–76. https://doi.org/10.1016/j.gastrohep.2021.02.022.

66. Bisgaard TH, Allin KH, Keefer L, Ananthakrishnan AN, Jess T. Depression and anxiety in inflammatory bowel disease: epidemiology, mechanisms and treatment. Nat Rev Gastroenterol Hepatol. 2022;19:717–26. https://doi.org/10.1038/s41575-022-00634-6.

67. Jayasooriya N, Blackwell J, Saxena S, Bottle A, Petersen I, Creese H, Hotopf M, Pollok RCG. Antidepressant medication use in inflammatory bowel disease: a nationally representative population-based study. Aliment Pharmacol Ther. 2022;55:1330–41. https://doi.org/10.1111/apt.16820.

68. Ke H, Li Z, Lin Q, Shen Z, Chen Y, Chen J. Inflammatory bowel disease is causally related to irritable bowel syndrome: a bidirectional two-sample Mendelian randomization study. Front Med (Lausanne). 2023;10:1166683. https://doi.org/10.3389/fmed.2023.1166683.

69. Vasant DH, Paine PA, Black CJ, Houghton LA, Everitt HA, Corsetti M, Agrawal A, Aziz I, Farmer AD, Eugenicos MP, Moss-Morris R, Yiannakou Y, Ford AC. British Society of Gastroenterology guidelines on the management of irritable bowel syndrome. Gut. 2021;70:1214–40. https://doi.org/10.1136/gutjnl-2021-324598.

70. Guo R, Chen LH, Xing C, Liu T. Pain regulation by gut microbiota: molecular mechanisms and therapeutic potential. Br J Anaesth. 2019;123:637–54. https://doi.org/10.1016/j.bja.2019.07.026.

71. Luczynski P, Tramullas M, Viola M, Shanahan F, Clarke G, O'Mahony S, Dinan TG, Cryan JF. Microbiota regulates visceral pain in the mouse. Elife. 2017;6:8. https://doi.org/10.7554/eLife.25887.

72. Rousseaux C, Thuru X, Gelot A, Barnich N, Neut C, Dubuquoy L, Dubuquoy C, Merour E, Geboes K, Chamaillard M, Ouwehand A, Leyer G, Carcano D, Colombel JF, Ardid D, Desreumaux P. Lactobacillus acidophilus modulates intestinal pain and induces opioid and cannabinoid receptors. Nat Med. 2007;13:35–7. https://doi.org/10.1038/nm1521.

73. de Boissieu D, Chaussain M, Badoual J, Raymond J, Dupont C. Small-bowel bacterial overgrowth in children with chronic diarrhea, abdominal pain, or both. J Pediatr. 1996;128:203–7. https://doi.org/10.1016/s0022-3476(96)70390-6.

74. Sinopoulou V, Gordon M, Akobeng AK, Gasparetto M, Sammaan M, Vasiliou J, Dovey TM. Interventions for the management of abdominal pain in Crohn's disease and inflammatory bowel disease. Cochrane Database Syst Rev. 2021;11:13531. https://doi.org/10.1002/14651858.CD013531.pub2.

75. Ringel-Kulka T, Goldsmith JR, Carroll IM, Barros SP, Palsson O, Jobin C, Ringel Y. Lactobacillus acidophilus NCFM affects colonic mucosal opioid receptor expression in patients with functional abdominal pain—a randomised clinical study. Aliment Pharmacol Ther. 2014;40:200–7. https://doi.org/10.1111/apt.12800.

76. Xu ZZ, Zhang L, Liu T, Park JY, Berta T, Yang R, Serhan CN, Ji RR. Resolvins RvE1 and RvD1 attenuate inflammatory pain via central and peripheral actions. Nat Med. 2010;16:592–7. https://doi.org/10.1038/nm.2123.

77. Perez-Berezo T, Pujo J, Martin P, Le Faouder P, Galano JM, Guy A, Knauf C, Tabet JC, Tronnet S, Barreau F, Heuillet M, Dietrich G, Bertrand-Michel J, Durand T, Oswald E, Cenac N. Identification of an analgesic lipopeptide produced by the probiotic Escherichia coli strain Nissle 1917. Nat Commun. 2017;8:1314. https://doi.org/10.1038/s41467-017-01403-9.

78. Spagnuolo R, Cosco C, Mancina RM, Ruggiero G, Garieri P, Cosco V, Doldo P. Beta-glucan, inositol and digestive enzymes improve quality of life of patients with inflammatory bowel disease and irritable bowel syndrome. Eur Rev Med Pharmacol Sci. 2017;21:102–7.

79. Chhibba T, Guizzetti L, Seow CH, Lu C, Novak KL, Ananthakrishnan AN, Bernstein CN, Kaplan GG, Panaccione R, Ma C. Frequency of opioid prescription at emergency department discharge in patients with inflammatory bowel disease: a nationwide analysis. Clin Gastroenterol Hepatol. 2021;19(2064–2071):e2061. https://doi.org/10.1016/j.cgh.2020.07.020.

80. Baillie S, Limdi JK, Bassi A, Fraser A, Parkes G, Scott G, Raine T, Lamb CA, Kennedy NA, Fumis N, Smith MA, Nicolaou A, Emms H, Wye J, Lehmann A, Carbery I, Goodhand J, Lees R, Beshyah W, Luthra P, Pollok R, Selinger C. Opioid use and associated factors in 1676 patients with inflammatory bowel disease: a multicentre quality improvement project. Frontline Gastroenterol. 2023;14:497–504. https://doi.org/10.1136/flgastro-2023-102423.

81. Coates MD, Seth N, Clarke K, Abdul-Baki H, Mahoney N, Walter V, Regueiro MD, Ramos-Rivers C, Koutroubakis IE, Bielefeldt K, Binion DG. Opioid analgesics do not improve abdominal pain or quality of life in Crohn's disease. Dig Dis Sci. 2020;65:2379–87. https://doi.org/10.1007/s10620-019-05968-x.

82. Lindstrom BF, Ruckle JL, Turner SA, Stauber K, Brierley SM, English BA, Yacyshyn B. P139 Olorinab, a peripherally restricted, highly selective agonist of the cannabinoid receptor type 2 for the management of visceral pain in inflammatory bowel disease (IBD)—preclinical and early clinical development. Gastroenterology. 2019;156:S92–3. https://doi.org/10.1053/j.gastro.2019.01.215.

83. Yacyshyn BR, Hanauer S, Klassen P, English BA, Stauber K, Barish CF, Gilder K, Turner S, Higgins PDR. Safety, pharmacokinetics, and efficacy of olorinab, a peripherally acting, highly selective, full agonist of the cannabinoid receptor 2, in a phase 2a study of patients with chronic abdominal pain associated with Crohn's disease. Crohns Colitis. 2021;3:89. https://doi.org/10.1093/crocol/otaa089.

84. D'Haens G, Panaccione R, Baert F, Bossuyt P, Colombel JF, Danese S, Dubinsky M, Feagan BG, Hisamatsu T, Lim A, Lindsay JO, Loftus EV Jr, Panes J, Peyrin-Biroulet L, Ran Z, Rubin DT, Sandborn WJ, Schreiber S, Neimark E, Song A, Kligys K, Pang Y, Pivorunas V, Berg S, Duan WR, Huang B, Kalabic J, Liao X, Robinson A, Wallace K, Ferrante M. Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. Lancet. 2022;399:2015–30. https://doi.org/10.1016/S0140-6736(22)00467-6.

85. Ghosh S, Sanchez Gonzalez Y, Zhou W, Clark R, Xie W, Louis E, Loftus EV, Panes J, Danese S. Upadacitinib treatment improves symptoms of bowel urgency and abdominal pain, and correlates with quality of life improvements in patients with moderate to severe ulcerative colitis. J Crohns Colitis. 2021;15:2022–30. https://doi.org/10.1093/ecco-jcc/jjab099.

86. Danese S, Tran J, D'Haens G, Rubin DT, Aoyama N, Zhou W, Ilo D, Yao X, Sanchez Gonzalez Y, Panaccione R. Upadacitinib induction and maintenance therapy improves abdominal pain, bowel urgency, and fatigue in patients with ulcerative colitis: a post hoc analysis of phase 3 data. Inflamm Bowel Dis. 2023;29:1723–9. https://doi.org/10.1093/ibd/izad016.

87. Wang C, Gu Y, Chu Q, Wang X, Ding Y, Qin X, Liu T, Wang S, Liu X, Wang B, Cao H. Gut microbiota and metabolites as predictors of biologics response in inflammatory bowel disease: a comprehensive systematic review. Microbiol Res. 2024;282: 127660. https://doi.org/10.1016/j.micres.2024.127660.

88. Castiglione F, Rispo A, Di Girolamo E, Cozzolino A, Manguso F, Grassia R, Mazzacca G. Antibiotic treatment of small bowel bacterial overgrowth in patients with Crohn's disease. Aliment Pharmacol Ther. 2003;18:1107–12. https://doi.org/10.1046/j.1365-2036.2003.01800.x.

89. Palumbo VD, Romeo M, Marino Gammazza A, Carini F, Damiani P, Damiano G, Buscemi S, Lo Monte AI, Gerges-Geagea A, Jurjus A, Tomasello G. The long-term effects of probiotics in the therapy of ulcerative colitis: a clinical study. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2016;160:372–7. https://doi.org/10.5507/bp.2016.044.

90. Iskandar HN, Cassell B, Kanuri N, Gyawali CP, Gutierrez A, Dassopoulos T, Ciorba MA, Sayuk GS. Tricyclic antidepressants for management of residual symptoms in inflammatory bowel disease. J Clin Gastroenterol. 2014;48:423–9. https://doi.org/10.1097/MCG.0000000000000049.

91. Colombel JF, Shin A, Gibson PR. AGA clinical practice update on functional gastrointestinal symptoms in patients with inflammatory bowel disease: expert review. Clin Gastroenterol Hepatol. 2019;17(380–390):e381. https://doi.org/10.1016/j.cgh.2018.08.001.

92. Barkhodari A, Lee KE, Shen M, Shen B, Yao Q. Inflammatory bowel disease: focus on enteropathic arthritis and therapy. Rheumatol Immunol Res. 2022;3:69–76. https://doi.org/10.2478/rir-2022-0012.

93. Srinath AI, Walter C, Newara MC, Szigethy EM. Pain management in patients with inflammatory bowel disease: insights for the clinician. Therap Adv Gastroenterol. 2012;5:339–57. https://doi.org/10.1177/1756283X12446158.

94. Korelitz BI. Role of nonsteroidal anti-inflammatory drugs in exacerbation of inflammatory bowel disease. J Clin Gastroenterol. 2016;50:97–8. https://doi.org/10.1097/MCG.0000000000000444.

95. Danese S, Dignass A, Matsuoka K, Ferrante M, Long M, Redondo I, Moses R, Maier S, Hunter

Gibble T, Morris N, Milch C, Abreu MT. Early and sustained symptom control with mirikizumab in patients with ulcerative colitis in the phase 3 LUCENT program. J Crohns Colitis. 2024. https://doi.org/10.1093/ecco-jcc/jjae088.10.1093/ecco-jcc/jjae088.

96. Armuzzi A, Hart A, Cappelleri JC, Mammar N, Hur P, Hoskin B, Hennessy F, Milligan G, Dignass A. Characteristics, clinical outcomes and patient-reported outcomes of patients with ulcerative colitis receiving tofacitinib: a real-world survey in the United States and five European countries. BMC Gastroenterol. 2023;23:17. https://doi.org/10.1186/s12876-023-02640-7.

97. Schmulson MJ, Chiu-Ugalde J, Saez-Rios A, Lopez-Colombo A, Mateos-Perez GJ, Remes-Troche JM, Sobrino-Cossio S, Soto-Perez JC, de la Tamayo Cuesta JL, Teramoto-Matsubara OT, Lopez-Alvarenga JC. Efficacy of the combination of pinaverium bromide 100 mg plus simethicone 300 mg in abdominal pain and bloating in irritable bowel syndrome: a randomized, placebo-controlled trial. J Clin Gastroenterol. 2020;54:e30–9. https://doi.org/10.1097/MCG.0000000000001242.

98. Kaichun W, Minhu C, Jiaming Q. Chinese clinical practice guideline on the management of ulcerative colitis (2023, Xi'an). J Chin Med Assoc. 2024;65:763–8. https://doi.org/10.13288/j.11-2166/r.2024.07.018.

99. Zhang S, Zhao L, Shen H, Tang Z, Qin D, Li J, Zhang B, Yang G, Chen M, Wu K, Liu Z, Yang H, Wang H, Zong Y, Chen Y, Xiao S, Cai Q. International clinical practice guideline on the use of traditional Chinese medicine for ulcerative colitis by Board of Specialty Committee of Digestive System Disease of World Federation of Chinese Medicine Societies (2023). Phytother Res. 2024;38:970–99. https://doi.org/10.1002/ptr.8087.

100. Yuan S, Li Y, Li J, Xue JC, Wang Q, Hou XT, Meng H, Nan JX, Zhang QG. Traditional Chinese medicine and natural products: potential approaches for inflammatory bowel disease. Front Pharmacol. 2022;13: 892790. https://doi.org/10.3389/fphar.2022.892790.

101. Xu J, Xi Y. Observation on the efficacy of Chinese medicine dialectic treatment of ulcerative colitis (in Chinese). Chin Gen Pract. 2023;26:41–3.

102. Dai YC, Zheng L, Zhang YL, Chen X, Chen DL, Tang ZP. Effects of Jianpi Qingchang decoction on the quality of life of patients with ulcerative colitis: a randomized controlled trial. Medicine (Baltimore). 2017;96: e6651. https://doi.org/10.1097/MD.0000000000006651.

103. Yan ZX, Liu YM, Ma T, Xu MJ, Zhang XB, Zha XJ, Yang JH, Jiang P, Chen X, Lin ZW, Wu YH, Zu RZ, Lin WR, Lin XY. Efficacy and safety of retention enema with traditional Chinese medicine for ulcerative colitis: a meta-analysis of randomized controlled trials. Complement Ther Clin Pract. 2021;42: 101278. https://doi.org/10.1016/j.ctcp.2020.101278.

104. Li PH, Tang Y, Wen HZ. Qingchang decoction retention enema may induce clinical and mucosal remission in left-sided ulcerative colitis: a case report. World J Clin Cases. 2022;10:3573–8. https://doi.org/10.12998/wjcc.v10.i11.3573.

105. Dai YC, Tang ZP, Ma GT, Gong YP, Liu W, Zhang YL. A review of Qingchang Shuan for treatment of ulcerative colitis. J Tradit Chin Med. 2010;30:237–40. https://doi.org/10.1016/s0254-6272(10)60049-0.

106. Song G, Fiocchi C, Achkar JP. Acupuncture in inflammatory bowel disease. Inflamm Bowel Dis. 2019;25:1129–39. https://doi.org/10.1093/ibd/izy371.

107. Oxelmark L, Lindberg A, Lofberg R, Sternby B, Eriksson A, Almer S, Befrits R, Fossum B, Karlen P, Brostrom O, Tysk C, Soibd BD. Use of complementary and alternative medicine in Swedish patients with inflammatory bowel disease: a controlled study. Eur J Gastroenterol Hepatol. 2016;28:1320–8. https://doi.org/10.1097/MEG.0000000000000710.

108. Wang X, Zhao NQ, Sun YX, Bai X, Si JT, Liu JP, Liu ZL. Acupuncture for ulcerative colitis: a systematic review and meta-analysis of randomized clinical trials. BMC Complement Med Ther. 2020;20:309. https://doi.org/10.1186/s12906-020-03101-4.

109. Bao C, Wu L, Wu H, Liu H, Zhao J, Zeng X, Ma L, Li J, Zhao C, Wang S. Active Crohn's disease treated with acupuncture and moxibustion: a randomized controlled trial. Zhongguo Zhen Jiu. 2016;36:683–8. https://doi.org/10.13703/j.0255-2930.2016.07.003.

110. Bao CH, Zhong J, Liu HR, Gu YP, Wu P, Gu K, Wang D, Weng ZJ, Shi Y, Wu HG. Effect of acupuncture-moxibustion on negative emotions and plasma tryptophan metabolism in patients with Crohn's disease at active stage. Zhongguo Zhen Jiu. 2021;41:17–22. https://doi.org/10.13703/j.0255-2930.20200814-k0003.

111. Yang L, Zhao J, Guan X, Wang X, Zhao C, Liu H, Wu L, Ji J, Cheng F, Liu X, Wu H. Observation on the effects of different partitioned moxibustion in treating ulcerative colitis. J Acupunct Tuina Sci. 2016;14:231–41. https://doi.org/10.1007/s11726-016-0931-5.

112. Jiang Y, Jarr K, Layton C, Gardner CD, Ashouri JF, Abreu MT, Sinha SR. Therapeutic implications of diet in inflammatory bowel disease and related immune-mediated inflammatory diseases. Nutrients. 2021. https://doi.org/10.3390/nu13030890.

113. de Graaf MCG, Spooren C, Hendrix EMB, Hesselink MAM, Feskens EJM, Smolinska A, Keszthelyi D, Pierik MJ, Mujagic Z, Jonkers D. Diet quality and dietary inflammatory index in Dutch inflammatory bowel disease and irritable bowel syndrome patients. Nutrients. 2022;14:8. https://doi.org/10.3390/nu14091945.

114. Gibson PR. Use of the low-FODMAP diet in inflammatory bowel disease. J Gastroenterol Hepatol. 2017;32(Suppl 1):40–2. https://doi.org/10.1111/jgh.13695.

115. Tapete G, De Bortoli N, Ceccarelli L, Mumolo MG, Vinci E, Albano E, Bertani L, Di Fluri G, Laino G, Ricchiuti A, Bellini M, Marchi S, Costa F. P.07.6 low-fodmaps diet improves intestinal symptoms in ibd patients with disease remission: randomized case-control study. Digest Liver Dis. 2018. https://doi.org/10.1016/s1590-8658(18)30556-5.

116. Tapete G, Ceccarelli L, De Bortoli N, Bertani L, Albano E, Svizzero GB, Di Fluri G, Guidi G, Mumolo MG, Marchi S, Costa F. P.06.16 low- versus high-fodmaps diet in controlling residual abdominal symptoms in inflammatory bowel disease patients: a randomized study with crossing over. Digest Liver Dis. 2019;51:85. https://doi.org/10.1016/s1590-8658(19)30446-3.

117. Chase HW, Boudewyn MA, Carter CS, Phillips ML. Transcranial direct current stimulation: a roadmap for research, from mechanism of action to clinical implementation. Mol Psychiatry. 2020;25:397–407. https://doi.org/10.1038/s41380-019-0499-9.

118. Volz MS, Farmer A, Siegmund B. Reduction of chronic abdominal pain in patients with inflammatory bowel disease through transcranial direct current stimulation: a randomized controlled trial. Pain. 2016;157:429–37. https://doi.org/10.1097/j.pain.0000000000000386.

119. Neeb L, Bayer A, Bayer KE, Farmer A, Fiebach JB, Siegmund B, Volz MS. Transcranial direct current stimulation in inflammatory bowel disease patients modifies resting-state functional connectivity: A RCT. Brain Stimul. 2019;12:978–80. https://doi.org/10.1016/j.brs.2019.03.001.

120. Moser G. The role of hypnotherapy for the treatment of inflammatory bowel diseases. Expert Rev Gastroenterol Hepatol. 2014;8:601–6. https://doi.org/10.1586/17474124.2014.917955.

121. Lee A, Moulton D, McKernan L, Russell A, Slaughter JC, Acra S, Walker L. Clinical hypnosis in pediatric Crohn's disease: a randomized controlled pilot study. J Pediatr Gastroenterol Nutr. 2021;72:e63–70. https://doi.org/10.1097/MPG.0000000000002980.

122. Keefer L, Taft TH, Kiebles JL, Martinovich Z, Barrett TA, Palsson OS. Gut-directed hypnotherapy significantly augments clinical remission in quiescent ulcerative colitis. Aliment Pharmacol Ther. 2013;38:761–71. https://doi.org/10.1111/apt.12449.

123. Tsubaki K, Taguchi K, Yoshida T, Takanashi R, Shimizu E. Long-term effects of integrated cognitive behavioral therapy for chronic pain: a qualitative and quantitative study. Medicine (Baltimore). 2023;102: e34253. https://doi.org/10.1097/MD.0000000000034253.

124. Wang C, Sheng Y, Yu L, Tian F, Xue Y, Zhai Q. Effects of cognitive behavioral therapy on mental health and quality of life in inflammatory bowel disease patients: a meta-analysis of randomized controlled trials. Behav Brain Res. 2023;454: 114653. https://doi.org/10.1016/j.bbr.2023.114653.

125. Salwen-Deremer JK, Siegel CA, Smith MT. cognitive behavioral therapy for insomnia: a promising treatment for insomnia, pain, and depression in patients with IBD. Crohns Colitis. 2020;2:52. https://doi.org/10.1093/crocol/otaa052.

126. Levy RL, Langer SL, Walker LS, Romano JM, Christie DL, Youssef N, DuPen MM, Ballard SA, Labus J, Welsh E, Feld LD, Whitehead WE. Twelve-month follow-up of cognitive behavioral therapy for children with functional abdominal pain. JAMA Pediatr. 2013;167:178–84. https://doi.org/10.1001/2013.jamapediatrics.282.

127. Stapersma L, van den Brink G, van der Ende J, Szigethy EM, Beukers R, Korpershoek TA, Theuns-Valks SDM, Hillegers MHJ, Escher JC, Utens E. Effectiveness of disease-specific cognitive behavioral therapy on anxiety, depression, and quality of life in youth with inflammatory bowel disease: a randomized controlled trial. J Pediatr Psychol. 2018;43:967–80. https://doi.org/10.1093/jpepsy/jsy029.

128. van den Brink G, Stapersma L, Bom AS, Rizopolous D, van der Woude CJ, Stuyt RJL, Hendriks DM, van der Burg JAT, Beukers R, Korpershoek TA, Theuns-Valks SDM, Utens E, Escher JC. Effect of cognitive behavioral therapy on clinical disease course in adolescents and young adults with inflammatory bowel disease and subclinical anxiety and/or depression: results of a randomized trial. Inflamm Bowel Dis. 2019;25:1945–56. https://doi.org/10.1093/ibd/izz073.

129. Levy RL, van Tilburg MA, Langer SL, Romano JM, Walker LS, Mancl LA, Murphy TB, Claar RL, Feld SI, Christie DL, Abdullah B, DuPen MM, Swanson KS, Baker MD, Stoner SA, Whitehead WE. Effects of a cognitive behavioral therapy intervention trial to improve disease outcomes in children with inflammatory bowel disease. Inflamm Bowel Dis. 2016;22:2134–48. https://doi.org/10.1097/MIB.0000000000000881.

130. Torres J, Ellul P, Langhorst J, Mikocka-Walus A, Barreiro-de Acosta M, Basnayake C, Ding NJS, Gilardi D, Katsanos K, Moser G, Opheim R, Palmela C, Pellino G, Van der Marel S, Vavricka SR. European Crohn's and Colitis Organisation topical review on complementary medicine and psychotherapy in inflammatory bowel disease. J Crohns Colitis. 2019;13:673–685e. https://doi.org/10.1093/ecco-jcc/jjz051.